SAFETY ASPECTS AND PATTERNS OF MEDICATION USE IN PREGNANCY

WITH SPECIAL FOCUS ON PSYCHOTROPIC MEDICATION AND MENTAL HEALTH

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Content

Abbreviations

AN	Anorexia nervosa
ATC	Anatomical Therapeutic Chemical classification system
BDS	Slone Epidemiology center's Birth Defect Study
BED	Binge eating disorder
BMI	Body mass index
BMQ-specific	Beliefs About Prescribed Medicines Questionnaire
BN	Bulimia nervosa
CDC	The Centers for Disease Control and Prevention
CHERRIES	Checklist for Reporting Results of Internet E-Surveys
CI	Confidence interval
CV	Cardiovascular
DAGs	Directed Acyclic Graphs
DSM	Diagnostic and Statistical Manual of Mental Disorders
EDNOS	Eating disorders not otherwise specified
EDNOS-P	Eating disorders not otherwise specified, purging type
ENTIS	European Network of Teratology Information Services
EPDS	The Edinburgh Postnatal Depression Scale
EUROCAT	European Concerted Action on Congenital Anomalies and Twins
FDA	Food and Drug Administration
GEE	Generalized Estimating Equation
GPRD	The General Research Practice Database
GW	Gestational week
HPA	Hypothalamic-pituitary-adrenal
IADB	InterAction Database
ICD	International Classification of Disease
LBW	Low birth weight
MBRN	Medical Birth Registry of Norway
MMAS-8	8-item Morisky Medication Adherence Scale
MoBa	The Norwegian Mother and Child Cohort study

NAMCS	Centers for Disease Control and Prevention's National Ambulatory Medical Care Survey
NBDPS	CDC-coordinated national Birth Defects prevention Study
NHAMCS	National Hospital Medical Care Survey
NSAIDs	nonsteroidal anti-inflammatory drugs
OAD	Other antidepressants
OR	Odds ratio
OTC	Over-the-counter
OTIS	Organization of Teratology Information Specialists
p	p-value
PPH	Postpartum hemorrhage
PPHN	Persistent pulmonary hypertension of the newborn
PRAMS	Pregnancy Risk Assessment Monitoring System
Q_{DF}	Cochran's Q with degree of freedom
Q1	Questionnaire 1
Q2	Questionnaire 2
Q3	Questionnaire 3
Q4	Questionnaire 4
RR	Relative risk
SCL-25	The Hopkins Symptom Checklist (25 items)
SCL-5	Short version of the Hopkins Symptoms Checklist (5 items)
SCL-8	Short version of the Hopkins Symptoms checklist (8 items)
SNRIs	Serotonin-noradrenalin reuptake inhibitors
SPSS	Statistical Package for Social Sciences
SSRIs	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants
TERIS	Teratology Information System
THIN	The Health Improvement Network
TNF	Tumor necrosis factor
UTIs	Urinary tract infections
WHO	World Health Organization

Abstract

Use of medications, including psychotropics, is common during pregnancy. Indeed, many women might be in need of pharmacotherapy during pregnancy in order to ensure maternal-fetal health. However, discordant findings or lack of information about neonatal and maternal safety after use of psychotropics, in particular antidepressants, have so far posed significant challenges on practicing clinicians when assessing the risk of pharmacotherapy versus the risk of not medicated maternal illness. In addition, women's unrealistic risk perception of exposure to antidepressants during pregnancy and individuals' beliefs about prescribed medicines may influence women's adherence to needed medications during pregnancy.

Thus, the aims of this doctoral work were: I) to explore from a multinational perspective patterns of and factors associated with use of medications during pregnancy, with particular focus on psychotropics for treatment of depression and/or anxiety; II) to investigate patterns of and associations between use of psychotropics and other relevant medications in the time around pregnancy and eating disorders; III) to explore patterns of and risk factors for low adherence to psychotropics during pregnancy; IV) to determine whether gestational exposure to antidepressants increases the risk of obstetric bleeding complications during pregnancy and postpartum.

In order to address these research questions, data from two studies were utilized. The Multinational Medication Use in Pregnancy Study, providing information about psychiatric and other disorders during pregnancy, related medications use and adherence during pregnancy as reported by participating women, was used to address aims nos. I and III. The Norwegian Mother and Child Cohort Study, comprising information on medication exposures and maternal characteristics during pregnancy, linked to the Medical Birth Registry of Norway providing information about birth outcomes, were utilized to address aims nos. II and IV.

Study I showed that about eight out of ten women used at least one medication during the course of the pregnancy, whereas five out of ten did so during the first trimester. There was a high degree of self-medication with OTC drugs (67%) during pregnancy. About 3% of women reported use of psychotropic medications during pregnancy, mostly SSRIs. Disadvantaged women (e.g. single or divorced, older, with low education, smokers and alcohol consumers

during pregnancy) or with an unplanned pregnancy were more likely to use psychotropics during pregnancy.

Study II showed that use of psychotropics is high among women with eating disorders before, during, and after pregnancy, particularly among women with AN or EDNOS-P. Having BN was found to be significantly directly associated with use (1.8-fold magnitude) and incident use (2.3-fold magnitude) of psychotropics during pregnancy. Having AN or EDNOS-P were found to be significantly directly associated with use of anxiolytics/sedatives postpartum (5.1- and 6.8-fold risk magnitude, respectively).

In study III, about 5% of the sample reported having a psychiatric disorder during pregnancy, mainly depression and/or anxiety, and within this group about 50% presented symptoms of depression. Of the women with a psychiatric disorder, 62% were medicated with psychotropics during pregnancy. About one out of two women medicated with psychotropics demonstrated low adherence during pregnancy. Risk factors for low medication adherence were smoking in pregnancy, ongoing symptoms of depression, elevated antidepressant risk perception, and women's individual beliefs about their prescribed psychotropics.

Study IV showed that exposure to antidepressants during the first or second trimester is not associated with an increased likelihood of vaginal bleeding in early or midpregnancy, respectively. Contrarily, women with depressive symptoms but not exposed to antidepressants during pregnancy had a moderate significant increased likelihood to experience these outcomes. Exposure to SSRIs/SNRIs between gestational week 30 and childbirth did not confer any increased odds for postpartum hemorrhage, compared to non-exposure; however, exposure to TCAs/OADs during this time window conferred a significant 3.8-fold increased odds of postpartum hemorrhage overall, but low statistical power impeded the analysis by mode of delivery.

The findings of this work highlight the need to increase awareness among healthcare providers that a large proportion of pregnant women will be in need of tailored evidence-based information about the fetal and maternal risks of medication exposures during pregnancy, but also about the risk of untreated psychiatric illness during pregnancy and postpartum.

List of publications

I: Lupattelli A, Spigset O, Twigg MJ, Zagorodnikova K, Mårdby AC, Moretti ME, Drozd M, Panchaud A, Hämeen-Anttila K, Rieutord A, Gjergja Juraski R, Odalovic M, Kennedy D, Rudolf G, Juch H, Passier A, Björnsdóttir I, Nordeng H. *Medication use in pregnancy: a cross-sectional, multinational web-based study*. BMJ Open. 2014 Feb 17;4(2):e004365.

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IV: Lupattelli A, Spigset O, Koren G, Nordeng H. *Risk of vaginal bleeding and postpartum hemorrhage after use of antidepressants in pregnancy: a study from the Norwegian Mother and Child Cohort Study*. J Clin Psychopharmacol. 2014 Feb;34(1):143-8.

1. Introduction

"*Nothing in life is to be feared, it is only to be understood.*
Now is the time to understand more, so that we may fear less"
- Marie Curie

Medication use in pregnancy has become an important public health concern in the latest years. Indeed, the mean age of women at first birth has dramatically increased in most developed countries,[1] which implies higher potential risks of obstetric and perinatal complications, and not least a higher likelihood that women will be suffering from chronic disorders already at conception.[2] Similarly, the burden of depression and other mental health conditions is on the rise globally, especially among women, and pregnancy is not a protective factor against their occurrence.[3,4] In all these instances, pharmacotherapy may be needed, even during pregnancy. Pharmacotherapy during pregnancy however involves weighing the possible risk of fetal exposure to medication against the potential adverse effects of untreated maternal illness to both the mother and child. To guide such decisions, it is critical to provide sound data about patterns of and factors associated with medication use in pregnancy, and not least their safety in pregnancy.

1.1 Lesson learned from the past and ethical considerations

Nearly every pregnant woman has faced the dilemma whether to take or not to take a medication during pregnancy because of fear of harming her unborn child. The rationale behind such fear is multifaceted and is triggered by several factors such as health care professionals' hesitation in advising and prescribing needed medications to pregnant women, medication labeling, lack of tailored evidence-based teratogenic counseling, receipt of conflicting information from different sources, and most importantly uncertainty about the safety profile of most marketed medications in human pregnancy.[5-9]

The "thalidomide disaster" from the early 60's has certainly contributed to such a scenario and shaped a strong common belief that women should not be exposed to anything during pregnancy, especially not medications, as they could potentially harm the fetus. The "thalidomide disaster" represents the most untoward event in the history of reproductive health,

which shattered the myth that there was a "placental barrier" through which nothing could cross. Thalidomide was a medication licensed in the late 50's as sedative and anti-nausea drug that could be safely used in pregnancy.[10] In the early 60's Drs. McBride and Lenz independently reported an increase in the incidence of infants with severe congenital anomalies after exposure *in utero* to thalidomide,[11,12] which was then withdrawn from the market. By this time, however, more than 10,000 children had been born with major thalidomide-related malformations.[10] Approximately one out of three women taking thalidomide during the first trimester of pregnancy gave birth to a child with congenital anomalies.[13] These mainly included amelia or phocomelia of extremities, and resulted from repeated use as well as from single intake during the critical period within the 27th to the 40th day of gestation.[14]

The abovementioned disaster gave rise to increased caution and reticence among pharmaceutical manufacturers in carrying out clinical studies including pregnant women, and the Food and Drug Administration (FDA) in the USA even promulgated new Ethics Research Guidelines supporting the exclusion of women in childbearing age from clinical studies investigating new medications.[15] In the years that followed, other drugs, such as isotretinoin and valproic acid, were correctly shown to be teratogenic, whereas other were wrongly alleged to be so, for instance the anti-emetic Bendectin® (doxylamine and pyridoxine). Although subsequent sound studies unsupported the allegations against Bendectin®,[16] they anyhow reinforced the general concern and unrealistic elevated perception of teratogenic risk of marketed medications, which sometimes even led women to terminate a wanted pregnancy.[17]

In 1992, the FDA urged the need of more studies of gender differences in prescription drug testing,[18] which represented an important shift in clinical research. The current *International Ethical Guidelines for Biomedical Research Involving Human Subjects* also provides guidance in how clinical research in pregnant women should be carried out, stating that "*Research in this population should be performed only if it is relevant to the particular health needs of a pregnant woman or her fetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity*".[19] These principles are also emphasized in the

Guidelines for inclusion of women in medical research – Gender as variable in all medical research, edited by the National Ethics Committee for medical research in Norway.[20]

The value of preclinical testing of medications in pregnant animals is somewhat limited since teratogenicity in animals does not always predict teratogenicity in humans, or the converse. For instance, thalidomide was not found to exert teratogenic effects in rats but it did cause malformations similar to those seen in humans in New Zealand white rabbits, highlighting the importance of species-specific mechanisms in teratogenicity.[21]

Since no studies of teratogenicity or of other adverse perinatal outcomes can be conducted during embryogenesis in humans, most medications are put into the market without their safety profile in human pregnancy being established. So far, few medications have been shown to be major teratogens, yet the risk of minor teratogenicity or of more subtle effects on fetal and child development still has to be determined for most of drugs.[13] Now it is time "*to understand more*" about patterns of use and safety of medications in pregnancy, so that practicing clinicians and pregnant women *"may fear less*" and thus ensure rationale and safe medication use among pregnant women worldwide.

1.2 Introduction to maternal disorders and medication use in pregnancy

"After the disasters of the past it is worrying thinking you may have to take medication at all in pregnancy"
- A 36-year-old woman from the United Kingdom, 39 weeks pregnant -

Pregnancy encompasses many biological and psychological changes in a woman's body. These physiological changes are often the cause of numerous short-term ailments such as nausea and vomiting, heartburn, headache or pelvic girdle pain, just to mention some, and may also increase a woman's susceptibility to urinary tract infections (UTIs). For instance, nausea and vomiting are estimated to affect 75% of pregnant women, whereas UTIs are expected to complicate 7-10% of the pregnancies.[22,23] Women with preexisting disorders do also get pregnant, and not least delayed childbearing is associated with increased risk of obstetrical complications such as gestational diabetes, preeclampsia, or hypertension.[2] Hence, for most of

these disorders, either short or long-term, pharmacotherapy during pregnancy may be required to ensure maternal-fetal health.

Several studies have shown that medication use is common during pregnancy. Daw *et al*.[24] have recently systematically reviewed all pregnancy drug utilization studies performed in developed countries and found that prescription drug use in pregnancy was highest in France (93%) and Germany (85%) and lowest in Northern European countries (44-47%). Most of the studies included in the systematic review used automated databases as source of information about drug utilization. However, in this latter review it was also pointed out that difference in study designs, calculation of length of pregnancy, and restriction or not to pregnancies ending in live births, impeded objective comparisons across the various studies.[24] The last cooperative study collecting data uniformly in various countries was carried out in 1987.[25]

Individual studies across Europe identified different estimates of prescribed medication use, ranging from 27% in Serbia to 46% in Finland, 48% in Italy, 57% in Norway, 79% in The Netherlands and 93% in France.[26-31] In the USA, use of medications, either prescribed or purchased over-the-counter (OTC), occurred in 89% of all pregnancies.[32] Overall, paracetamol (acetaminophen) is the most commonly used medication in pregnancy, followed by medication for the alimentary tract and metabolism (e.g., antacids, laxatives, and antiemetics), antibiotics, anti-asthmatics and psychotropics.[30,33-35] In Norway, the most recent study utilizing patients as source of information about medication use in pregnancy (via self-completed questionnaires), was carried out in the period 2008-2010;[36] it was found that 58% of women used psychotropics and/or analgesic medications during pregnancy, with analgesics being the most common drug group (56%). Among the women who reported using analgesics prior to pregnancy, 71% also did so during pregnancy.[36]

Most of the recent studies on medication use in pregnancy stem from automated databases analyses that are often limited to prescription-only medications. In fact, the available literature about the extent and typology of OTC medication used in pregnancy is not extensive. Werler *et al*.[37] found that use of OTC is common in pregnancy, with 65%, 18% and 15% of women reporting use of paracetamol, ibuprofen, and pseudoephedrine, respectively, during pregnancy. Another study[38] among Hispanic women residing in the USA found that the self-reported rate

of OTC drug use during pregnancy was 23%, while higher estimates were observed by Refuerzo *et al*. (63%).[39] In the latter study, paracetamol, antacids and ibuprofen were the most commonly reported OTC drugs (37%, 26% and 10%, respectively).[39]

Several studies have also attempted to estimate the prevalence of use of medications with a potential for fetal harm among pregnant women.[26,40-42] In the study by Andrade *et al*.,[40] for instance, 1.1% of women in the USA were exposed to a teratogenic medication during gestation based on the assessment of clinical teratologists, most commonly fluconazole, carbamazepine, prophylthiouracil and tetracycline. A recent study[43] examined the prevalence and fetal risks of medications most commonly used specifically during the first trimester of pregnancy. There were 54 medications used by more than 0.5% of the pregnant population during the first trimester, and among these only two drugs (promethazine and doxylamine) had "good to excellent" data available to assess their teratogenic risks in human pregnancy according to the Teratology Information System (TERIS); the majority of the remaining medications (63%) had "very limited to fair" data about their teratogenic risks.

1.3 Psychiatric disorders and related pharmacotherapy during pregnancy

1.3.1 The burden of psychiatric disorders in pregnancy

Psychiatric disorders such as depression, anxiety and eating disorders, are important illnesses primarily affecting the childbearing-age female population, and pregnancy is not a protective factor against their onset.[4] Depression and anxiety constitute the most common psychiatric disorders in pregnancy. Studies have shown that between 8.5% and 11.0% of women may experience depression during pregnancy, with variations according to time of gestation.[44] However, when we deal with symptoms of depression rather than diagnosis of major or minor depression, the prevalence estimates rise to 25%,[45] with peaks especially in the second and third trimester.[46,47] Anxiety disorders, which are highly comorbid to depression, account for 8.5% of the pregnancies.[48] However, prevalence estimates of anxiety disorders may vary from study to study, both related to the gestational time when women were assessed and to the screening/diagnostic tool utilized.

Eating disorders are also not uncommon during pregnancy. However, since women with eating disorders tend to not disclose any eating disorder, either past or present, to their treating obstetricians, these conditions may be under-recognized in prenatal routine care.[49] According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV and DSM-5,[50,51] eating disorders are classified into anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), and eating disorders not otherwise specified (EDNOS). A recent study among women attending their first routine ultrasound (mean gestational week: 11.5) found that the prevalence of AN, BN, BED and EDNOS were 0.5%, 0.1%, 1.8% and 5.0%, respectively.[52] Another study from the Norwegian Mother and Child Cohort (MoBa) found that the prevalence of BN, BED and EDNOS purging type (EDNOS-P) in early pregnancy were 0.2%, 4.8% and 0.1%, respectively.[53] In general, eating disorder symptoms have been shown to decrease during pregnancy. They do not disappear completely, and some women with a past eating disorder history can have a resurgence of symptoms in pregnancy.[54] Improvement in symptoms may be limited to the pregnancy period and perhaps for a brief period of time postpartum, but a significant portion of women returns to eating disorders symptoms after giving birth. Eating disorders are characterized by a high rate of psychiatric comorbidity, most commonly depression and anxiety.[55] Indeed, high levels of anxiety and depression in the postpartum period have been found to be associated with active eating disorder symptoms in pregnancy.[56] Other psychiatric disorders such as bipolar disorders, schizophrenia, obsessive-compulsive disorders, are not presented here since they are not within the scope of this work.

1.3.2 Psychotropic medication use in pregnancy

"I am concerned about the effects of sertraline on my child, but when I tried to gradually reduce my dose before pregnancy and during the first trimester I relapsed into a terrible depression. I even thought about suicide"
- A 33-year-old woman from Canada, 23 weeks pregnant -

Psychiatric disorders frequently require pharmacological treatment, even in pregnancy.[57] Antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line pharmacological treatments for depressive and anxiety disorders since they carry a low risk of toxicity in overdose.[4] SSRIs seem to moderately reduce the symptoms of BN and

BED, but exert little effect on full recovery.[58-60] To date, fluoxetine is the only antidepressant approved for treatment of BN,[61] and in January 2015 the psychostimulant lisdexamfetamine was approved by the FDA for treatment of BED.[62] No psychotropic medication is approved for treatment of AN; indeed, clinical trials investigating the effect of antidepressants and antipsychotics for treatment of AN have shown disappointing results. Psychotropic medications are however used by patients with AN, often for treatment of comorbid psychiatric disorders or symptoms.[63,64]

In Norway, approximately 3,000 children (5%) a year are exposed to psychotropic drugs during fetal life, most frequently antidepressants.[28] Recent research has suggested that there is a steadily increasing trend of antidepressant use during pregnancy. Mitchell *et al*.[32] examined trends of antidepressant use from 1976 to 2008 in the USA and found that exposure to these medications increased from 1% in 1988-1990 to 7.5% in 2008. Similarly, a study in The Netherlands found that exposure to SSRIs from three months before conception to delivery increased from 1.2% in 1995/1996 to 2.9% in 2003/2004.[65] Tables 1a-1d below provide an overview of drug utilization studies published in the last ten years (February 2005 – February 2015) that were conducted in Western countries (i.e. Europe, North America and Australia) and provided estimates of use of any psychotropic medication in pregnancy, specifically antidepressants, antipsychotics or anxiolytics/sedatives. Although antiepileptics can be used for treatment of psychiatric illnesses such as bipolar disorders, this medication group was not taken into account in this work. Studies are grouped according to the source of information utilized (i.e., questionnaires, interviews, prescribers' medical records, automated databases) and sorted by country of origin. Although general practice databases fall within the classification of automated databases, they were presented as drug utilization studies using prescribers' medical records as source of information about medication exposures in pregnancy. Whenever studies evaluated trends of mediation use overtime, we present the most recent estimate.

As shown in Tables 1a-1d, most studies published in the last decade utilized automated databases, including general practice medical records, as source of information about medication use. Overall, antidepressants represent the psychotropic drug group most widely used in pregnancy in Europe, North America and Australia. The prevalence of antidepressant use in USA and Canada (ranging from 1.4% to 13.4%) is higher than that observed in European studies

(ranging from 0.8% to 4.5%). Also, drug utilization estimates extracted from interviews and questionnaires were substantially lower than those obtained from studies using medical records or automated databases. Indeed, these latter studies have measured rates of prescriptions (either filled or not) and therefore suffer from the main limitation as to whether pregnant women actually administered the prescribed drug(s). However, medical records and automated database are population-based data sources, as opposed to questionnaire or interview-based studies, which generally are covering a smaller segment of the target population.

Table 1a: Overview of drug utilization studies in pregnancy using interview as source of information about exposure to psychotropics in pregnancy

Study		Sample			Medication use in pregnancy			
Authors	**Publication year**	**N**	**Year of delivery**	**Data source**	**Any psychotropic**	**Anti-depressants**	**Anxiolytics and sedatives**	**Anti-psychotics**
					%	%	%	%
EUROPE								
• **IRELAND**								
Cleary *et al.* [66]	2010	61,252	2000-2007	Interview Maternity hospital	-	0.9*	-	-
• **SPAIN**								
Checa *et al.* [67]	2005	1,103	Jan-Dec 2002	Interview Maternity ward in one hospital	0.8	-	-	-
De Las Cuevas *et al.* [68]	2007	1,332	May-July 2006	Interview Maternity wards in two public hospitals	2.5	0.8	1.9	-
NORTH AMERICA								
• **USA**								
Thorpe *et al.* [43]	2013	5,381	2006-2009 (BDS) 2004-2007 (NBDPS)	Computer-assisted telephone interviews BDS & NBDPS	-	Sertraline: 1.5§ Paroxetine: 0.6§ Fluoxetine: 1.0§ Escitalopram: 0.7§	Alprazolam: 0.5§	-
Mitchell *et al.* [32]	2011	25,313 (BDS) 5,008 (NBDPS)	1976-2008 (BDS) 1997-2003 (NBDPS)	Computer-assisted telephone interviews BDS & NBDPS	-	BDS estimates: Sertraline: 2.2§ Fluoxetine: 1.4§ Escitalopram: 1.0§ Any: 7.5	-	-
Alwan *et al.* [69]	2011	6,582	1998-2005	Computer-assisted telephone interviews NBDPS	-	4.5¶	-	-

Abbreviations: BDS = Slone Epidemiology center's Birth Defect Study; NBDPS = CDC-coordinated national Birth Defects prevention Study. *The estimate includes antidepressants and antipsychotics. [§]Indicates medication use specifically during the first trimester of pregnancy. [¶]Indicates medication use from 3 months preconception to the end of pregnancy.

Table 1b: Overview of drug utilization studies in pregnancy using questionnaire as source of information about exposure to psychotropics in pregnancy

Study		Sample			Medication use in pregnancy			
Authors	**Publication year**	**N**	**Year of delivery**	**Data source**	**Any psychotropic**	**Anti-depressants**	**Anxiolytics and sedatives**	**Anti-psychotics**
					%	%	%	%
EUROPE								
• **ICELAND**								
Axelsdottir *et al.* [70]	2014	1,111	2009-2010	Questionnaire Health care centers	6.0	3.0	1.0-2.0	-
• **NORWAY**								
Nordeng *et al.* [36]	2012	1,984	2008-2010	Questionnaire Maternity ward	1.8	-	-	-
Ystrom *et al.* [71]	2012	835	Sep-Oct 2008	Questionnaire (electronic)	-	1.9	1.4	-
NORTH AMERICA								
• **USA**								
Roberson *et al.* [72]	2014	4,735	2009-2011	Questionnaire PRAMS survey data	1.4	-	-	-
AUSTRALIA								
Sawicki *et al.* [73]	2011	819	Feb-May 2009	Questionnaire Maternity hospital	-	1.5	-	-

Abbreviations: PRAMS = Pregnancy Risk Assessment Monitoring System

Table 1c: Overview of drug utilization studies in pregnancy using prescribers' medical records as source of information about exposure to psychotropics in pregnancy

Study		Sample			Medication use in pregnancy			
Authors	**Publication year**	**N**	**Year of delivery**	**Data source**	**Any psychotropic**	**Anti-depressants**	**Anxiolytics and sedatives**	**Anti-psychotics**
					%	%	%	%
EUROPE								
• **UNITED KINGDOM**								
Petersen *et al.* [74]	2014	495,953	1995-2012	THIN primary care database	-	-	-	0.2
Margulis *et al.* [75]	2014	421,645	1989-2010	GPRD primary care database / Mother-Baby Link	-	1.3-2.8	-	0.3-1.3
Cea-Soriano *et al.* [76]	2013	148,544	1996-2010	THIN primary care database	-	3.6*	0.6-1.7*	-
Petersen *et al.* [77]	2011	114,999	1992-2006	THIN primary care database	-	3.0	-	-
Hardy *et al.* [78]	2006	81,975	1991-1999	GPRD primary care database	-	0.2*	0.3*	-
NORTH AMERICA								
• **USA**								
Yamamoto *et al.* [79]	2014	37.8 millions	2006-2010	Ambulatory and hospital outpatient records NAMCS & NHAMCS	-	2.2	-	-
Meunier *et al.* [80]	2013	27,328	2002-2010	Ambulatory and hospital outpatient records NAMCS & NHAMCS	-	2.1	-	-
• **CANADA**								
Daw *et al.* [81]	2012	163,082	2001-2006	Hospital records linkage to outpatient prescription-drug claims	-	4.5	3.3	-

Abbreviations: THIN = The Health Improvement Network; GPRD = The General Research Practice Database; NAMCS = Centers for Disease Control and Prevention's National Ambulatory Medical Care Survey; NHAMCS = National Hospital Medical Care Survey. *Indicates medication use specifically during the first trimester of pregnancy.

Table 1d: Overview of drug utilization studies in pregnancy using automated databases as source of information about exposure to psychotropics in pregnancy

Study		Sample			Medication use in pregnancy			
Authors	**Publication year**	**N**	**Year of delivery**	**Data source**	**Any psychotropic**	**Anti-depressants**	**Anxiolytics and sedatives**	**Anti-psychotics**
					%	%	%	%
EUROPE								
• **DENMARK**								
Askaa *et al.* [82]	2014	911,017	1997-2010	Medical Birth Registry and Register of Medicinal Product Statistics linkage	-	-	0.2	-
Jimenez-Solem *et al.* [83]	2013	912,322	1997-2010	Medical Birth Registry and Register of Medicinal Product Statistics linkage	-	3.2	-	-
Munk-Olsen *et al.* [84]	2012	86,216	1996-2007	Civil Registration System and Register of Medicinal Product Statistics linkage	-	0.9-1.5	-	-
Bjorn *et al.* [85]	2011	85,710	1999-2009	Medical Birth Registry and Aarhus University Prescription Database linkage	-	2.2	-	-
• **FRANCE**								
Lacroix *et al.* [30]	2009	10,008	2004-2005	Health Insurance Service database and Mother and Child Protection Centre Database and Antenatal Diagnostic Centre Database linkage	-	2.0	1.0-3.0	-
• **FINLAND**								
Artama *et al.*	2011	739,924	1996-2006	National health registries	1.1-3.8[§]	-	-	-

Study		Sample			Medication use in pregnancy			
Authors	**Publication year**	**N**	**Year of delivery**	**Data source**	**Any psychotropic**	**Anti-depressants**	**Anxiolytics and sedatives**	**Anti-psychotics**
[86]				linkage				
• **ITALY**								
Gagne *et al.* [27]	2008	33,343	Jan-Dec 2004	Population-based longitudinal health care database	-	Paroxetine: 0.3	-	-
• **NORWAY**								
Riska *et al.* [87]	2014	345,703	2004-2011	Medical Birth Registry and Prescription Database linkage	-	-	1.5	-
Engeland *et al.* [28]	2008	106,329	2004-2007	Medical Birth Registry and Prescription Database linkage	-	0.4-1.1	0.5-1.0	0.2-0.9
• **THE NETHERLANDS**								
Bakker *et al.* [65]	2008	14,902	1995-2004	Prescription Database	-	2.1*	-	-
Ververs *et al.* [88]	2006	29,005	2000-2003	Health insurance claims	-	1.8-2.0	-	-
Bakker *et al.* [29]	2006	5,412	1994-2003	Prescription drug dispensing data from community pharmacies	0.9-1.9¶	-	1.2-1.5	-
• **SWEDEN**								
Stephansson *et al.* [89]	2011	102,995	Jan-Dec 2007	Medical Birth Registry and Prescription Database linkage	-	1.0-2.0	0.2-0.7	0.1-0.7
• **MULTINATIONAL: DENMARK, UNITED KINGDOM, THE NETHERLANDS AND ITALY**								
Charlton *et al.* [90]	2014	862,943	2004-2010	Electronic healthcare databases	-	1.5-4.5¥	-	-
NORTH AMERICA								
• **USA**								
Hanley *et al.* [91]	2014	343,299	2006-2011	Insurance claims Truven Health MarketScan	10.6	6.5	4.2	1.1

Study		Sample			Medication use in pregnancy			
Authors	**Publication year**	**N**	**Year of delivery**	**Data source**	**Any psychotropic**	**Anti-depressants**	**Anxiolytics and sedatives**	**Anti-psychotics**
				database				
Toh *et al.* [92]	2013	585,615	2001-2007	Automated administrative databases Health plan care claims within nine US states	-	-	-	0.7
Epstein *et al.* [93]	2013	296,817	1985-2005	Insurance claims Tennessee Medicaid data linked to birth certificates	-	-	-	0.4
Huybrechts *et al.* [94]	2013	1,106,757	2000-2007	Medicaid Analytic eXtract	-	8.1	-	-
Hayes *et al.* [95]	2012	228,876	1995-2007	Insurance claims Tennessee Medicaid	-	2.8-7.4	6.1	1.2
Andrade *et al.* [96]	2008	118,935	2001-2005	Automated administrative databases from the health plans Health plan care claims within seven US states	-	6.6	-	-
Cooper *et al.* [97]	2007	105,335	1999-2003	Insurance claims Tennessee Medicaid	-	13.4	-	-
• **CANADA**								
Berard *et al.* [98]	2014	289,688	1998-2008	Administrative databases linkage	-	4.5	4.0	-
AUSTRALIA								
Colvin *et al.* [99]	2013	96,698	2002-2005	Administrative databases linkage	-	4.6	-	-

*Indicates medication use specifically during the first trimester of pregnancy. [§]The estimate includes all medications under the ATC groups N05 and N06 in the period one month prior to pregnancy and/or during pregnancy. [¶]The estimate includes antidepressants and antipsychotics. [¥]The estimates refer to SSRI antidepressants only.
[**]Indicates use from 60 days before pregnancy through delivery.

1.3.3 The impact of maternal psychiatric disorders on maternal-fetal health

- Depression and anxiety

Depression and anxiety are per se physiologically important exposures in pregnancy; they can affect maternal homeostatic systems such as appetite and stress response as well as lifestyle factors such as substance use and engagement in prenatal care, thereby subsequently, either directly or indirectly, impact maternal-fetal health.[4] From a biological perspective, depression is known to alter the hypothalamic-pituitary-adrenal (HPA) axis, which is the core endocrine stress system in humans, with a subsequent increase in the level of circulating glucocorticoids.[100] Maternal increased level of circulating glucocorticoids implies a higher fetal exposure to these agents, with a subsequent HPA axis dysfunction in the fetus; as shown in animal studies, this scenario is responsible for smaller birth weight, HPA axis function, and anxiety-related behaviors.[101]

Although anxiety and depressive disorders are highly comorbid, most studies have so far explored the impact of depression on perinatal outcomes, and very little is known about the sole effect of anxiety.[102,103] Two recent meta-analyses have in fact attempted to pool results of various studies on the relationship between not medicated depression and perinatal outcomes such as low birth weight or prematurity.[104,105] Grote *et al.*[105] pooled results of studies published in the period 1980-2009, which reported data on prematurity (< 37 weeks gestation), low birth weight (< 2,500 g) and intrauterine growth restriction (<10th percentile for gestational age) using random-effects methods. The findings of this meta-analysis suggested that antenatal depression (when used as categorical variable) conferred a significantly increased risk for prematurity (pooled relative risk [RR]: 1.39; 95% Confidence Interval [CI]: 1.19-1.61), low birth weight (pooled RR: 1.49; 95% CI: 1.25-1.77), and intrauterine growth restriction (pooled RR: 1.45; 95% CI: 1.05-2.02). Using severity of depression as continuous variable attenuated these measures of associations (magnitude range of the pooled RR: 1.02-1.03). In a more recent meta-analysis, Grigoriadis *et al.*[104] pooled results of both retrospective and prospective studies published from inception to June 2010. In the overall analysis it was found that maternal depression was significantly associated with premature delivery (pooled Odds Ratio [OR]: 1.37; 95% CI: 1.04-1.81) and diminished breastfeeding initiation (pooled OR: 0.68; 95% CI: 0.61-0.76); however no significant associations were found in relation to other outcomes such as birth weight, low

birth weight, gestational age, Apgar scores at one and five minutes, neonatal intensive care unit admission, and preeclampsia.[104]

Beyond having an impact on immediate pregnancy outcomes, antenatal depression and anxiety are important risk factors for maternal mental health postpartum.[106] Sutter-Dallay *et al*.[48] found that women with an anxiety disorder during pregnancy presented a significant 3-fold increased risk of developing intense postnatal depressive symptoms, independently from the presence or absence of concomitant depression during gestation. A meta-analysis by Beck[107] evaluating predictors of postpartum depression found that antenatal depression, in any of the three trimesters, was one of the strongest predictors for postpartum depression. Another study[108] of small sample size (n=201) investigated the risk of relapse of major depression during pregnancy among women with a history of major depression prior to pregnancy. It was found that women who discontinued their medication at conception relapsed more frequently (68%) compared to those women who maintained their medication throughout the pregnancy (26%) (Hazard ratio: 5.0; 95% CI: 2.8-9.1).

- Eating disorders

In the last decade there has been an increasing number of studies examining perinatal outcomes among women with eating disorders, often showing conflicting results.[54] No study has however discerned the effect of medicated versus not medicated maternal eating disorder on perinatal outcomes. Bulik *et al*.[109] explored birth outcomes among women with eating disorders before and/or during pregnancy in the MoBa study and found that only women with BED had higher risk for delivering higher birth weight babies and large for gestational age babies; women with AN did not present higher rates of premature or small for gestational age children. Similarly, findings from the Generation R study suggested that while AN was positively associated with suspected fetal distress neither AN nor BN women presented higher rates for babies with lower weight or prematurity compared to controls.[110] In both studies, increased gestational weight gain during pregnancy was thought to have mitigated the association between AN and having low birth weight babies. A Finnish study[111] has instead observed higher rates of low birth weight babies among mothers with AN or BN, compared to controls; maternal AN, in particular, was also associated with very premature birth (OR: 4.59; 95% CI: 1.25-16.87), being born small for gestational age (OR: 2.20; 95% CI: 1.23-3.93) and perinatal death (OR: 4.06; 95% CI: 1.15-14.35). In a recent meta-analysis it was found that women with past or active AN

were more likely than healthy controls to have babies with lower birth weight (-0.19 kg; 95%: -0.25, -0.15).[112]

Studies investigating the association between mood and eating disorders have found significantly higher rates of postnatal depression in this group compared to controls. In particular, studies on clinical samples of women with active or previous eating disorder found that about one-third or more of these had postnatal depression.[113,114] A recent cohort study[56] showed that high levels of anxiety and depression in the postpartum period are associated with active eating disorder symptoms in pregnancy.

1.4 Adherence to pharmacotherapy with psychotropics during pregnancy

"*I stopped using antidepressants as soon as I found out I was pregnant (5 weeks)*"
- A 28-year-old woman from Italy, 29 weeks pregnant –

Adequate clinical management of maternal psychiatric disorder during pregnancy is essential to ensure maternal-fetal health.[105,108] Pregnancy represents an important time window for recognition of potential psychiatric symptomatology, establishment of their treatment, and not least tailored interventions by healthcare professionals to ensure that needed medications are taken as prescribed. Medication adherence is defined as "the extent to which patients take medications as prescribed by their health care providers", and is based on a therapeutic alliance between the patient and the physician.[115] Poor adherence to chronic therapies is a well-known public health concern. It is estimated that approximately 50% of medications for chronic diseases are not taken as prescribed in the general population.[116]

Several methods can be employed to measure medication adherence. Osterberg *et al*.[115] categorized these methods as either direct or indirect. Direct methods include directly observed therapy (e.g., measurement of the level of medicine or metabolite in blood) and are considered more robust than indirect methods; indeed, these are accurate and objective, however they are expensive and difficult to implement in daily clinical practice. Indirect methods are often based on patient self-report via questionnaires or diaries, pill counts, rates of prescription refill, or measurement of physiological markers. These are generally

easy to perform, inexpensive, and can also be objective (e.g., pill counts and rates of prescription refill).[115] However, indirect methods may suffer from drawbacks such as patient's attitude in reporting and recall, and prescription refill, for instance, does not necessarily reflect patient's intake of the medication. Despite their limitations, indirect methods can more easily be implemented in clinical settings and are therefore the preferred choice for assessment of medication adherence also in clinical research.[115]

To date, little is known about patterns of medication adherence in pregnant subjects and factors associated with non-adherence.[117] Two studies from the UK primary care database have shown that pregnancy is a major determinant for discontinuation of antidepressants and antipsychotics; specifically, of the women on treatment with antidepressants, atypical antipsychotics or typical antipsychotics before pregnancy, only 10%, 38% and 19%, respectively, were still taking these medications at the beginning of the third trimester.[74,77] However, no study has so far investigated the medication-taking behavior and the extent of adherence to psychotropic medications among those women who decide to maintain this pharmacotherapy in pregnancy. Although the literature pertaining to non-pregnant subjects is extensive, no study has attempted to understand and identify what maternal factors might have an impact on adherence to psychotropic medications in pregnancy.

1.4.1 Factors associated with medication adherence

Research in the general non-pregnant population has shown that non-adherence to medications is a complex and multifaceted behavior where unintentional causes (practical barriers, capacity, resources) as well as intentional causes (motivational beliefs, preferences, perceptual barriers) are in place.[118] In the last decade several studies have explored the role of individual beliefs about medications on adherence.[119-121] Horne *et al.*[120] investigated the role of beliefs about prescribed medicines on adherence, which include the "necessity of the prescribed medication" (for maintaining the individual's health) and the "concerns about the prescribed medications" (i.e., the potential adverse effects of taking them, such as becoming too dependent on the medication or that regular use would lead to long-term adverse effects). This study found that while factors such as gender, educational level, or the number of prescribed medication were not major predictors of medication adherence, individuals' beliefs significantly correlated with the level of medication adherence.[120]

Pregnant women's beliefs will likely impact their decision whether to use a medication or not during pregnancy. In a previous study[122] from our research group we found that pregnant women agreeing with the statement that it is better to abstain from using medication whilst pregnant despite being ill, presented a significant increased likelihood of low adherence (OR: 2.17; 95 % CI: 1.09–4.34) to chronic pharmacotherapy for treatment of somatic disorders, compared to those women who disagreed. Similarly, women agreeing with the statement that herbal remedies rather than conventional medications should be used during pregnancy, presented a significant increased likelihood of low adherence (OR: 3.74; 95 % CI: 1.73–8.06) compared to those who disagreed. Hence, beliefs about medications act as an important determinant of poor medication adherence, even in pregnancy.

Fear of teratogenic drug effects may possibly result in even lower adherence to prescribed treatments in pregnancy. A number of studies have been conducted to assess the perception of teratogenic risk and how this factor affects decision-making regarding whether or not to take a medication during pregnancy. One study examined the effects of information presentation (framing) on women's perception of fetal risk, and their intention to use a safe drug during pregnancy. Women who were given negatively framed information (e.g., a 1–3% chance of having a malformed child) had a significantly higher perception of teratogenic risk when compared to women who were given positively framed information (a 97–99% chance of having a normal child).[6] In another study,[7] researchers evaluated the impact of negative information from various sources on women who had taken an antidepressant during pregnancy.[7] More than half of the women who continued the medication throughout the pregnancy frequently considered discontinuing, despite reassurance of no harm to their children. Negative information was recalled far more often than reassuring information and information from friends, family, and health care providers had a negative impact on decision-making regarding treatment of depression with pharmacotherapy during pregnancy.

Nevertheless, it is important to recognize that the heightened fear of teratogenicity among pregnant women and their negative attitudes towards psychotropic medications, especially antidepressants, can be ascribed, at least in part, to the discordant findings of the studies investigating fetal risks after exposure *in utero* to these medications.

1.5 Safety of antidepressants in pregnancy

Antidepressants are the psychotropic medications most commonly used in pregnancy for treatment of various psychiatric disorders, as outlined in section 1.3.2 above. Therefore most of the literature in the last decade has been focusing on their safety profile in pregnancy. The following section will consequently focus on this medication group.

1.5.1 Neonatal safety

To date, several studies have investigated the risk of neonatal outcomes after exposure *in utero* to antidepressants, although producing conflicting results. With respect to congenital malformations, some studies have reported an increased risk[123,124] while others have documented no increased risk for major malformations.[125,126] Different studies have singled out specific SSRIs associated with increased risk of different malformations most notably various types of cardiovascular malformations, with paroxetine,[127-129] sertraline[123] and citalopram[123] as being more risky than others. Studies investigating other clinically relevant outcomes such as birth weight, prematurity and perinatal complications have also reported conflicting results. Some studies reported increased risk of these outcomes[129-131] whereas others did not.[132] These inconsistencies strongly suggest that the various studies may suffer from uncontrolled and possibly unrecognized sources of bias.

Given this scenario, meta-analyses and systematic reviews pooling data from studies having quality above a certain threshold, are therefore of value in order to synthesize the available data and increase study power. Table 2 outlines the most recent and thorough meta-analyses assessing the risk of perinatal outcomes after exposure *in utero* to antidepressants. As indicated by the pooled results, exposure to antidepressants *in utero* seem to increase the risk of prematurity (53-96% increased risk),[133-135] low birth weight (44% increased risk),[133] persistent pulmonary hypertension of the new-born (2.5 to 3.3-fold increased risk),[136] neonatal adaptation (5.1-fold increased risk),[137] and cardiac malformations (36% increased risk), especially paroxetine (43% increased risk).[138]

Lately, a growing number of studies have investigated the long-term potential effects of *in utero* exposure to psychotropics, especially antidepressants. It has been hypothesized that prenatal exposure to these medications may affect the neurotransmitter systems in the brain and have long-lasting consequences on neurodevelopment in the offspring. Findings of a recent systematic review[139] have pointed out that although some studies indicate a relation

between prenatal exposure to antidepressants and adverse neurodevelopmental outcomes such as delayed motor development/motor control, social difficulties, internalizing problems and autism, confounding by indication is still a major drawback, and a causal association has by no means been established. Also, as pointed out by Hermansen *et al*.,[140] most of the published studies investigating the association between prenatal exposure to antidepressants and adverse neurodevelopmental outcomes presented an insufficient statistical power (range: 40-60%).

The task of assessing the risks and benefits of antidepressant use for the treatment of depression during pregnancy is complicated. The magnitude of the impact, in absolute terms, of the observed associations between antidepressant exposure *in utero* and various perinatal and long-term outcomes, is of utmost importance to guide such assessment (cf. section 1.6.3). Further, since two meta-analyses have shown that non-medicated maternal depression as such may confer an increased risk of prematurity and low birth weight,[104,105] this raises the concern about potential confounding by indication in most studies and whether these perinatal outcomes are more likely to be secondary to the underlying maternal psychiatric disorder rather than to the medication.

Table 2: Overview of the recent meta-analyses and pooled measure of associations between exposure *in utero* to antidepressants and specific perinatal outcomes

Study			**Sample**		**Main findings and related notes**
Authors	**Publica-tion year**	**Search criteria**	**Studies included/ Design/**	**Examined exposure(s)/ Outcome measures**	**Pooled association measures: OR or RR (95% CI)**
Huybrechts *et al.* [134]	2014	Inception /Sep 2012	41 21 prospective 4 bi-directional 16 retrospective	Any antidepressants/ Prematurity Prematurity	Studies were grouped by level of confounding adjustment and by timing of antidepressant use during pregnancy <u>Pooled association measure(s) (ORs) adjusted for potential confounders /Heterogeneity/included studies (n):</u> Any time in pregnancy: 1.53 (1.40-1.66) / $Q_{df}=19.72_{16}$, p=0.233 / n=17 Early pregnancy: 1.16 (0.92-1.45) / $Q_{df}=46.47_{7}$, p<0.001 / n=8 Late pregnancy: 1.96 (1.62-2.38) / $Q_{df}=69.26_{11}$, p<0.001 / n=12 <u>Pooled association measure(s) (ORs) adjusted for psychiatric illness/ Heterogeneity/included studies (n):</u> Combined timing of exposure Controls with psychiatric illness: 1.61 (1.26-2.05) / $Q_{df}=20.47_{11}$, p=0.039 / n=12 Controls without psychiatric illness: 1.88 (1.48-2.40) / $Q_{df}=7.46_{6}$, p=0.280 / n=7
Huang *et al.* [133]	2014	Inception /Dec 2012	28 15 prospective 13 retrospective	Any antidepressants/ Prematurity LBW	<u>Pooled association measure(s) (RRs) /Heterogeneity/included studies (n)</u> Any time in pregnancy: 1.69 (1.52-1.88) / $Q_{df}=49.4_{27}$, p=0.005 / n=28 Any time in pregnancy: 1.44 (1.21-1.70) / $Q_{df}=37.1_{14}$, p=0.001 / n=15
Ross *et al.* [135]	2013	Inception /Jun 2010	23	Any antidepressant/ Spontaneous abortion Prematurity Gestational age	The exposure windows were not specified in this meta-analysis <u>Pooled association measure(s) (ORs or standardized means) for studies above quality threshold /Heterogeneity/included studies (n)</u> 1.47 (0.99-2.17) / p=0.055 / n=3 1.55 (1.38-1.74) / p<0.001 / n=13 -0.23 (-0.34 to -0.12) / p<0.001 [the mean difference was -0.5 weeks] / n=15

Study			Sample		Main findings and related notes
Authors	**Publica-tion year**	**Search criteria**	**Studies included/ Design/**	**Examined exposure(s)/ Outcome measures**	**Pooled association measures: OR or RR (95% CI)**
				Birth weight Apgar score at 1 min Apgar score at 14 min	-0.10 (-0.16 to -0.03) / p=0.003 [the mean difference was -74 g] / n=20 -0.19 (-0.30 to -0.08) / p=0.001 [mean difference was 0.37 points] / n=10 -0.33 (-0.47 to -0.20) / p<0.001 [mean difference was 0.18 points] / n=14
Grigoriadis *et al.* [136]	2014	Inception /Dec 2012	7 5 prospective 2 retrospective	SSRIs/ PPHN	Studies were pooled based on the timing of exposure (such as exposure to antidepressants in early versus late pregnancy). Assessment for the effects of potential moderating variables (study design, congenital malformations, and meconium aspiration) did not account for significant sources of heterogeneity Pooled association measure(s) (ORs) /Heterogeneity/included studies (n): Early pregnancy: 1.23 (0.58-2.60) / $Q_{df}=9.00_2$, p=0.01 / n=3 Any time in pregnancy: 1.55 (0.79-3.04) / $Q_{df}=0.14_1$, p=0.71 / n=2 Most/all of pregnancy: 3.33 (1.58-7.02) / $Q_{df}=0.18_1$, p=0.67 / n=2 Late pregnancy: 2.50 (1.32-4.73) / $Q_{df}=8.31_4$, p=0.08 / n=5
Grigoriadis *et al.* [137]	2013	Inception /Jun 2010	12	Any antidepressant/ Neonatal adaptation Respiratory distress Tremors	Subgroup analyses were run to according to convenience sample, study quality, timing of exposure, and the use of adjusted data. The results here stem from the sub-analysis on timing of exposure in late pregnancy. Pooled association measure(s) (ORs) /Heterogeneity/included studies (n): Late pregnancy: 5.13 (2.86-9.21) / $Q_{df}=4.98_4$, p=0.290 / n=5 Late pregnancy: 2.64 (1.69-4.14) / $Q_{df}=7.94_5$, p=0.160 / n=6 Late pregnancy: 7.89 (3.33-18.73) / $Q_{df}=5.41_3$, p=0.144 / n=4
Grigoriadis *et al.* [138]	2013	Inception /Jun 2010	27	Any antidepressant, paroxetine and fluoxetine	The pooled measures of association stem from studies with quality above threshold

Study			Sample		Main findings and related notes
Authors	**Publica-tion year**	**Search criteria**	**Studies included/ Design/**	**Examined exposure(s)/ Outcome measures**	**Pooled association measures: OR or RR (95% CI)**
				Any antidepressant/	Pooled association measure(s) (RRs) /Heterogeneity/included studies (n):
				Congenital malformations	1. trimester: 0.93 (0.85-1.02) / p=0.984 / n=12
				Major malformations	1. trimester: 1.07 (0.99-1.17) p=0.857 / n=11
				CV malformations	1. trimester: 1.36 (1.08-1.71) / p=0.134 / n=13
				Paroxetine/	
				Congenital malformations	1. trimester: 1.03 (0.87-1.22) / p=0.821 / n=6
				Major malformations	1. trimester: 1.11 (0.88-1.39) p=0.322 / n=5
				CV malformations	1. trimester: 1.43 (1.08-1.88) / p=0.899 / n=7
				Fluoxetine/	
				Congenital malformations	1. trimester: 1.10 (0.84-1.44) / p=0.215 / n=4
				Major malformations	1. trimester: 1.20 (0.98-1.48) p=0.375 / n=4
				CV malformations	1. trimester: 1.17 (0.89-1.55) / p=0.424 / n=4

Abbreviations: OR = Odds Ratio; RR = Relative Risk; CI = Confidence Interval; p = p-value; Q_{df} = Cochran's Q with degree of freedom; LBW: low birth weight; PPHN: Persistent pulmonary hypertension of the newborn; SSRIs: selective serotonin re-uptake inhibitors; CV = Cardiovascular.

1.5.2 Maternal safety

The literature about the risk of obstetric complications or maternal health after use of antidepressants in pregnancy is not extensive. It has been hypothesized that maternal stress, anxiety and depression may trigger pathogenic vascular processes through the altered release of vasoactive hormones or other neuroendocrine transmitters, and thereby damage the vascular endothelium of the developing placenta.[141,142] Serotonin plays a critical role in hemostasis and SSRIs are able to affect the circulating serotonin level;[143,144] hence, exploring the association between SSRIs and preeclampsia by distinguishing the effect of the medications from that of maternal depression, became an important research question. Two studies have suggested that use of SSRIs in pregnancy may increase the risk of preeclampsia and gestational hypertension.[145,146] However such findings could not be replicated in a more recent study. Palmsten *et al.*[147] in fact found no association between SSRIs and preeclampsia (RR: 1.00; 95% CI: 0.93-1.07) compared to women with depression and taking no antidepressants; on the contrary, exposure to serotonin-noradrenalin reuptake inhibitors (SNRIs) or tricyclic antidepressants (TCAs) conferred a significantly increased risk of preeclampsia (SNRIs, RR: 1.52; 95% CI: 1.26-1.83); (TCAs, RR: 1.62; 95% CI: 1.23-2.12).[147] In an additional study, Palmsten *et al.*[148] observed an increased risk for preeclampsia among women exposed to SNRIs and TCAs, but not SSRIs, raising the question whether these associations may reflect drug effects, more severe depression, or other unmeasured maternal factors.

A study from the Swedish Medical Birth Registry[149] examined several obstetric outcomes and found that use of any antidepressant in early and/or late pregnancy was significantly associated with gestational diabetes (37% increased risk), preeclampsia (28-50% increased risk), placenta previa (21-38% increased risk), and bleeding during partum (45-58% increased risk). However, because of the multiple testing, we cannot exclude that some of the significant results were in fact caused by chance. Indeed a recent meta-analysis[150] did not find evidence of an increased risk of gestational diabetes in women with psychiatric illness who took psychiatric medications compared to non-medicated women with psychiatric illness.

SSRIs can hinder the reuptake of serotonin from plasma into the platelets, with consequent inhibition of platelet aggregation and clot formation, resulting in bleeding events.[143,144] Studies among non-pregnant subjects have shown that SSRIs or antidepressants with high

affinity to the serotonin transporter might be implicated in bleeding-related outcomes from the gastrointestinal tract.[151-153] Not surprisingly, bleeding events have also been reported in patients treated with antidepressants exhibiting non-selective serotonin reuptake inhibitor activity such as venlafaxine.[154] Reis *et al*.[149] found that exposure to antidepressants in early pregnancy, but not in late pregnancy, conferred an increased risk (11%) to experience bleeding after partum. Four additional studies[155-158] have investigated the relationship between use of antidepressants and postpartum hemorrhage and found conflicting results. In a nested case-control study, Salked *et al*.[155] found that exposure to SSRIs within 90 days before delivery (based upon prescription claims) did not increase the risk of postpartum hemorrhage (OR: 1.30; 95% CI: 0.98-1.72), and similar results were found when the exposure window was restricted to 30 days before delivery (OR: 1.33; 95% CI: 0.94-1.89). On the contrary, in a sub-cohort of Medicaid women diagnosed with mood or anxiety disorders, Palmsten *et al*.[156] found that women with a monotherapy supply of an SSRI, an SNRI or a TCA that overlapped with the delivery date, had a 1.42-, 1.90- and 1.77-fold increased risk to experience postpartum hemorrhage respectively, compared to controls. The sensitivity analyses and adjustment for high dimension propensity score did not confer major changes to these findings. A recent hospital-based study found that compared to non-exposed, women taking SSRIs during pregnancy presented a significant 2.6-fold increased risk of postpartum hemorrhage as well as for anemia following a vaginal delivery.[157] Another recent case-control study[158] using data from the linked administrative and hospital database of the Québec Pregnancy Cohort found that exposure to any antidepressant, measured by filling a prescription in the six months prior to index date (i.e., delivery date), conferred a significant 48% and 40% increased risk for any and atonic postpartum hemorrhage, respectively. However the latter two studies suffers from important drawbacks, primarily lack of an active comparator group including women with not medicated depression during pregnancy, proof of timely exposure to SSRIs near delivery and lack of distinction between antidepressants showing different affinity to the serotonin transporter.

1.6 Pharmacoepidemiology

The majority of studies described in the previous sections are of observational nature. Ethical reasons preclude inclusion of pregnant women in the vast majority of pre-marketing clinical trials,[159] and therefore pregnancy research is mainly based on

observational studies. Pharmacoepidemiology, defined as "the study of the effects of drugs in large numbers of people", is a discipline bridging epidemiology and clinical pharmacology. It applies epidemiological methods to studies of the use of drugs at a population level. Pharmacoepidemiology is the best discipline enabling us to explore the prevalence and safety of medication exposure in pregnancy.[160] These two elements, prevalence and safety, are interdependent and complementary within each other. Indeed, drug utilization research set the basis and priorities for analytic pharmacoepidemiological studies.

1.6.1 Drug utilization research

Drug utilization research was defined by the World Health Organization (WHO) as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences".[161] The scope of this research is to provide information about the prevalence of drug use in a defined population, trends of use over-time, and also non-pharmacological factors influencing such use (e.g. sociodemographics). Ideally, quantitative drug utilization studies should also include information about the diagnosis or indication for use of the medication of interest, the dosage used, the timing of use, and should provide information on the specific substance-level.[162]

Every year new medications are placed into the market while others are withdrawn, prescription medications may become available as OTC drugs, clinical protocols for treatment of specific disorders can change, and hence there is the potential of a constant shift in type and extent of exposure to medications during pregnancy. The need of drug utilization research in pregnancy is thus warranted.[163]

To date, several sources of information about medication use in pregnancy are available to researchers, and these can be grouped under three main domains: patients, prescribers, and automated databases. An overview of the various data sources of information, each with its inherent most common advantages and disadvantages, is outlined in Table 3.

1.6.2 Observational, analytic pharmacoepidemiology

Observational, analytic pharmacoepidemiology is a discipline providing information about the magnitude of the association between specific exposures during pregnancy and

determined immediate or long-term pregnancy outcomes. The terminology "analytic" is used in order to emphasize the ability to determine measures of associations. Studies addressing the safety of those medications most commonly used by women in pregnancy (since a moderate increase in the relative risk for a specific outcome may have a significant impact in terms of absolute risk), as well as those medications for treatment of disorders that, if sub-optimally treated, may jeopardize maternal-fetal health, are usually a central part of analytic pharmacoepidemiology research.

Analytic observational pharmacoepidemiological studies can be retrospective or prospective in nature. In retrospective case-control studies, cases with a specific pregnancy outcome are compared to controls without that outcome, looking whether there are differences in antecedent exposures during gestation. In prospective cohort studies a specific maternal exposure is ascertained during pregnancy and the pregnancy outcome is evaluated and compared to a control group.[164] The main characteristics of prospective and retrospective study designs, along with most common advantages and disadvantages, are outlined in Table 4.

Data for such studies, i.e., information about exposure, outcome and covariates, may stem from one or more sources combined. The sources of information about exposure to medication in pregnancy are various, as outlined in Table 3, and can be self-reported by the women or abstracted from automated databases and prescribers' records. Ideally, health outcomes should be clinically ascertained (e.g., via medical diagnosis) or extrapolated from validated psychometric instruments rather than self-reported by the women.

- Follow-up of women exposed to medication in pregnancy

In pregnancy research, women exposed to specific medications can be identified in various ways. For instance, physicians can enroll their pregnant patients using medications into relevant pregnancy registries. Pregnant women can also enroll themselves into pregnancy registries upon calling teratology information services or when visiting the service webpage.[165] Pregnancy registries are often used as a source population for cohort studies or case–control studies.[166] Pregnancy registries are observational studies collecting uniform data to evaluate outcomes for a particular population defined by a particular exposure, of pregnant women which can be based on a common exposure to a medication, or on a common outcome of the pregnancy (e.g., congenital anomalies). These registries are most

useful when they strive to include all exposed women, rather than relying on passive or spontaneous reporting.

An important advantage of this way of enrollment is that women exposed to specific medications are identified early in pregnancy and before knowing the outcome of the pregnancy. On the other hand, this type of studies suffers from important drawbacks such as loss to follow-up, self-referral bias, and appropriate selection of a control group.

To date there are several ongoing pregnancy registries run by pharmaceutical industries (e.g., the Seasonal Influenza Vaccine Pregnancy Registry by GlaxoSmithKline), general hospitals (e.g., the National Pregnancy Registry for Atypical Antipsychotics by the Center for Women's Mental Health at Massachusetts General Hospital), or non-profit organizations (e.g., the OTIS AutoImmune Diseases Study by the Organization of Teratology Information Specialists [OTIS]; the prospective multicenter observational study on safety of TNF-alpha inhibitors in pregnancy by the European Network of Teratology Information Services [ENTIS]).[167]

Table 3: Overview of the available sources of information about drug utilization in pregnancy studies

Source of information	Study example	Most common advantages	Most common disadvantages
PATIENTS			
• Interview Trained interviewers collect information about medication use by interviewing patients (face-to-face or by telephone) and via utilization of standardized questionnaires	The BDS in the USA[32]	· Higher response rate than paper-based postal questionnaires · The interviewer can ask clarifying questions · Specificity of questioning	· Risk of selection bias · Risk of recall bias · Subjective influence of the interviewer · Time-consuming and costly · Sensitive questions may not been truly answered
• Questionnaire Paper postal questionnaires. Responders usually send back the questionnaires by ordinary mail after completion	The Childbirth and Health Study in Primary Care Study in Iceland [70]	· Possibility to use prompts · Lower risk of recall bias if questions refer to recent timing · Sensitive questions can be answered more correctly than in a face-to-face interview	· Risk of selection bias · Risk of recall bias · Risk of information bias · Low response rate · Time-consuming · Questionnaires can be filled with delay
• Electronic questionnaire Electronic questionnaires are accessible and can be completed by responders online	SnartGravid study in Denmark[168]	· Possibility to reach a wide segment of the birthing population · Economically affordable method and not time consuming · Sensitive questions can be answered privately and therefore more correctly than in a face-to-face interview · Possibility to use prompts	· Risk of self-selection of participants · Usually more educated or motivated women participate · Risk of information bias · Inability to quantify a conventional response rate · Not suitable for countries with low internet penetration rates
PRESCRIBERS			
• Hospital/ambulatory outpatient records Registry collecting data on women receiving prenatal care and from outpatient prenatal visits	The NAMCS and NHAMCS in the USA[80]	· Large samples · Economically affordable method and not time consuming · Collection of data about medication use and diagnoses	· Depending on the setting, risk of selection bias · No information about actual drug intake · Not always accurate in registering medication use during pregnancy · No information about use of OTC or herbal drugs · Lack of important covariates · Usually measure number of visits rather than individuals

Source of information	Study example	Most common advantages	Most common disadvantages
• Medical records Registry of primary care medical records, also linking to secondary care datasets	The GPRD in the UK[75]	· Large sample size · Longitudinal records · Possible data linkage with other databases · Economically affordable method and not time consuming	· No information about actual drug intake · No information about use of OTC or herbal drugs · Lack of important covariates · Old medical records may not reflect current practice · No information about miscarriages
AUTOMATED DATABASES			
• Pharmacy records (dispenser regulated) Registry of prescriptions dispensed from community pharmacies	The IADB in The Netherlands [29]	· Large sample size · No selection bias · No recall bias · Irrespective of insurance · Information about indication for use is often recorded	· Gestational time can be inaccurate or unavailable · No information about use of OTC or herbal drugs or drugs dispensed during hospitalization · No information about pregnancies ending in abortions/miscarriages
• Prescription database (Authority regulated) Based on filled prescriptions, reimbursed or not, dispensed at pharmacies to individual patients treated in ambulatory care	The Norwegian Prescription Database [28]	· Large sample size · No selection bias · No recall bias · Not costly once established and running · Reimbursement code is often registered (a proxy for diagnosis)	· No information about actual intake of drugs · No information about use of OTC or herbal drugs or not reimbursed drugs · Lack of important covariates · Lack of indication for use – however the reimbursement code is specific
• Claims and other administrative databases Registry containing information about insured-events and pharmacy refund claims	The Tennessee Medicaid data linked to birth certificates in the USA[93]	· Large size · Drug refund claims · Accurate information about dispensed drugs · No recall bias · Not costly	· Depending on the setting, risk of selection bias (e.g., low income population) · No information about actual intake of drugs · No information about use of OTC or herbal drugs or not reimbursed drugs · Lack of important covariates · Other prescriptions are not captured

Abbreviations: BDS = Slone Epidemiology center's Birth Defect Study; NAMCS = Centers for Disease Control and Prevention's National Ambulatory Medical Care Survey; NHAMCS = National Hospital Medical Care Survey; GPRD = The General Research Practice Database; IADB = InterAction Database.

Table 4: Overview of study designs in analytic pharmacoepidemiology of relevance in pregnancy-related research[169]

Study design Main characteristics	Pregnancy study example(s)	Most common advantages of the study design	Most common disadvantages of the study design
CASE-CONTROL			
· Defines cases and controls with and without a specific outcome · Retrospective exposure assessment · Controls must be drawn from the same source population as the cases	The BDS Study[145] The Hungarian Case-Control Surveillance of Congenital Abnormalities[170]	· Can explore uncommon outcomes · Statistical power can be increased by having more than one control per case · Matching possibility · Can study multiple exposures · Logistically easier and faster	· Potential for recall bias · Potential for biased exposure · Selective participation of controls based on exposure
COHORT STUDIES			
Prospective cohort			
· Defines a cohort and record exposure · Prospective follow-up of endpoint(s)	The Generation R Study[171] The Danish National Birth Cohort Study[172]	· Exposure is assessed before onset of the outcome · Can study several exposures and several outcomes · Exposure and covariates can be measured over-time · Incidence data available · Possibility to calculate the attributable or excess risk, more relevant in absolute terms	· Not suitable for rare outcomes · Expensive · It can take years to complete · Lost to follow-up
Retrospective (historical) cohort			
· Defines a cohort and collect exposure and endpoint(s) from available records · Groups of subjects are identified from previously-documented exposure data	Records from the Coombe Women and Infants University Hospital in Ireland (H1N1 vaccination in pregnancy)[173]	· More economical than a prospective cohort · Exposure and endpoint(s) are retrieved more quickly · Can study several exposures and several outcome · Possibility to calculate the attributable or excess risk, more relevant in absolute terms	· Initial purpose of data collection was not for research · Lack of important confounders
Nested case-control study			
· It is a case-control in a cohort study, i.e., the cohort represents the source population that gave rise to the cases	The nationwide Medicaid Analytic eXtract [174]	· More efficient design than prospective cohort studies · Exposure and endpoint(s) are retrieved more quickly	· No follow-up of subjects

Abbreviations: BDS = Slone Epidemiology center's Birth Defect Study.

1.6.3 Critical appraisal of observed associations in pregnancy studies

- Addressing causation in pregnancy studies: the importance of the temporality and plausibility criteria

Analytic observational pharmacoepidemiology provides information about measures of associations and generally, association does not imply causation. In the latest years though, there has been a growing interest and discussion in the field of epidemiology research about the need of a conceptual model of causation.[175] Already in the mid 60's Dr. Austin Bradford Hill proposed a set of viewpoints that could be of use in addressing causation in epidemiology.[176] However, the Hills' viewpoints are not a "hard-and-fast rule" to judge causation.[175] The Hills' viewpoints underwent various interpretations and applications in various fields, including teratology. Drs. Shepard and Brent in fact adapted some of the Hills's viewpoints as criteria of proof of teratogenicity. The list of Hill's viewpoints and their translation into the Shepard's criteria of proof of teratogenicity are outlined in Figure 1.

Figure 1: Hill´s viewpoints and Shepard´s criteria of proof of teratogenicity

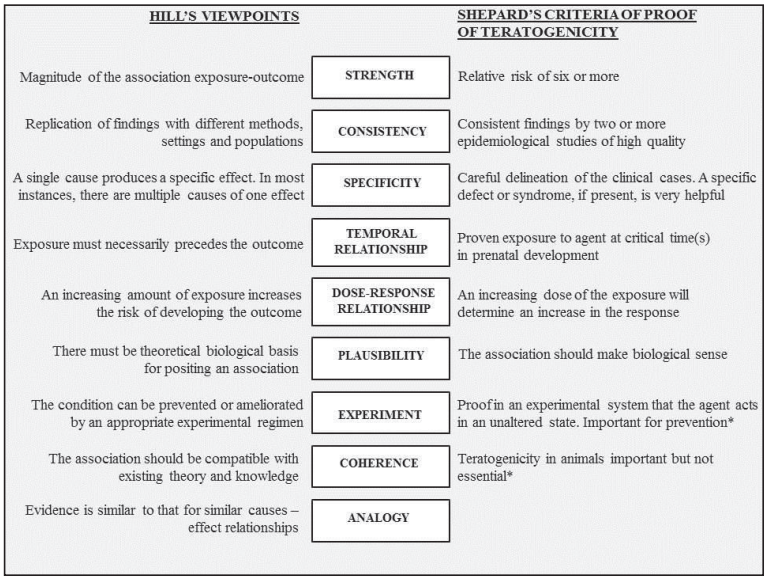


Figure adapted from Hill, Shepard and Scialli.[176-178]
*The author of this thesis performed adaptation of the Experiment and Coherence viewpoints.

Several considerations should then be addressed in the appraisal of study results presenting associations between medication exposures in pregnancy and pregnancy outcomes (concerning the health of either mother or child or both). Temporality is the only necessary and sufficient criterion for determining whether an observed association is causal.[175] Indeed, exposure should occur at critical time of fetus (for studies investigating the risk of congenital malformations and other perinatal outcomes), or pregnancy development (for studies investigating maternal obstetric outcomes). Figure 2 outlines the timing of fetal development and the critical windows of vulnerability to medication exposure for determined perinatal outcomes.

Figure 2: Fetal development and time windows of susceptibility to medication exposure

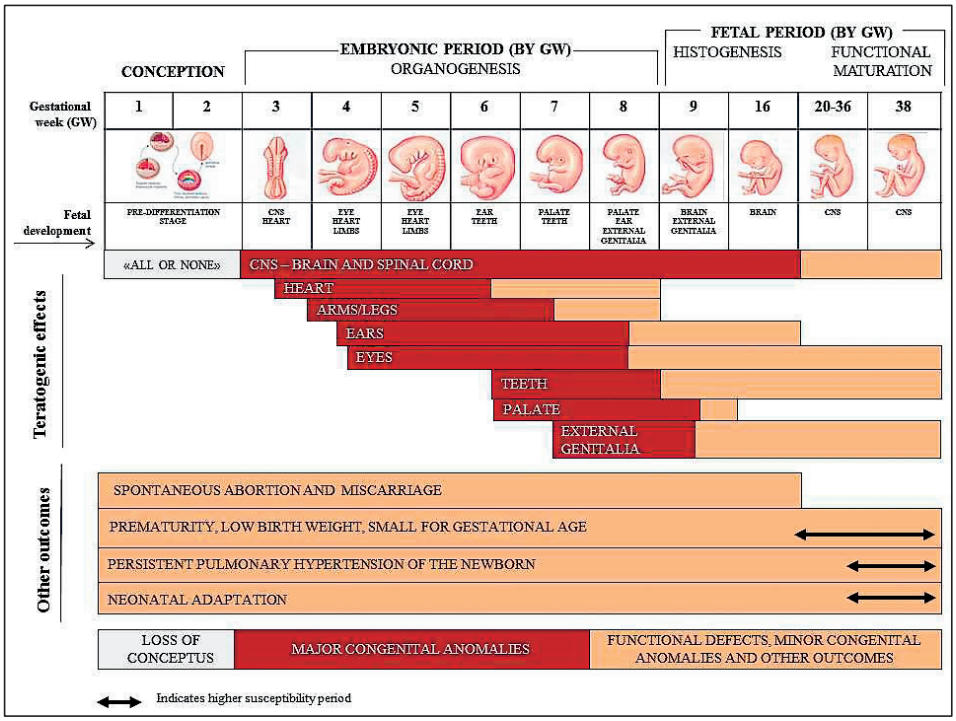


Figure adapted from Moore, 2013.[179]

Biological plausibility is another important factor to address in causal inference. In the field of teratology though, the underlying mechanisms of teratogenicity are often completely unknown, which makes adoption of this criterion difficult. However, this criterion can be of higher relevance when assessing causal relationship between medication exposures in pregnancy and maternal obstetric outcomes. For instance, when assessing the

relationship between use of SSRIs in pregnancy and postpartum hemorrhage, it is crucial to ensure that the exposure occurred during plausible time windows in order for the medication to exert its pharmacological properties and evoke bleeding complications. Specifically, it is known that the antiplatelet effect of SSRIs is completely over two weeks after its withdrawal (including the drug's elimination half-life plus platelet half-life).[144] Hence, evaluation of exposure windows in relation to postpartum hemorrhage outside this specific time window would not have any biological plausibility.

The dose-response relationship, comprising the concepts of dose, duration and cumulative dose of exposure, is indeed another important criterion to account for. Roca *et al*.,[180] for instance, evaluated the effects of prenatal exposure to SSRIs on obstetrical and neonatal outcomes and found that upon stratification on SSRI dose, women treated with a high dose were those mainly more likely to have premature babies. Wisner *et al*.[181] explored the concept of duration of exposure and found that infants exposed to SSRIs continuously during pregnancy were more likely to be born preterm than infants with partial or no exposure. However, in this latter study analogue findings were observed for infants continuously exposed to maternal not medicated depression. Similarly, Oberlander *et al*.[182] examined in a population-based setting whether late gestational exposure to SSRIs was associated with an increased risk of perinatal outcomes compared to early exposure. This study found that length of gestational exposure to SSRIs, rather than timing, conferred an increased risk for outcomes such as neonatal respiratory distress, lower birth weight and reduced gestational age, even after accounting for maternal illness and medication dose.[182]

Since pregnancy research is mainly based on observational studies, replication of study findings (i.e., the Consistency criterion) is of relevance when attempting to infer causality. In this context, it is worth mentioning the value of meta-analyses in pregnancy research. This study type can be used to examine the reasons/sources of discrepancy among study findings, combine small comparable studies and provide pooled effect measures.[183] Although meta-analyses can provide pooled association measures and potentially detect safety signals earlier, it is important to critically appraise the clinical and methodological quality and homogeneity of the included studies.

1.6.4 Proof of exposure in pregnancy

Proof of exposure in pregnancy is fundamental in pharmacoepidemiological studies. In the latest years most studies assessing the safety of antidepressants in pregnancy stem from automated databases where information about exposure derives from insurance claims or filled prescriptions, thus questioning whether these medications were actually taken. Several studies have recently been carried out with the aim to validate information about medication exposure in pregnancy in automated databases. Skurtveit *et al.*[184] examined the impact of exposure misclassification on risk associations when using the Norwegian Prescription Database as the source for SSRI exposure in pregnancy. The validity of the Norwegian Prescription Database data was estimated using self-reported use in the MoBa study as the reference standard. It was found that expanding the exposure time window regarding the filling of a prescription to periods before pregnancy could lead to lower specificity and underestimation of risk associations. Results from another validation study indicated that there is a high concordance between self-report and prescription data for long-term/chronic medication groups used in pregnancy; contrarily, the concordance is poor for those medications used intermittently or in short courses.[185] In a validation study embedded in Eurocat Northern Netherlands, Van Gelder *et al.*[186] compared pregnancy exposure to medication from a self-administered questionnaire completed by mothers of children with major birth defects, with pharmacy prescription data that have been previously checked against maternal interview. The observed sensitivity for any prescription medication was 0.57, whereas specificity was high (0.93-1.00). According to this study, the validity of the self-administered questionnaire for prescription medication use during pregnancy was moderate to poor. Hence, combination of information about exposure from two or more sources, e.g. self-reported data, electronic medical records, and prescription or claims records, along with data about maternal adherence to such medication during pregnancy, would probably represent a better option in the ascertainment of medication exposure during pregnancy. Yet, the golden standard of proof of exposure to medications during pregnancy would obviously be represented by the plasma concentration of medications during gestation.[187]

1.6.5 Extrapolation of relative measures into absolute terms

Most studies exploring associations between a determined medication exposure in pregnancy and a perinatal/obstetric outcomes present relative measures of association, and

only a few extrapolate these relative measures into absolute terms. This often represents an important drawback for many studies, which fail to address the impact of their findings in terms of absolute risk, number needed to harm, or population attributable risk. In the field of teratology, for instance, the absolute impact of a relative measure (OR) of 2.5 for the association between exposure to antidepressants during late gestation and risk of persistent pulmonary hypertension in the newborn would imply one additional case for every 286-351 women treated with an SSRI in late gestation.[136] Similarly, in the assessment of the association between SSRI use near delivery and postpartum hemorrhage, Palmsten *et al*. described an adjusted excess risk of 1.26% (95% CI: 0.90% to 1.62%), with a number needed to harm of 80. Such information is crucial in the assessment of medication safety in pregnancy, and it provides clinically relevant guidance to healthcare professionals when evaluating the benefit-risk ratio of medication exposure in pregnancy and providing evidence-based teratogenic counseling to expectant women.

2. Objectives

The overall objective of this work was to increase knowledge about the extent of use, adherence and safety of medication during pregnancy, with special focus on psychotropics, through a series of studies that addressed the following specific objectives:

Study I:

- To explore from a multinational perspective patterns of medication use in pregnancy according to type of medication and self-reported indications for use, with particular focus on psychotropics
- To identify maternal background factors associated with medication use for acute/short-term illnesses, medication use for chronic/long-term disorders and OTC medication use during pregnancy, and also with chronic use of psychotropics for treatment of depression and anxiety

Study II:

- To investigate patterns of use of psychotropics and other relevant medication groups (i.e., analgesic and gastrointestinal medications) before, during, and after pregnancy among women with eating disorders
- To explore the relationship between eating disorders and use of these specific medications during pregnancy and the postpartum, including whether there was a direct association between eating disorders and medication use or whether the association was indirect

Study III:

- To estimate the level of adherence to psychotropic medication during pregnancy for treatment of depression, anxiety and other psychiatric disorders
- To explore whether maternal socio-demographics, maternal depressive symptoms, women's beliefs and antidepressant risk perception, were associated with medication adherence during pregnancy

Study IV:

- To examine whether women exposed to antidepressants during gestation were more likely than non-exposed to experience vaginal bleeding in early and midpregnancy, and postpartum hemorrhage

3. Materials and Methods

The Multinational Medication Use in Pregnancy Study provided the data for studies I and III, whereas studies II and IV were based on the MoBa study and the Medical Birth Registry of Norway (MBRN). Figures 3 and 4 provide a short methodological overview of the studies included in this work according to the main study source.

Figure 3: Methodological summary of studies I and III

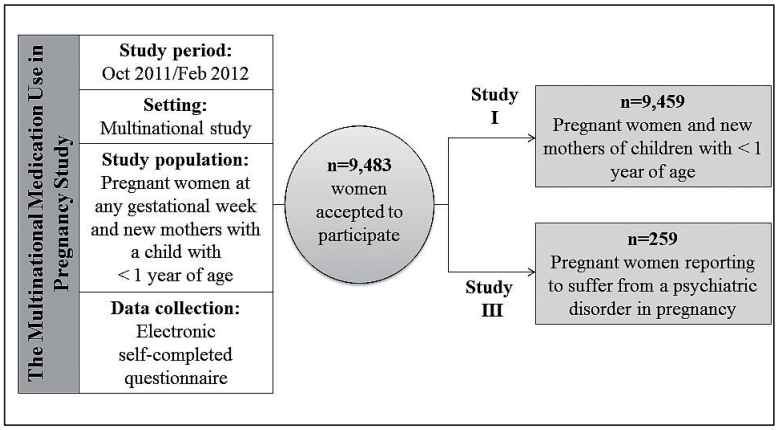
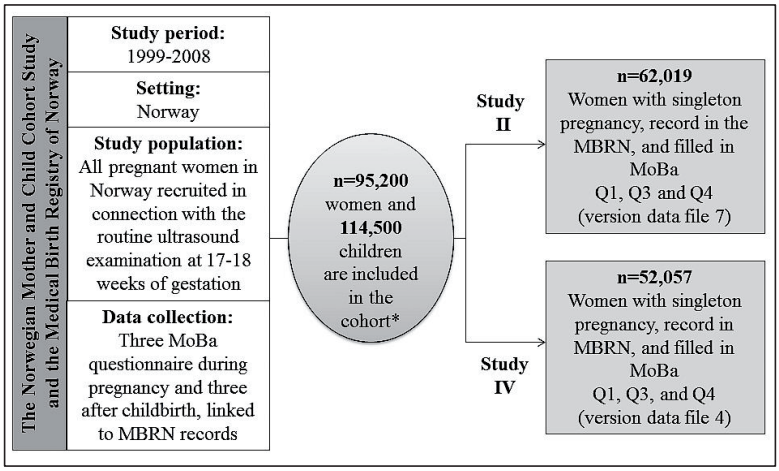


Figure 4: Methodological summary of studies II and IV



Abbreviations: The Norwegian Mother and Child Cohort Study = MoBa; Medical Birth Registry of Norway = MBRN; Questionnaire 1 = Q1; Questionnaire 3 = Q3; Questionnaire 4 = Q4. *Estimates according to the latest files released for research including women who delivered between 1999 and 2009.

3.1 Study design and data collection

3.1.1 The Multinational Medication Use in Pregnancy Study

The Multinational Medication Use in Pregnancy Study is a cross-sectional, multinational, web-based study carried out within the period 1-Oct-2011 to 29-Feb-2012. Pregnant women at any gestational week and mothers of children less than one year of age were eligible to participate. Member countries of the ENTIS, OTIS in North America, MotherSafe in Australia and European institutions conducting public health research were invited to take part in the project. Of these, centers from 18 countries participated (Australia, Austria, Canada, Croatia, Finland, France, Iceland, Italy, Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, United Kingdom and USA). Via OTIS we also collected data originating from some South and Central American countries. The study was conducted in accordance to the CHERRIES statement.[188]

An electronic anonymous questionnaire administered by Quest Back (http://www.questback.com) was utilized to collect relevant data. The questionnaire was available and accessible on-line for a period of two months in each participating country within the main study period stated above. The study was an open survey; the questionnaire was open to the public via utilization of banners (invitations to participate in the study) on 2-3 national websites and/or social networks and/or pregnancy forums commonly visited and consulted by pregnant women and/or new mothers. The questionnaire was carefully designed to suit the internet administration approach. To improve the questionnaire completion rate we applied specific technical features such as multiple page design, routing of questions and progress indicator of completion. National websites were selected by the study coordinators in the country according to the number of daily users. Detailed information about recruitment tools utilized and internet penetration rates in each participating country is summarized in the Appendix 2 of paper I.

The questionnaire was first developed in Norwegian and English and then translated into the other relevant languages. The study coordinator in each participating country ensured quality, comprehension, and adaptation of the translated questionnaire to the relevant national context; for instance, the question about use of OTC medications during pregnancy was aided with examples of brand names of OTC drugs marketed in the specific

country. Information about translated versions of the psychometric instruments used in the questionnaire is provided in section 3.5.

A pilot study was carried out in September 2011 in four countries (Finland, Italy, Norway and Sweden) (n=47) to ensure comprehension of the questionnaire, its suitability to the national context, and functionality of the electronic questionnaires. The pilot study elicited no major change to the questionnaire. Data from the pilot were not included in the study dataset.

Collected data were scrutinized for the presence of potential duplicates (based on reported country of residency, socio-demographic characteristics, date and exact time of questionnaire completion) but none were identified. Since the study was anonymous, no information about IP addresses was collected. The complete questionnaire is presented in Appendix 1 of paper I.

Studies I and III are based on the unique original version of the Multinational Medication Use in Pregnancy Study dataset.

3.1.2 The Norwegian Mother and Child Cohort Study

MoBa is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[189] The aim of the MoBa is to identify causes of serious diseases in mothers and children. The cohort is dynamic and comprises more than 100,000 pregnancies from all over Norway recruited from 1999 to 2008.[190] The recruitment began in Western Norway in 1999 and by the end of January 2006, a total of 50 out of 52 hospital and maternity units in Norway with more than 100 births annually, participated in the study. The women consented to participation in 40.6% of all pregnancies.[189] The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. Participants were recruited through a postal invitation in connection with a routine ultrasound examination offered to all pregnant women in Norway at 17-18 weeks of gestation. The invitation included an informed consent form, the first of six self–administered questionnaires and an information brochure. There were no exclusion criteria.

The study is based on self-administered questionnaires. Participants completed three questionnaires during pregnancy: The first questionnaire (Q1) was completed around gestational weeks 13 to 17 (covering the period between six months prior to pregnancy and

gestational week 18); the second questionnaire (Q2) was completed at gestational week 22 and covered information about dietary habits in pregnancy; the third questionnaire (Q3) (covering the second and part of the third trimester of pregnancy [until gestational week 29+]) was completed at gestational week 30. The fourth questionnaire (Q4) was distributed when the infant was six months old and comprised information on the last period of pregnancy (from the 30th gestational week until childbirth). Q1, Q3 and Q4 collected a wide range of information on socio-demographic characteristics, outcomes of previous pregnancies, medical history, maternal health, lifestyle habits, and medication exposures as well as other exposures during pregnancy.[189] The questionnaires Q1, Q3 and Q4 are outlined in Appendix 1. The study participants also received, and are still receiving, additional questionnaires at 18 months, three years, five years, seven years, and by 2012, eight years postpartum. Among those who agreed to participate in the MoBa, the response rate was 95% for Q1, 92% for Q3, and 87% for Q4.[189] Biological specimens have also been collected from both parents during pregnancy and postpartum and from the offspring.[190,191]

Updated versions of the original MoBa dataset are released for research purposes each year. Study II is based on version 7 of the quality-assured data file including women who delivered between 1999 and 2009. Study IV is based on version 4 including women who delivered between 1999 and 2006.

3.1.3 The Medical Birth Registry of Norway

The MBRN was established in 1967 and encompasses all births in Norway. The registry is based on compulsory notification of all live births, stillbirths and induced abortions after gestational week 12 (after week 16 up to 2002).[192,193] Information on maternal health prior to and during pregnancy, the course of pregnancy and pregnancy complications, delivery and postpartum complications and interventions, and the health of the neonate is available from standardized forms, as outlined in Appendix 2. These forms were filled in by midwives and obstetricians and/or gynecologists at each delivery and also include antepartum obstetric records that are completed by general practitioners, gynecologists, or midwives throughout the pregnancy. Medical conditions within the mother and/or child are coded according to the International Classification of Disease (ICD) and related health problems and using unique codes created by the MBRN.[194]

3.2 Study population

The selection of the study population in studies I-IV reflected the individual research questions investigated. Studies I and III were based on the Multinational Medication Use in Pregnancy Study dataset and included responses from women residing in one of the 18 eligible countries (cf. section 3.1.1 above) and from South American countries (the various countries in South America were aggregated into one region) (the South American region was only included in study I). Responders from Central American countries were excluded (isolated responses). In both studies, participating women were categorized according to the reported country of residency and grouped into six regions: Western Europe, Northern Europe, Eastern Europe, North America, South America and Australia.

As depicted in Figure 3, study I included women who were pregnant (at any gestational week) or mothers of a child younger than one year of age. The final study population comprised 9,459 women.

In study III we only included pregnant women who reported to suffer from a psychiatric disorder, namely depression, anxiety, or other psychiatric disorders (i.e., bipolar, panic or personality disorders), and completed at least six of the eight items (≥75% completion) on the Morisky Medication Adherence Scale (MMAS-8).[195] The final study population comprised 259 pregnant women.

As depicted in Figure 4, studies II and IV were based on the MoBa and MBRN datasets. Data from MoBa was linked to the MBRN via the women's personal identification number, which is assigned to every subject registered in the National Population Register as being a resident of Norway. In both studies we included pregnant women with a singleton pregnancy and a record in the MBRN, and who had completed the MoBa Q1, Q3 and Q4. Completion of Q4 by default implies delivery of a live-born child.

In study II, we excluded women with missing age, implausible weight before and/or during pregnancy, implausible height, those with pregnancies ending in stillbirth, those who returned the survey after birth, those participating in the pilot version of the survey, those women participating in the MoBa with more than one pregnancy, and women who did not answer to the eating disorder items in Q1. The final study population comprised 62,019 women.

In study IV we excluded women reporting use of unspecified medication for depression and those using SSRIs/SNRIs concomitantly with TCAs/other antidepressants (OADs). Women could participate with more than one pregnancy in this study. The final study population included 57,279 women.

3.3 Ethics

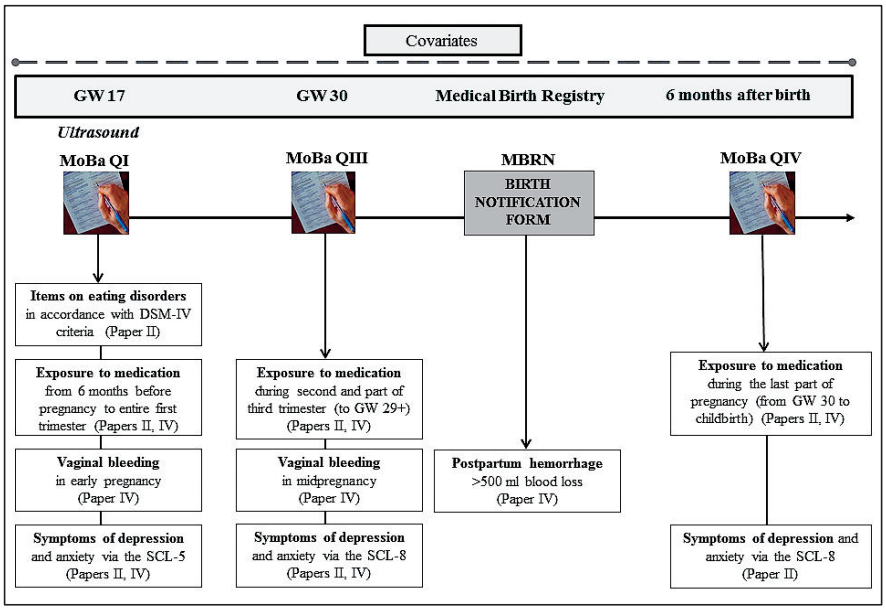
The Multinational Medication Use in Pregnancy Study was approved by the Regional Ethics Committee, Region South-East in Norway. Ethical approval or study notification to the relevant national Ethics Boards was achieved in specific countries as required by national legislation. All participants gave informed consent by answering "Yes" to the question "Are you willing to participate in the study?" All data were handled and stored anonymously.

The MoBa study was approved by The Regional Committee for Ethics in Medical Research, Region South, and the Norwegian Data Inspectorate. Informed written consent was obtained from each participant.

3.4 Measures

In Studies I and III, information about outcome and explanatory variables and covariates originated from the electronic questionnaire within the Multinational Medication Use in Pregnancy Study. In studies II and IV, which are based on the MoBa and MBRN datasets, such information stemmed from the three MoBa questionnaires and the MBRN. An overview of how this information was retrieved in the latter instance is outlined in Figure 5.

Figure 5: Overview of data collection in the MoBa study and MBRN



Abbreviations: GW: gestational week; MBRN: Medical Birth Registry of Norway; SCL-5: Short version of the Hopkins Symptoms Checklist (5 items); SCL-8: Short version of the Hopkins Symptoms checklist (8 items); DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, version IV.

3.4.1 Outcome variables

- Use of medication during pregnancy and postpartum (studies I and II)

The outcome measures "Medication use during pregnancy" (studies I and II) and "postpartum" (study II) were dichotomous (yes/no). In both studies, this information was self-reported by the respondents and was retrieved from the unique electronic questionnaire within the Multinational Medication Use in Pregnancy Study, and the MoBa Q1, Q3 and Q4, respectively.

Respondents were asked to report medication use for numerous chronic, short-term, and pregnancy-related conditions as free entry text, along with the timing of use, as described in detail in studies I and II. In both studies, we measured medication use for any disorder listed in the relevant questionnaire.

A medicine was defined as a single product containing one or more active ingredients. All recorded medications were coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes at the ATC 5th level (i.e. the substance level) whenever possible, otherwise into higher ATC levels, in accordance with the WHO ATC index.[196] Iron, mineral supplements, vitamins, herbal remedies and any type of alternative medicine were recorded separately and excluded from the estimation of medication use. In study I, each national coordinator was responsible for the accuracy of medication coding into their corresponding ATC codes. A different person reviewed all coded data and any disagreement was settled.

In study I, we explored use of any medication during pregnancy as well as medication use by indication, i.e., for treatment of acute/short-term illnesses and chronic/long-term disorders, as well as OTC medication use. Details about the disorders and OTC types included in these groups are presented in detail in study I. For the purpose of this thesis, we additionally explored the outcome variable "use of psychotropic medications during pregnancy", referring to use of any psychotropic medication during pregnancy for treatment of chronic/long-term psychiatric disorders, namely depression and anxiety.

In study II, our outcome measures were use and incident use of psychotropic, gastrointestinal, and analgesic medications during pregnancy and postpartum. Incident use of medication "during pregnancy only" referred to women who started taking the medication in pregnancy and were not using that medication neither before nor after pregnancy. Incident use of medication "postpartum only" referred to women who started taking the medication postpartum and were not using that medication neither before nor during pregnancy. Details about the medication types included in these groups are presented in detail in study II.

- Adherence to psychotropic medication in pregnancy (study III)

This outcome measure was derived from a validated psychometric instrument, the MMAS-8,[195] and used as both a continuous variable and a dichotomous variable (categorized as low versus medium/high adherence) in the analysis. The MMAS-8 has been described in detail in study III. In brief, the MMAS-8 is a structured, self-reported medication adherence measure consisting of seven yes/no items and one 5-point Likert scale. Each item measures specific medication-taking behaviors.[195] The seven yes/no items are

assigned values 0 or 1 (1=higher adherence), whereas the value of the Likert scale item is standardized from 0-4 into 0-1 (this item is divided by 4 when calculating the summated score). The total scale has a range from 0 to 8. Categorization of the adherence level is as follows: low (sum score<6), medium (sum score 6 to <8) and high (sum score=8). The predictive validity of the MMAS-8 has been examined through associations with blood pressure control among patients treated with antihypertensive drugs, where correct classification for high/medium adherence was 80.3%.[195]

- Bleeding complications during pregnancy and postpartum (study IV)

Our outcome variables were: Vaginal bleeding in early pregnancy (any type of bleeding, bleeding as trace of blood, medium blood loss or clots, multiple bleeding episodes); vaginal bleeding in midpregnancy (any type of bleeding, bleeding as trace of blood, medium or large blood loss, multiple bleeding episodes); postpartum hemorrhage (> 500 ml blood loss at delivery). The outcome variables concerning maternal vaginal bleeding during pregnancy were self-reported by the responders and retrieved from the MoBa Q1 and Q3. They were all used as dichotomous variables (yes/no). In both Q1 and Q3, women could report details about two bleeding episodes: the first and last episode in Q1, and the second last and last episode in Q3. Information about type of bleeding and duration (in days) could be reported for each individual episode. If such episodes differed in typology (trace versus large/medium amount of blood loss), we based our analysis on woman's most severe bleeding experience. The outcome "bleeding in early pregnancy" was defined as any occurrence of vaginal bleeding during the first trimester of pregnancy. "Bleeding in midpregnancy" was defined as any occurrence of vaginal bleeding during the second trimester of pregnancy. Bleeding type in early and midpregnancy was subdivided into trace of blood or spotting, moderate/large amount of blood loss or clots, or multiple episodes irrespective of amount of blood loss. The outcome "postpartum hemorrhage" was available from MBRN records and is medically confirmed information. The MBRN does not classify postpartum hemorrhage according to mode of delivery, i.e. as an estimated blood loss >500 ml after vaginal birth or >1,000 ml after cesarean delivery. Postpartum hemorrhage was defined as blood loss >500 ml regardless of delivery mode.

3.4.2 Explanatory variables

- Maternal sociodemographics and life-style factors (studies I and III)

In studies I and III, these explanatory variables were all self-reported by the respondents and comprised: maternal age in years (≤20; 21-30; 31-40; ≥41 or 20; 21-30; ≥31), educational level (less than high school; high school; more than high school; others/unspecified), first language different from the official main language in the country of residency (yes; no), working status at time of conception (employed, but not as healthcare provider; healthcare provider; student; housewife; job seeker; others), previous children (yes; no), marital status (married/cohabiting; single/divorced/others), unplanned pregnancy (yes; no), smoking status during pregnancy (no; yes, but less than before pregnancy; yes, the same or more than before pregnancy or yes; no), alcohol consumption after awareness of pregnancy (yes; no). Study I additionally comprised region of residency (Western Europe; Northern Europe; Eastern Europe; North America; South America; Australia) as explanatory variable, whereas gestational age (continuous variable ranging from 1 to 42), folic acid use before and/or during pregnancy (yes; no), and number of psychotropics (=1; >1) were so in study III.

- Maternal psychiatric disorders and mental health (studies II, III)

Eating disorder (i.e., AN, BN, EDNOS-P or BED) before and/or during pregnancy was the main explanatory variable in study II and was retrieved from items in MoBa Q1. These items on eating disorder symptoms and behaviors were designed in accordance with the criteria for eating disorders in the DSM–IV.[50] These criteria have previously been used for studies on eating disorders in the MoBa sample[53,109] and in the Norwegian Institute of Public Health Twin Panel.[197] Diagnostic algorithms and hierarchies were constructed to define the presence of eating disorders in the six months prior to pregnancy (retrospective assessment) and during pregnancy. Detailed information about definition and hierarchy classification of the eating disorder subtypes is described in study II.

In study III, underlying maternal mental health during pregnancy was measured via The Edinburgh Postnatal Depression Scale (EPDS). The EPDS is a screening self-rating questionnaire for symptoms of depression during pregnancy and postpartum, comprising 10 items. The scale is validated for major and minor depression in clinical settings and with satisfactorily Cronbach's alpha reliability (0.87).[198] Each question was scored 0-3, producing a total score of 0-30. The cut-off for probable depression was set to 13.[198] This variable was used as dichotomous (yes; no) in the multivariate analysis of study III.

- Risk perception and beliefs about medication (study III)

The perceived risk of antidepressant exposure during pregnancy was measured via a numeric scale ranging from 0 ('not harmful to the fetus') to 10 ('very harmful to the fetus'). Women could also select the option "unknown substance", if applicable. This variable was initially utilized as continuous, but it was then categorized in three groups (risk 0-3; 4-5; ≥6) because of non-linearity in the logit link function.

Women's beliefs about medicines were explored via the Beliefs About Prescribed Medicines Questionnaire (BMQ-specific), which comprises two subscales: the BMQ-Necessity (5 items) and BMQ-Concerns (5 items).[120,199] Respondents indicated their degree of agreement with each statement on a 5-point Likert scale (1=strongly disagree, 2=disagree, 3=uncertain, 4=agree, 5=strongly agree). Individual item scores were added, giving a total score of 5-25. Higher scores indicate stronger beliefs in the concepts represented by the subscale. The belief variables were used as continuous in the analysis. The Necessity-Concerns differential was also calculated. The Necessity-Concerns differential is the difference between the BMQ-Necessity and BMQ-Concerns scores (positive scores indicate that the patient perception of the benefits of medication outweigh the risks whereas a negative score indicates the converse).

Three statements were additionally used to explore women's beliefs about medication use during pregnancy: i) "I have a higher threshold for using medicines when I am pregnant than when I am not pregnant"; ii) "Even though I am ill and could have taken medicines, it is better for the fetus that I refrain from using them"; iii) "Pregnant women should preferably use herbal remedies than conventional medicines". Respondents could indicate their degree of agreement with each statement on a 5-point Likert scale (0=strongly

disagree, 1=disagree, 2=uncertain, 3=agree, 4=strongly agree). The belief variables were used as continuous (score range 0-4) in the analysis.

- Antidepressant exposure (study IV)

Information about type and timing (by trimester) of antidepressant exposure in pregnancy was retrieved from MoBa Q1, Q3 and Q4. We explored exposure to antidepressant in first trimester, second trimester, and last part of the pregnancy (from gestational week 30 to childbirth), according to the outcome investigated. Antidepressants were subdivided into two main groups: 1) SSRIs (ATC code N06AB) and SNRIs (ATC codes N06AX16 and N06AX21); 2) TCAs (ATC code N06AA) and other antidepressants (OADs) (ATC codes N06AX03, N06AX06, N06AX11, N06AX12 and N06AX18). SSRIs and SNRIs were grouped together since both drug groups significantly inhibit serotonin reuptake.[144] Even though clomipramine, belonging to the TCA group, is known to have high affinity to serotonin transporters, its active metabolite desmethylclomipramine is not particularly serotonin-selective, and it was therefore kept under the TCA group. TCAs and OADs were grouped together in order to increase power secondary to the low number of women reporting use of these drug groups. A disease comparison group, defined as no exposure to antidepressants but presence of depressive symptoms at both gestational week 17 and 30, was also created.

In each questionnaire several indications for antidepressant drug treatment were specifically named: unusual tiredness/sleepiness, sleeping problems, anorexia/bulimia/other eating disorders, depression, anxiety and other long-term illnesses or mental health problems. For each indication, women could specify use of several medicinal products and the corresponding periods of exposure. Details about the available exposure windows in the MoBa questionnaire and its classification are provided in study IV.

3.4.3 Other variables

In studies I and III, we sought to build predictor models of factors associated with the specific outcomes; hence, all variables analyzed in these two studies have been dealt with in the section 3.4.2 above 'Explanatory variables'. This section only applies to studies II and IV.

- Socio-demographic, life-style and health characteristics

Information about maternal age stemmed from the MBRN and was used as both continuous (study II) and categorical variable (<20; 20-29; 30-39; ≥40 years) (study IV). Additional covariates originating from the MBRN were used in study IV and were: parity (previous pregnancies after gestational week 12; no previous pregnancies after gestational week 12), placenta previa (yes; no), placental abruption (yes; no), coagulation defects before and/or during pregnancy (yes; no), instrumental delivery (i.e., use of vacuum or forceps) (yes; no), and type of delivery (vaginal; cesarean section).

The following covariates stemmed from the MoBa Q1, Q3 and Q4 and were: body mass index (BMI) at conception, used as both continuous (study II) and categorical variable (<18.5; 18.5-24.9; 25.0-29.9; ≥30)(study IV), weight gain during pregnancy and weight decrease six months after delivery (both as continuous variable)(study IV), educational level (primary; secondary; tertiary short; tertiary long or primary/secondary; university/higher degree) (studies II and IV), socioeconomic status as household minimum yearly income (0-499,999 NOK; 500,000-999,999 NOK; >1 million NOK; unknown)(study II), comedication during pregnancy with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or antithrombotic agents (yes; no)(study IV), smoking status during pregnancy (yes; no) (studies II and IV), history of abortions/miscarriages (yes; no)(study IV), marital status (married or cohabiting; others) (studies II and IV), and breastfeeding status in the 0-6 months period after childbirth (yes; no) (study II).

- Maternal mental health

The severity of maternal underlying depressive and anxiety symptoms during pregnancy and postpartum was measured via the short versions of The Hopkins Symptom Checklist-25 (SCL-25) that is, the Symptom Checklist-5 (SCL- 5) in Q1, and the Symptom Checklist-8 (SCL-8) in Q3 and Q4.[200,201] The scale is considered a reliable screening instrument for depression and anxiety as defined by the ICD-10.[202] Both SCL-5 and SCL-8 are highly correlated to the SCL-25.[201,203] For each item of the scales, a score from 1 to 4 can be assigned. For all three instruments, the mean score was separately computed.

When used as covariates, these variables were all used as continuous in studies II and IV. In study II, we summed the mean scores for the SCL-5 in Q1 and the SCL-8 in Q3 in order to measure symptoms of depression and anxiety throughout the pregnancy. In study IV, we

additionally utilized a cutoff score greater than 2.0 in the SCL-5 in Q1 and greater than 1.85 in the SCL-8 in Q3 to define the disease comparison group, i.e. women with depressive and anxiety symptoms throughout the pregnancy but not exposed to antidepressants.[200]

3.5 Use and translation of psychometric instruments

In the Multinational Medication Use in Pregnancy Study we used translated versions of the following psychometric instruments: the MMAS-8, the EPDS, and the BMQ-Specific. Copyright agreements were signed with Prof. DE. Morisky and Prof. R. Horne in order to utilize the MMAS-8 and BMQ-Specific, respectively. Use of the EPDS for research purposes could be done without seeking permissions from Prof. J. Cox.[204] Information about validation properties and translation process has been described in study III.

3.6 Statistical analysis

The statistical analyses were performed using the Statistical Package for Social Sciences SPSS (IBM® SPSS® Statistics) version 20.0 (studies I, III, IV) and 22.0 (study II).

Descriptive analyses were performed in all studies. The Pearson chi-square or Fisher exact tests, and the Student's t-test or one-way analysis of variance (ANOVA) were utilized to compare proportions and mean scores between independent groups, respectively. In all analyses, missing values were less than 5% of the total. In studies I, III and IV, a two-tailed p-value of < 0.05 was considered statistically significant. Because of the numerous analyses conducted in study II, we undertook a conservative approach and considered two-tailed p-values of ≤ 0.01statistically significant.

3.6.1 Associations between explanatory and outcome variables

- Logistic regression

Logistic regression analyses were utilized to determine any association between the explanatory and outcome variables (studies I, IV). In study I, we first fit the univariate logistic regression model for all explanatory variables. The multivariate model was then built and adjusted for all remaining covariates.

In study IV, we first fit the univariate logistic regression model for the exposure and candidate confounding variables. Candidate variables were selected based on a univariate p-value of <0.15 and added into the multivariate model. Variables having no role (p-value >0.05) or yielding a change smaller than 15% in the beta coefficients of the retained variables were removed.

In both studies, the main effect model was checked for the presence of clinically relevant interactions. The final multivariate model included statistically significant independent variables and clinically significant variables. Goodness of fit of the final multivariate model was assessed by using the Hosmer and Lemeshow test.[205]

- Generalized Estimating Equation

Generalized Estimating Equation (GEE) with a Poisson distribution was utilized in study II. A Poisson regression provides direct estimates of relative risks and was therefore considered the preferable choice compared to logistic regression. However, a Poisson regression applied to binary data (without adjustments) provides conservative results by overestimating the standard error for the risk estimates. To remove this bias, a robust variance estimator was used. We carried out two sets of analyses: in Model 1, we computed the total association between eating disorders and the outcomes of interest by adjusting for the the minimal sufficient set of variables; these variables were identified via utilization of Directed Acyclic Graphs (DAGs) using DAGitty version 2.2 (one DAG for each medication-outcome pair).[206] In Model 2 we entered the set of confounders from Model 1 plus additional covariates (as directed by the DAGs) in order to estimate the direct association between eating disorders and the outcomes of interest.

In study III, a GEE analysis with a binomial distribution was performed to take into account clustering on region of residency. The multivariate GEE model was built as follows: candidate variables were selected based on a univariate p-value<0.15; variables having no role (p-value>0.05) or yielding a change smaller than 15% in the beta coefficients of the retained variables were removed; continuous variables were checked for linearity in the logit link. Because of non-linearity, the variable antidepressant risk perception was categorized according to the non-linearity midpoints (risk 0-3; 4-5; ≥6). The final multivariate model included statistically significant independent variables and potential confounders.

- Directed Acyclic Graphs

DAGs were employed in study II with the aid of DAGitty version 2.2[206] in order to identify potential confounding and mediating factors of the association between eating disorder subtypes before and/or during pregnancy and medication use during pregnancy or postpartum.

DAGs graphically encode relationships between variables, and they enable us: 1) to identify whether there is confounding; 2) to identify which variables need to be controlled for; 3) identify which variables should not be controlled for. Employing DAGs require to clearly setting down assumptions about causal relationship and direction of the association between variables.[175,207] A description of our assumptions about the direction of the association between variables is provided in study II. The six individual DAGs utilized in study II are outlined in Appendix 3.

- Correlation analyses

In study III, we used the Spearman's rank correlation coefficient to explore the correlation between the medication adherence sum scores and beliefs about medications.

3.6.2 Sensitivity analysis

In study I, we built multivariate models of factors associated with the outcomes of interest separately for each region. In these instances, region of residency was not included in the model. We also carried out GEE analyses with a binomial distribution taking into account clustering on region of residency, in order to evaluate whether the measure of association between the other explanatory variables and the outcomes of interest differed substantially from those obtained in the logistic regression analyses.

In study II, we included BMI at conception as additional covariate in Model 1 because of the uncertainty in the direction of the association between BMI and eating disorders. In this study we excluded from the sample those pregnancies ending in a stillbirth, and therefore we could not evaluate patterns and factors associated with medication use among these women.

In study III, we explored the role of the explanatory variables, namely smoking during pregnancy, depressive symptoms or risk perception of antidepressant exposure, for which a

clustering effect on individual country of residency could not be ruled out. Hence, we performed sensitivity analyses taking into account clustering on country of residency, even though this led to lower statistical power.

In study IV, we explored whether there was a difference in the mean duration (in days) of vaginal bleeding episodes between the exposed and non-exposed women. Additional analyses on individual antidepressant level were also performed when statistical power allowed doing so. Antidepressants were also regrouped according to the level of affinity to the serotonin transporter. We also explored the association between antidepressant exposure and postpartum hemorrhage among women who delivered vaginally with or without instrumental intervention (i.e. forceps and/or vacuum). Since we included women with multiple participations in the MoBa study, we performed sensitivity analyses restricted to women who participated only one time in the study, leading to the exclusion of 18.5% of the MoBa population. We additionally carried out sensitivity analyses including only the first pregnancy of those women participating more than once in the MoBa study, leading to the exclusion of 9.3% of the MoBa population. We also carried out GEE analyses taking into account such dependency within the data, with the maternal id being the repeated measure.

3.6.3 Power calculation

Information about sample size calculation (using 5% precision with 95% confidence interval) for the prevalence of medication use in pregnancy on country and region level has been described in Appendix 4 of study I. Sample size calculations were performed in Epi Info TM 7.[208]

In study II, no power calculation was carried out due to the lack of previous studies about medication use in pregnancy among women with eating disorders.

In study III, the overall prevalence of low adherence to psychotropics could be calculated with a precision of ±8%. No power calculation about the minimal detectable magnitude of the association between the various maternal factors and low medication adherence was performed due to lack of previous similar studies. Sample size calculations were performed in Epi Info TM 7.[208]

In study IV, post hoc sample power analysis for the exposure group SSRIs/SNRIs revealed that we could detect a 25% and 50% increase in the odds of vaginal bleeding in early

pregnancy and midpregnancy, respectively, with an 80% power. With respect to the outcome of postpartum hemorrhage, we had power to detect a 60% increase in the odds. The sample size calculator developed by Dr. Stigum was utilized.[209]

3.6.4 Imputation

In studies II, III and IV we imputed missing values on scale variables, namely the SCL-5, SCL-8, MMAS-8, and BMQ-Specific, using the estimation-maximization algorithm.[210] Information about the percentage of imputed values and the criteria applied for each imputation is provided in each individual study.

4. Main findings

4.1 Study I: Medication use in pregnancy: a cross-sectional, multinational web-based study

Of the 9,459 women in the study, 7,678 (81.2%) reported use of at least one medication, either prescribed or OTC, during the course of the pregnancy. The prevalence estimates of any medication use ranged from 75.7% in Eastern Europe to 86.2% in Australia. There were inter-region variations in the estimates of the self-reported disorders and related medication use, for all medication sub-types explored.

Medications for the nervous system (ATC class N) were the most commonly used during pregnancy (57.5%), mostly due to paracetamol and its combinations, followed by medications for the alimentary tract and metabolism (ATC class A) (45.2%), mostly comprising antacids and laxatives, medications for the respiratory system (ATC class R) (27.6%) and anti-infectives for systemic use (ATC class J) (14.6%). During the first trimester of pregnancy, about 50% of the sample reported to be exposed to at least one medication. The most frequently used medication groups during this time window were analgesics (38%), antacids (22%), nasal preparations (11%), systemic antibiotics (9%), antihistamines (8%), thyroid medication (4%), NSAIDs (4%), drugs for obstructive airway diseases (3%), antidepressants (2%) and anxiolytics/sedatives (2%).

Use of OTC medication during pregnancy was reported by 66.9% of the women, with analgesics (mostly paracetamol), antacids, sympathomimetic nasal decongestants, laxatives and antinauseants being the most common. Maternal factors positively associated with use of OTC medication were: having previous children, education lower than high school, working as a healthcare provider and consumption of alcohol after awareness of pregnancy. Women residing in Northern Europe (1.5-fold magnitude) and Australia (1.6-fold magnitude) were more likely than those in Western Europe to use OTC drugs during pregnancy. Women residing in the remaining regions (Eastern Europe, North America and South America) were less likely than Western Europeans to report use of OTC medication during pregnancy.

Overall, 68.4% of the sample reported use of medications during pregnancy for treatment of acute/short-term illnesses, mainly headache, heartburn, pain, nausea and UTIs. The most commonly used medications for these illnesses were paracetamol, antacids (mainly aluminum, salt combinations, antiflatulents, alginic acid complex/sucralfate/bismuth), first generation antihistamines, metoclopramide and penicillins.

Use of medication for treatment of chronic/long-term disorders during pregnancy was reported by 17.0% of the sample, with hypothyroidism, asthma, allergy and depression being the leading indications for such use. Compared to Western European women, those residing in Northern Europe, North America and Australia were more likely to use chronic medications during pregnancy (1.7-2.8 fold increased likelihood). Older women, those working as housewives, with education lower than high school, or with an unplanned pregnancy, were more likely to use chronic medications in pregnancy. Immigrant women in Western (adjusted OR: 0.55, 95% CI: 0.34-0.87) and Northern Europe (adjusted OR: 0.50, 95% CI: 0.31-0.83) were less likely to report use of medication for chronic/long-term disorders during pregnancy than non-immigrants.

With respect to the psychiatric disorders investigated in this study, namely depression and anxiety, 464 women (4.9%) reported to suffer from either condition during pregnancy, and 281 (3.0%) reported to be medicated. In general, SSRIs were the most common psychotropic medications used for treatment of depression and anxiety, followed by SNRIs and benzodiazepines, as outlined in Appendix 4a. There was a substantial inter-region variability in the extent of self-reported disorders and related psychotropic medication use. The results of the analysis of factors associated with psychotropic medication use during pregnancy for treatment of depression and/or anxiety are outlined in Appendix 4b. The obtained measures of associations did not substantially differ from the main analysis on chronic medication use in general, although stronger measures of association were detected. Specifically, women residing in Northern Europe (2.1-fold magnitude), North America (3.0-fold magnitude) and Australia (4.4-fold magnitude) were more likely than those in Western Europe to use psychotropic medications. Other factors significantly associated with such use were: older maternal age (≥31), being single or divorced, being a student or housewife, having lower education than high school, an unplanned pregnancy, smoking during pregnancy and alcohol consumption after awareness of pregnancy.

4.2 Study II: Medication use before, during, and after pregnancy among women with eating disorders: a study from the Norwegian Mother and Child Cohort Study

This study included 62,019 women. The prevalence of eating disorder subtypes before and/or during pregnancy was: 0.09% for AN (n=54), 0.94% for BN (n=585), 0.10% for EDNOS-P (n=61) and 5.00% for BED (n=3,104). The remaining 93.87% did not have any eating disorder (reference group). Women within the AN, BN, EDNOS-P, and BED groups more frequently had less education and lower socio-economic status than the reference group, and showed significantly higher rates of depressive and anxiety symptoms throughout the pregnancy.

Women with AN or EDNOS-P reported the highest rate of psychotropic medication use prior to pregnancy (AN: 22.2%; EDNOS-P: 9.8%), during (AN: 11.1% in first trimester to 3.7% in third trimester; EDNOS-P: 8.2% in first trimester to 4.9% in third trimester), and after pregnancy (AN: 9.3% at 4-6 months postpartum; EDNOS-P: 8.2% at 4-6 months postpartum). Use of psychotropics decreased during pregnancy across all eating disorders compared to the period before conception. The discontinuation rate of psychotropics from the six months period prior to conception to first trimester was about 50% in women with AN or BED or no eating disorder, and lower among women with BN (about 35%) or EDNOS-P (about 16%). However, at 4-6 months postpartum the AN and EDNOS-P groups were characterized by a significant increase in such use (mainly anxiolytics and sedatives). Antidepressants comprised the medication class most widely used before, during, and after pregnancy. Continuous use of antidepressants before, as well as during and after pregnancy was more common among women with AN (1.9%), BN (1.2%), EDNOS-P (1.6%) or BED (0.5%) than the reference group (0.3%).

After adjusting for the minimum sufficient set of confounders, all eating disorder subtypes were totally significantly associated with use of psychotropics during pregnancy (magnitude of the associations ranging from 1.7-fold for BED to 5.6-fold for AN). Having BN was significantly directly associated with use (1.8-fold magnitude) and incident use of psychotropics during pregnancy (2.3-fold magnitude). In the analysis on specific

psychotropics, BN was found to be directly associated with use of anxiolytics/sedatives during pregnancy (adjusted RR: 2.36; 99% CI: 1.26-4.41), whereas BED (adjusted RR: 1.45; 99% CI: 1.01-2.08) was so in relation to use of antidepressants during this time window, compared to women with no eating disorders. AN and EDNOS-P were directly associated with an increased likelihood of using anxiolytics/sedatives in the postpartum period (adjusted RR: 5.11; 99% CI: 1.53-17.01; adjusted RR: 6.77; 99% CI: 1.41-32.53, respectively).

Women with any eating disorder were characterized by a high use of gastrointestinal drugs during pregnancy (especially in the second and third trimester) and postpartum. Compared to the reference group, all eating disorder subtypes were characterized by a higher rate of laxative use at some point before, during, or after pregnancy. Only the EDNOS-P subtype (1.7-fold magnitude) was significantly directly associated with gastrointestinal drug use during pregnancy (specifically for antacids and laxatives). BN was significantly directly associated (1.6-fold magnitude) with use of gastrointestinal drugs postpartum compared to the reference group.

Even though not always significantly different, use of analgesics was at almost all time points higher among women with AN than the reference counterpart. Women with BED were characterized by a significantly higher use of any type of analgesics before, as well as during and after pregnancy. However, none of the eating disorder subtypes was directly associated with use of analgesics during pregnancy or postpartum.

4.3 Study III: Patterns and factors associated with low adherence to psychotropic medications during pregnancy - a cross-sectional, multinational web-based study

Of the 4,938 eligible pregnant women, 259 (5.2%) reported to suffer from at least one psychiatric disorder and filled in the MMAS-8, and were therefore included in the analysis. This sample included 160 (61.8%) and 99 (38.2%) women who reported use and non-use, respectively, of psychotropic medications during pregnancy. Women who did not use psychotropic medications most strongly believed that the necessity of medications did not

outweigh their concerns and that despite being ill, it was better for the fetus to refrain from taking medications. Compared to non-users, women using psychotropics during pregnancy were more often older, with previous children, with an unplanned pregnancy, or consumed alcohol after awareness of pregnancy. The presence of depressive symptomatology (as measured by the EPDS score ≥13) was comparable between the two groups (49% among psychotropic users vs. 52% among non-users).

Among the women using psychotropics during pregnancy, antidepressants (mainly SSRIs) were the medication group most commonly used and most women (75%) were on monotherapy. According to the MMAS-8, 48.8% of the women (95% CI: 41.1-56.4%) demonstrated low adherence to psychotropics during pregnancy. The rates of low adherence were 51.3% for anxiety, 47.2% for depression and 42.9% for other psychiatric disorders.

In the multivariate analysis, smoking during pregnancy, psychotropic monotherapy, elevated risk perception of antidepressants and depressive symptoms during pregnancy were significantly associated with low adherence. Specifically, women smoking during pregnancy had a 3.9-fold increased odds to show low adherence compared to non-smokers; women on polytherapy presented a 68% reduced odds to be low adherers compared to women on monotherapy; women with depressive symptoms during pregnancy (EPDS ≥ 13) had a 2.5-fold increased odds to demonstrate low adherence compared to absence of depressive symptoms; women with a moderately high (4-5) and elevated risk perception (≥6) of antidepressant exposure during pregnancy presented a significant 1.3- and 2.3-fold increased odds, respectively, to be low adherers.

An individual's belief about medications was significantly correlated with adherence to psychotropics in pregnancy. There was a positive correlation between the perception that the benefit of pharmacotherapy outweighed the risks and increasing level of adherence to psychotropic medication ($r=0.282$; $p<0.001$). There was a negative correlation between agreement with the statement that it is better to use herbal remedies than conventional medication during pregnancy and increasing level of adherence to psychotropic medication and ($r= - 0.243$; $p<0.01$).

4.4 Study IV: Risk of vaginal bleeding and postpartum hemorrhage after use of antidepressants in pregnancy: a study from the Norwegian Mother and Child Cohort Study

Of the 57,279 women included in the study, 587 (1.02%) reported use of antidepressants during pregnancy. The most frequently used antidepressants were SSRIs/SNRIs (0.92%), in particular citalopram (0.31%), sertraline (0.16%) and escitalopram (0.15%). A total of 123 women (0.2%) reported continuous use of any antidepressant at all trimesters. Overall, 5.9% and 6.3% of the sample presented depressive symptoms at week 17 and 30, respectively, whereas 32.5% had lifetime history of depression. Maternal underlying depression in pregnancy was more severe among women in the disease comparison group than the medicated counterparts.

Compared to non-exposed, women using either SSRIs/SNRIs (adjusted OR: 0.91; 95% CI: 0.72-1.16) or TCAs/OADs (adjusted OR: 0.83; 95% CI: 0.36-1.92) during the first trimester did not show any increased risk of vaginal bleeding of any kind during early pregnancy. Compared with non-exposed women, those in the disease comparison group had a significant 1.2-fold increased risk of bleeding of any kind during early pregnancy (adjusted OR: 1.22; 95% CI: 1.06-1.39).

Compared to non-exposed women, those using SSRIs/SNRIs (adjusted OR: 0.81; 95% CI: 0.50-1.31) or TCAs/OADs (adjusted OR: 0.96; 95% CI: 0.26-3.53) during the second trimester did not present any increased risk of vaginal bleeding of any kind during midpregnancy. Compared to non-exposed women, those in the disease comparison group had a significant 1.3-fold increased risk of bleeding of any kind during midpregnancy (adjusted OR: 1.28; 95% CI: 1.07-1.55).

Exposure to SSRIs/SNRIs between gestational week 30 and childbirth did not confer any increased risk for postpartum hemorrhage overall (adjusted OR: 0.97; 95% CI: 0.57-1.65) and upon stratification by mode of delivery, compared to non-exposure. Compared to non-exposed women, exposure to TCAs/OADs between gestational week 30 and childbirth was associated with a 3.75-fold increased risk of postpartum hemorrhage (adjusted OR: 3.75; 95% CI: 1.09-12.94). Due to low statistical power, no stratification by mode of delivery

could be carried out and therefore such association cannot be further examined. Compared to non-exposed, the adjusted OR for women in the disease comparison group was 1.14 (95% CI: 0.97-1.34) for postpartum hemorrhage. Stratification by type of delivery did not confer any change to such a scenario.

4.5 Sensitivity analyses

In study I, the results of the sensitivity analyses taking into account clustering on region of residency showed that the direction and magnitude of the association between the various maternal factors and medication use outcomes (for acute/short-term illnesses; chronic/long-term disorders; OTC) were generally similar to those obtained in the main analyses, except for educational level (which was no longer associated with use of chronic medication or OTC medication during pregnancy), working as a healthcare provider and smoking during pregnancy (which both became significantly associated with medication use for chronic/long-term disorders). The directions and magnitudes of the associations between the explanatory variables and psychotropic medication use for treatment of depression and/or anxiety were overall similar to those observed in the main logistic regression analysis (cf. Appendix 4b). However, in the GEE analysis we found that women working as a healthcare provider (32% magnitude) or seeking for job (66% magnitude) were significantly more likely than the reference group to use psychotropic medications in pregnancy.

In study II we included BMI at conception as additional covariate in Model 1 because of the uncertainty in the direction of the association between BMI prior to conception and eating disorders before and/or during pregnancy. The observed results were principally similar to those observed in the main analyses.

In study III we performed a GEE analysis taking into account clustering on individual country of residency, and not region of residency. The magnitude of the measure of association observed in the GEE analysis adjusted on clustering for country of residency did not differ from those obtained in the GEE adjusted on clustering on region of residency; in the former analysis the 95% CI were wider than those observed in the latter analysis, and the association between antidepressant risk perception and non-adherence lost statistical significance for score category 4-5.

In study IV, the analyses restricted to women with a single participation in the MoBa study (cf. Appendices 5a and 5b) revealed slightly different results than those observed in the main analyses for the disease-comparison group, but not for the two exposure groups. Specifically, women in the disease-comparison group presented a significant 35% increased odds of vaginal bleeding in medium/large amount during midpregnancy, an association which was not reflected in the main analysis. Similarly, these women presented a significant 18% increased odds of postpartum hemorrhage regardless of delivery type, an association which was borderline significant in the main analysis. However, there were no differences in the results in the stratified analyses by mode of delivery.

The results of the analyses including only the first pregnancy for those women participating more than once in the MoBa study were principally similar to those observed in the main analyses for bleeding complications in early and midpregnancy, as well as postpartum (cf. Appendices 6a and 6b).

Similarly, the results of the GEE analyses taking into account the dependency within the data because of multiple participation in the study (with the maternal id being the repeated measure) were also similar to those observed in the main analyses (cf. Appendices 7a and 7b).

The analyses on individual antidepressants for all bleeding outcomes did not reveal different patterns than those observed for the two antidepressant groups (i.e., SSRIs/SNRIs and TCAs/OADs). The analysis of antidepressants regrouped according to their level of affinity to serotonin transporter (high, intermediate or low affinity) did not identify any significant association between antidepressants and bleeding complications during pregnancy and postpartum. With respect to the postpartum hemorrhage outcome, a sensitivity analysis restricted to women who delivered vaginally without any instrumental intervention (i.e. forceps and/or vacuum) showed no statistically significant association between exposure to SSRIs/SNRIs between gestational week 30 and childbirth and postpartum hemorrhage (adjusted OR: 0.98; 95% CI: 0.49-1.95).

The sensitivity analyses examining the duration (mean number of days) of bleeding in early and midpregnancy was restricted to women reporting plausible time extents, i.e. not more than 90 days, and exposed to antidepressants in first or second trimester. Women exposed to SSRIs/SNRIs (mean: 4.4 days; ANOVA test, p=0.96) or TCAs/OADs (mean: 3.2 days; ANOVA test, p=0.67) did not bleed significantly longer than non-exposed (mean:

4.3 days) during early pregnancy; however women in the disease comparison bled significantly longer than non-exposed women (mean: 5.9 days; ANOVA test, $p < 0.001$). There were no differences in terms of bleeding duration during midpregnancy across the groups (mean non-exposed: 3.1 days; mean SSRIs/SNRIs: 2.1 days; mean TCAs/OADs: 1.6 days; mean disease comparison group: 3.1 days).

5. Discussion

5.1 Summary of the most relevant findings

The summary of the most relevant findings of this work are presented below and discussed in this section of the thesis. The selection of the most relevant findings was based on their clinical relevance or novelty, and their relation to maternal mental health and psychotropic medication use during pregnancy and postpartum.

- Study I: Use of medication at any time during pregnancy (about 80%) and during the first trimester (about 50%) is common. Similarly, about 67% of women used at least one OTC medication during pregnancy. A number of socio-demographic and life-style factors, including region of residency, were significantly associated with use during pregnancy of the different types of medications. The observed estimate of psychotropic medication use during pregnancy was approximately 3%, with SSRIs being the preferred therapeutic choice. Disadvantaged women (e.g. single or divorced, older, with low education, smokers and alcohol consumers during pregnancy) or with an unplanned pregnancy were more likely to use psychotropics during pregnancy.
- Study II: The prevalence of eating disorders before and/or during pregnancy was 0.09% for AN, 0.94% for BN, 0.10% for EDNOS-P, 5.00% for BED; 93.87% of the sample did not present any eating disorder. The crude estimates of psychotropic medication use were highest among women with AN or EDNOS-P before, during and after pregnancy, as well as continuous use throughout these time periods. Antidepressants were the most commonly used medication group within the psychotropics. In the multivariate analysis, having BN was found to be significantly directly associated with use (1.8-fold magnitude) and incident use (2.3-fold magnitude) of psychotropics during pregnancy. Having AN or EDNOS-P was significantly directly associated with use of anxiolytics/sedatives postpartum (5.1- and 6.8-fold risk magnitude, respectively).
- Study III: About 5% of the sample reported having a psychiatric disorder during pregnancy, mainly depression and/or anxiety, and within this group about 50% presented symptoms of depression as measured by the EPDS. Of the women reported having a psychiatric disorder during pregnancy, 62% were medicated with psychotropics, mostly SSRIs. The group of not medicated women more strongly

believed in refraining from using medicines during pregnancy than the medicated counterpart. According to the MMAS-8, about 49% of the medicated women demonstrated low adherence to psychotropics during pregnancy. Factors positively associated with low adherence were smoking in pregnancy (3.9-fold magnitude), presenting symptoms of depression (2.5-fold magnitude), and elevated antidepressant risk perception (range 1.3-2.3 fold magnitude). Women's belief that the benefit of pharmacotherapy outweighed the risks positively correlated ($r=0.282$; $p<0.001$) with medication adherence, while preference for herbal remedy use over conventional medicines during pregnancy negatively correlated with medication adherence ($r=-0.243$; $p<0.001$).

- Study IV: Antidepressant use during pregnancy, mostly SSRIs, was reported by 1.02% of the sample. Compared to non-exposed, women exposed to either SSRIs/SNRIs or TCAs/OADs during the first or second trimester were not more likely to experience vaginal bleeding in early or midpregnancy, respectively. Compared to non-exposed, women exposed to SSRIs/SNRIs between gestational week 30 and childbirth did not present any increased odds for postpartum hemorrhage, overall and by mode of delivery. Exposure to TCAs/OADs during this time window conferred a significant 3.8-fold increased odds of postpartum hemorrhage overall, but low statistical power impeded the analysis by mode of delivery. Compared to non-exposed, women in the disease-comparison group had a significant increased likelihood to experience vaginal bleeding episodes in both early (1.2-fold magnitude) and midpregnancy (1.3-fold magnitude), but not postpartum hemorrhage.

5.2 Interpretation and comparison with other studies

The discussion section of this thesis will mainly focus on the most relevant findings (as summarized above). Other specific results of studies I-IV are discussed and compared with other studies in the discussion section of each paper and will not be fully repeated here.

5.2.1 Overall medication use in pregnancy

No previous study has examined medication use in pregnancy on a multinational level and via utilization of a web-based data collection approach. The latest intercontinental study was performed in 1987 and included about 15,000 women delivering at 148 selected hospitals in 22 countries; however, this study was hospital-based and examined the extent

of prescription drug use only.[25] Because of the over-time change in therapeutic strategies and shift in drug availability, conversion of prescription drugs into OTC and changes in prescribing attitudes, updated estimates of medication use in pregnancy allowing for inter-country comparability were warranted.[24,163]

In study I we found that overall eight out of ten women reported use of at least one medication, either prescribed or OTC, during the course of the pregnancy, which is in line with findings of previous research utilizing patients' interviews as sources of information about drug utilization.[32] Our observed estimates of medication use differed across the individual participating countries. Specifically, women residing in countries such as Croatia, Serbia, Slovenia or Italy were those reporting the least use of any medication (range 62-71%) during pregnancy, as opposed to women residing in Finland, Iceland, or The Netherlands who reported the highest use (range 92-95%). This approximate 30% difference in the extent of any medication use across specific countries could be explained by several factors, primarily dissimilarities in culture, prenatal care, access to medicine and healthcare costs, but also by differences in women's self-perception of illness and reporting attitudes. Since most of the country-specific drug utilization studies published in the last ten years used prescription claim databases as source of information,[28-30,65,82,85,86,91-93,98] comparison between our finding and those of these latter studies is difficult; in our study women were not specifically enquired about use of medication prescribed by their treating physicians, but rather on any medication use according to indication and additionally about OTC medication use. The current literature however indicates that use of prescribed medication during pregnancy is higher in countries such as Canada, USA, The Netherlands or France (range 59-93%) compared to countries such as Serbia (26%).[26-31,33,98] Thus, since knowledge about the extent of prescribed medication use may, at least to some extent, be an indicator of the degree of total medication use in pregnancy, our results can be deemed to be in line with previous research.

Notably, about 50% of our sample was exposed to a medication during the first trimester. In accordance with previous studies,[43,78,211] the most common exposures were represented by analgesics, antacids, nasal preparations, systemic antibiotics, antihistamines, thyroid medication, NSAIDs, drugs for obstructive airway diseases, antidepressants and anxiolytics/sedatives. While the effectiveness, safety and benefit-risk ratio of pharmacotherapy versus untreated illness is established for some of these exposures (e.g., thyroid medication), there is still controversy and disagreement in the literature pertaining

to other exposures (e.g., antidepressants, NSAIDs), and for many medications the risk of teratogenicity and for other subtle outcomes remain undetermined.[13,212] Awareness that one out of two pregnant women may inadvertently or not be exposed to medication during the most sensitive period for fetal organogenesis has important clinical implications. Indeed, this finding urges the need to increase awareness among healthcare providers that a large proportion of pregnant women will be in need of tailored evidence-based information about the fetal risk of medication exposures during pregnancy.

The specific analysis on OTC medication use showed that overall, 67% of the sample reported use of at least one OTC drug during the course of the pregnancy, indicating a high degree of self-medication during pregnancy. This may be cause for concern, especially in certain countries such as Finland, Iceland, United Kingdom or The Netherlands which presented the highest estimates of OTC use (range 82-85%). The available literature about the extent and typology of OTC medication used in pregnancy is not extensive.[213] In our study the most common OTC medications utilized were analgesics, antacids and nasal decongestants, as also observed in previous studies.[37,39] Paracetamol was the most common medication among the analgesics (ranging from 25-27% in South America and Eastern Europe to 62-67% in Northern Europe and Australia), however a surprisingly high proportion of women also reported use of OTC NSAIDs during pregnancy, ranging from 17.1% in South America to 7.5% in North America, 6.5% in Northern Europe and about 3% in the remaining regions. To date, there is not enough evidence to recommend use of NSAIDs during the first trimester. Several studies have suggested an increased risk of congenital malformations such as for heart defects or gastroschisis, as well as spontaneous abortion/preimplantation loss associated with this exposure.[13] Nevertheless, women should be advised against use of NSAIDs in the third trimester since it may increase the risk of premature closure of the *ductus arteriosus*, oligohydramnios, and inhibition of labor.[13]

The observed estimate of use of OTC aspirin (in a high dose) and metamizole (dipyrone) were surprisingly high in Eastern Europe (about 1.4%) compared to the other regions (range 0.2-0.6%). Use of OTC metamizole was also high in South America (3.5%). Although differences in medical practices and access to medications might explain this finding, use of high dose aspirin should be avoided in pregnancy since it may increase the risk of hemorrhage, premature closure of the *ductus arteriosus,* and other important perinatal complications, including specific birth defects.[13] Similarly, very little is known about the fetal risk associated with gestational exposure to metamizole,[214,215] and more

intensively studied analgesics, e.g., paracetamol, should be considered the first choice in pregnancy for treatment of fever and pain.[13] Given this scenario and in light of recent findings showing an association between prolonged use of paracetamol during gestation and adverse neurodevelopmental outcomes in the offspring,[216] it is of utmost importance that healthcare providers enquire their pregnant patients during the routine prenatal check-ups about the types of OTC medications used, if any, and duration of such use. Subsequent tailored counseling about safety of these medications is essential to ensure maternal-fetal health.

Having previous children, an educational level lower than high school, working as a healthcare provider and using alcohol after awareness of pregnancy were factors positively associated with use of OTC medication during pregnancy, possibly reflecting women's higher confidence in self-treatment and/or less anxiety for the pregnancy outcome. Contrary to previous studies indicating an association between higher maternal education and more prevalent use of medication during pregnancy,[39,217,218] we found that lower education was associated with a higher use of OTC medications as well as medication for chronic/long-term disorders (30-50% increased risk). Results of similar magnitude (30% increased risk) were also observed by Olesen *et al*.,[219] whereas Stokholm *et al*.[220] identified a stronger association (2.3-fold increased risk) between low maternal education and use of antibiotic for respiratory tract infections during pregnancy. However, in the sensitivity analysis taking into account clustering on region of residency, we no longer observed a significant association between educational level and OTC medication use, probably secondary to an underlying difference in educational level across the regional clusters. Given the high degree of self-medication with OTC drugs during pregnancy, it is important for health care personnel in care of pregnant women to remember to ask for and discuss OTC-medications at maternity check-ups.

5.2.2 Psychotropic medication use in pregnancy

- Women with depression and/or anxiety

In The Multinational Medication Use in Pregnancy Study the total prevalence of depression or anxiety during pregnancy as self-reported by the participating women was approximately 5% in the analysis on the entire study population comprising pregnant women and new mothers (study I), as well as in the analysis restricted to pregnant women only (study III). This estimate is similar to finding of previous studies evaluating the extent

of depression in pregnancy as diagnosed by clinicians during prenatal ambulatory care visits.[79,80] However, studies conducted in more disadvantages populations[94] or using psychometric instruments as screening tools for depressive symptoms[46,221] have shown higher estimates of depression and/or anxiety during pregnancy. Indeed, women's self-report of depression and/or anxiety during pregnancy is most likely based on a previous medical diagnosis and/or received treatment (either pharmacological or cognitive behavioral). Also, in our electronic questionnaires, women were specifically asked to report chronic or long-term depression or anxiety, which might have caused a missed detection of women with less severe or transitory illnesses and other types of psychiatric disorders; however, on the other hand, it cannot be excluded that women with more severe psychiatric disorders might have been less likely than healthy women to engage in a research study. As addressed by Gavin *et al*.[222] in a systematic review, the prevalence estimates for perinatal depression may vary according to trimester of pregnancy and diagnostic tool utilized, however it can be estimated that approximately up to 5% and 11% of pregnant women suffer from major depression, or major and minor depression, respectively, during pregnancy.

The overall self-reported use of psychotropic medications for treatment of depression and/or anxiety was approximately 3% in both studies I and III. The variability in the self-reported use of psychotropic medications during pregnancy across the various regions in study I can probably be ascribed to differences in medical practice, maternity care, access to medications and specialist healthcare, and not least women's sociodemographics. Our observed estimates of use of psychotropic medications for treatment of depression are generally similar to those observed in previous studies carried out in North American (5.4% versus 4-8%),[32,81,91,95,98,223] Western European (1.9% versus 1.3-3.0%),[29,30,65,75,77,90] and Northern European (3.5% versus 1.0-3.0%),[28,70,71,86,89] countries, although higher in the Australian sample (8.2% versus 1.5-4.6%).[73,99] In the latter instance, different recruitment strategies, i.e., web-based questionnaire in study I versus hospital outpatient clinics and dispensing records, may explain such a discrepancy. Indeed, it cannot be excluded that women with chronic disorders and/or taking medications during pregnancy might have sought the internet for information and thus being more likely to fill out the online questionnaire. The self-reported prevalence of depression and/or anxiety and related medication use in the South American and Eastern European regions was substantially lower than that reported in the other regions. Ethnical differences pertaining to the risk of

psychiatric disorders, but also differences in perception of illness and negative attitudes towards pharmacotherapy and psychological help-seeking, may, at least to some degree, explain this finding.[224] Qualitative studies in the non-pregnant population have in fact shown that there are differences in symptom interpretation and definitions of illness among persons with different ethno-racial backgrounds, and that stigma and concerns about dependence on medication represent barriers to treatment.[225,226] However, knowledge about mental health and related medication use during pregnancy in South American and Eastern European countries is to date scarce and further research is needed in these regions.

Overall, SSRIs were the most common psychotropic medications reported for treatment of depression and anxiety, followed by SNRIs and benzodiazepines. Indeed, SSRIs are considered the preferred therapeutic choice in pregnancy for treatment of both depression and anxiety.[4] In study I, women using psychotropics were more likely to be older, single or divorced, smokers, to have lower education than high school, an occupation as student or housewife at conception, an unplanned pregnancy, or to consume alcohol after awareness of pregnancy, as also shown by previous research.[70] However, marital status, occupation at conception, and smoking during pregnancy did not significantly differ in the crude comparison between users and non-users of psychotropic medication during pregnancy performed in study III, which was restricted to women suffering from depression or anxiety; these maternal factors may in fact represent risk factors of the psychiatric disorder itself rather than of the pharmacotherapy.[227,228]

Disentangling maternal determinants of psychiatric illness from those of psychotropic medication use in pregnancy is surely challenging. Furthermore, the maternal decision whether to use or not a psychotropic medication during pregnancy is multifaceted and driven by additional components such as severity of the underlying illness, risk perception, attitudes, personality traits and not least fear to harm the fetus.[71,229] This scenario became clearer in study III where it was found that women suffering from depression or anxiety but not using psychotropics had significantly different perceptions from women using psychotropics, specifically that their necessity of the psychotropic therapy did not outweigh their concerns, and that it was better to refrain from using medications during pregnancy for the sake of the fetus.

- Women with eating disorders

Research about perinatal mental disorders and related medication use has so far largely focused on depression, whereas other important psychiatric conditions such as eating disorders have not been extensively explored, especially in a population-based setting. Study II was the first to address the extent of psychotropic medication use in relation to pregnancy among women with eating disorders. Several of the findings in study II are novel and relevant for clinical practice. First, use of psychotropic medication, especially antidepressants, was found to be common among women with any eating disorder in the preconception period as well as during pregnancy and postpartum. Our observed rates of use of psychotropics in the preconception period were lower than those found in three previous studies among women with AN (53%), BED (18%), or all eating disorders (97%).[63,230,231] These discrepancies could probably be explained by different recruitment strategies, that is, population-based recruitment in the present study versus clinical research recruitment in others, country-specific therapeutic traditions and access to special care in different countries. Factors such as pregnancy planning might have also deflated our estimates; because of fear to harm the unborn child and elevated risk perception of medication exposure, many women may discontinue their needed pharmacotherapy during pregnancy or when attempting to conceive.[6,77]

Second, in this study it was also found that about 50% of women with AN or BED discontinued their pharmacotherapy with psychotropics in the first trimester of pregnancy, though lower rates were observed for the BN (about 35%) and EDNOS-P (about 16%) groups. However the lack of information about the presence of alternative non-pharmacological therapies among these women impedes any further evaluation of this finding, and it cannot be corroborated whether the decision to discontinue the pharmacotherapy was woman or physician driven.

The lack of drug utilization studies among women with eating disorders during pregnancy unfortunately impedes any comparison of our observed estimates of use during pregnancy of antidepressants (highest for AN: 13.0%), anxiolytics and sedatives (highest for EDNOS-P and BN: 3.9% and 3.3%, respectively) and antipsychotics (highest for AN: 3.7%) with the existing literature. Not surprisingly, our estimates for use of psychotropic drugs in the AN, BN and EDNOS-P groups, but not BED, were substantially higher than those observed by Engeland *et al.*[28] in a population-based study from the Norwegian Prescription

Database in the period from three months before to three months after pregnancy. Clinical trials have in fact shown that antidepressants, especially SSRIs, can moderately reduce the symptoms of BN and BED and fluoxetine is the only medication approved for treatment of BN;[61] however the effect of these medications on full recovery is small.[58-60] Although there is no evidence supporting general use of antidepressants or antipsychotics for the treatment of AN, Kaye *et al.*[232] showed in a double-blind placebo-controlled trial that use of fluoxetine may be useful in improving outcome and preventing relapse of patients with AN after weight restoration; since most women with AN are weight restored during the course of the pregnancy, SSRI antidepressants, and in particular fluoxetine, may actually be more beneficial in this setting than before conception.

In study II the relationship between eating disorders and use of psychotropics during pregnancy was also addressed, including whether the association was direct or indirect, e.g. via an underlying maternal depression and anxiety. In the adjusted analysis, all eating disorder subtypes were significantly associated with use of psychotropics during pregnancy, with a magnitude for the total association ranging from 1.7-fold for BED to 5.6-fold for AN. However, in the analyses of direct associations on overall and specific psychotropic groups, only BN was found to be directly associated with use of psychotropics during pregnancy (1.8-fold magnitude), in particular with use of anxiolytics/sedatives (2.4-fold magnitude), compared to women with no eating disorders. The direct associations between BN and use of anxiolytics/sedatives during pregnancy could be secondary to an important anxiety symptomatology among these women. One study carried out in a clinical setting found that women with BN using laxatives as purging method experienced very high level of anxiety when laxatives were acutely discontinued for treatment purposes.[233] In study II, the self-reported use of laxatives among women with BN was actually higher during pregnancy than in the period prior to pregnancy, however it cannot be excluded that these women attempted to reduce other purging symptoms, for instance vomiting, or their bingeing behaviors during gestation, which might as well have affected the anxiety symptomatology with subsequent requirement of pharmacotherapy.

Previous research has in fact shown that, in general, there is an improvement of eating disorder symptoms during pregnancy and perhaps for a brief period of time postpartum, however a significant portion of women return to eating disorder symptoms after giving birth.[54] A previous study[53] using MoBa data found that the most common pattern for BN was remission or partial remission of symptoms from the pre-pregnancy period to early

pregnancy, and incident cases were rare. However in study II it was found that BN was the only eating disorder subtype directly associated with incident use (2.3-fold magnitude) of psychotropics during pregnancy. Given this scenario, we cannot exclude the possibility that pharmacotherapy with psychotropics might have contributed, at least to some extent, to remission of symptoms among women with BN. Also, women with BN might have sought specialist care and treatment once pregnant for the well-being of the fetus. Two previous studies have for example shown that use of dietary supplements and nutritional intake during pregnancy were similar among women with and without eating disorders,[234,235] underscoring how these women do their utmost to ensure the well-being of the developing fetus. The lack of significant direct associations between AN or EDNOS-P and psychotropic use during pregnancy could be ascribed to the small sample size and/or to the role of other factors, namely severity of depressive and anxiety symptoms, BMI at conception and weight gain throughout the pregnancy, in the path from eating disorder to the outcome of interest.

In the 4-6 months postpartum period, women with AN or EDNOS-P were characterized by a substantial increase in the use of psychotropics (estimate range 8-9%), mainly anxiolytics and sedatives, compared to women with no or other eating disorders (estimate range 1-3%). In the multivariate model, all eating disorder subtypes were significantly associated with use of psychotropics in the 0-6 months period postpartum, with a magnitude of the total association ranging from 1.5-fold for BED to 9.6-fold for AN. The general analysis on all psychotropics showed that only EDNOS-P was directly associated with such use postpartum (4.5-fold magnitude) compared to women with no eating disorders; however, in the specific analyses by psychotropic group, it was found that both AN (5.1-fold magnitude) and EDNOS-P (6.8-fold magnitude) were directly associated with use of anxiolytics/sedatives postpartum, even after cancelling out the effect of factors such as weight decrease postpartum or depressive and anxiety symptoms. The substantial physical changes accompanying motherhood may represent a special challenge for women with AN, being characterized by a profound fear of gaining weight and by a distorted perception of body shape. Although about 50% of women with AN or EDNOS-P have been shown to remit at 18 months postpartum,[236] little is known about the course of these disorders in the earlier postpartum period. Women with AN or EDNOS-P were found to lose the gestational weight more quickly than controls over the first six months postpartum,[237] thus for these women a return to restrictive weight control behaviors and a worsening of the

anxiety symptomatology in the early postpartum period, requiring use of sedatives/anxiolytics, cannot be excluded.

5.2.3 Adherence to psychotropics in pregnancy

Study III was the first to examine how closely pregnant women follow their pharmacotherapy with psychotropics in the context of ongoing use. It is well established that pregnancy constitutes a major determinant of discontinuation of antidepressants and other psychotropics,[74,77,224] however to date there is no knowledge about the medication-taking behavior of those women who continue their therapy with psychotropic medication upon awareness of pregnancy. This group of women may in fact still cut or reduce the medication dosage because they fear to harm the unborn child, or being non-adherent because of unintentional causes such as forgetfulness. Thus, understanding the extent of and maternal risk factors for low adherence to psychotropics during pregnancy represents an important clinical question: indeed, suboptimal drug therapy of the underlying psychiatric disorder, and not only drug discontinuation, may lead to a relapse of the disorder over the course of the pregnancy and to adverse pregnancy outcomes.[102,105,108]

In study III, the self-reported prevalence of depression and/or anxiety was equal to 5.3%, which although lower than estimates detected in more disadvantaged population, it does align with the estimates of previous studies using medical diagnosis of depression (as described in detail in section 5.2.2 above). The validity of the self-report of depression and/or anxiety may, at least in part, be corroborated by the level of underlying depressive symptomatology as measured by the EPDS. Indeed, in the total sample, about one of two women had a score on the EPDS $\geq$ 13, which is a cut-off score widely used to indicate probable depressive symptoms.[198] Although women not using psychotropics during pregnancy presented a slightly higher mean score on the EPDS (13.3) than the medicated counterpart (12.5), this difference did not reach statistical significance. The lack of information about ongoing treatments other than pharmacotherapy (e.g., cognitive behavioral therapy) impeded us to infer whether the similarity in severity of depressive symptomatology could be ascribed, at least in part, to ongoing non-pharmacological therapies.

The prevalence of low adherence to psychotropic medication as measured by the MMAS-8 was notably high during pregnancy. Indeed, almost one out of two women taking psychotropics for treatment of depression or anxiety or other psychiatric disorders during

pregnancy, demonstrated low adherence (48.8%). There was no substantial difference in the level of low medication adherence across the various disorders (51.3% for anxiety, 47.2% for depression, and 42.9% for other psychiatric disorders), indicating that low-adherence is an important widespread clinical problem in psychiatry. A recent study[238] among a low-income insured Medicaid population explored the extent of treatment persistence among women diagnosed with major depression. The authors found that about 45% of the women who commenced therapy with antidepressants during pregnancy, showed a gap ≥ 15 days between two prescriptions. Despite the conceptual difference of medication persistence from medication adherence (i.e., medication persistence may be defined as "the duration of time from initiation to discontinuation of therapy", whereas medication adherence is defined as "the extent to which patients take medications as prescribed by their health care providers", and is based on a therapeutic alliance between the patient and the physician)[115,239] and the different study methodologies, both constructs underline the concern that about one out of two women with a psychiatric disorder may be at risk of suboptimal control of the underlying maternal illness during pregnancy.

The estimates of low medication adherence observed in study III were found to be similar to those detected in the general non-pregnant population with psychiatric disorders (40-53%),[240,241] but higher than what was previously found among women with somatic illness during pregnancy (36%).[122] Several factors might explain the reason as to why women with psychiatric disorders have poorer medication adherence than women with somatic disorders during pregnancy: women's perception that the mental disorder may get better during pregnancy, preference of non-pharmacological therapeutic methods, decisional conflicts about the necessity of their medication during a sensitive time period such as pregnancy, but also uncertainty about how to treat the illness given the battery of contradictory findings about the safety of e.g. antidepressants during pregnancy.[242] The controversies between study findings have indeed posed important challenges on practicing clinicians when assessing the risk of untreated depression versus the risk of pharmacotherapy, but also on the pregnant patient when weighing the fear of teratogenicity versus the necessity of the medication.[243]

Study III was also novel in providing insights into the role played by women's beliefs on adherence to psychotropic medications during pregnancy. Overall, both the BMQ-Necessity ($r=0.208$; p-value<0.01) and BMQ-Concern ($r=-0.213$; p-value<0.01) subscales

were significantly associated with adherence to psychotropics during pregnancy. Also, the perception that the benefit of pharmacotherapy outweighed the risks (r=0.282; p-value<0.001) and that herbal remedies should be preferred to conventional medications during pregnancy (r=- 0.243; p-value<0.01) were positively and negatively associated, respectively, with an increasing level of medication adherence during pregnancy. Analogue results were obtained in the analysis of medication adherence specifically for treatment of depression, but not for the remaining disorders. However, in the latter instances, the small sample sizes might explain such a discrepancy. The magnitude of the observed correlation coefficients was not large, but it was however similar to those observed in a previous study among non-pregnant subjects treated for disorders such as asthma or cardiac disease (r=0.21-0.28 for the necessity-adherence association).[120] Nonetheless, factors weakly correlating with medication adherence can still be deemed noteworthy and of importance in clinical settings. Indeed, medication adherence is a composite and multifaceted medication-taking behavior affected by several practical and perceptual factors, and therefore even factors with weak influence could be considered relevant for its overall improvement. Yet, the significant correlation between increasing agreement with the concept that herbal remedies should be preferred to conventional medications during pregnancy and decreasing medication adherence underscores the need to promote evidence-based counseling about exposure to medication and other agents during gestation. If the current knowledge on the immediate and long-term effects of gestational exposure to medications is limited, even less is known about the risk associated with exposure to the vast array of herbal remedies. Furthermore, the proof of efficacy of herbal remedies in the treatment of important disorders is questionable also during pregnancy, which raises the additional concern about suboptimal treatment of important disorders which may jeopardize maternal-fetal health.[244]

In the multivariate analysis, smoking during pregnancy, psychotropic monotherapy, elevated risk perception of antidepressants and depressive symptoms during pregnancy were the only maternal factors significantly associated with an increased likelihood of low medication adherence in women with depression and/or anxiety. The effect estimates were largest for smoking during pregnancy (3.9-fold increase) and having symptoms of depression (2.5-fold increase) indicating that these women should be especially targeted for discussions on medication adherence. In relation to the latter association, the study design impeded any corroboration as to whether low medication adherence led to poorer

mental health or the converse. Women on monotherapy were also found to demonstrate poorer adherence than those on polytherapy. A previous study by Horne *et al.*[120] showed that patients' sociodemographic and clinical factors, including the number of medications, did not significantly predict adherence to pharmacotherapy for treatment of asthma or cardiac diseases. However, another study[245] conducted specifically among patients with depression found that patients receiving polytherapy presented better compliance than those on monotherapy. In the pregnancy scenario, it can be assumed that women on polytherapy with psychotropics are most likely those with a more severe or longer history of psychiatric disorders, which may lead to better knowledge of the medications that are regularly taken, and not least higher awareness of the correct administration schedule. However, in study III we could not verify this assumption because of lack of information about maternal history of psychiatric disorders before conception, and whether the onset of maternal depression or anxiety took place before or during pregnancy.

The odds of demonstrating low adherence to psychotropic during pregnancy was increasingly higher among women assessing the risk of antidepressant exposure in the range 4-5 (1.3-fold magnitude) or ≥6 (2.3-fold magnitude), compared to baseline (score 0-3). This finding highlights the relevance of women's risk perception in shaping their medication-taking behavior, even in relation to pharmacotherapy for important psychiatric illnesses.

5.2.4 Maternal safety after use of antidepressants in pregnancy

Study IV was the first to address the risk of vaginal bleeding during early and midpregnancy following gestational exposure to antidepressants using a large cohort followed prospectively and with inclusion of a disease comparison group including not medicated women with persistent depressive symptoms in pregnancy. About 20% and 9% of the cohort reported vaginal bleeding episodes during early and midpregnancy, respectively. These estimates are supported by previous epidemiological data addressing the burden of vaginal bleeding in pregnancy; indeed, up to 21% of pregnant women are expected to experience this symptom, especially during the first trimester.[246] Vaginal bleeding during the first half of pregnancy is often a sign of abortion (threatened, spontaneous, missed), while bleeding in the second half of pregnancy is a risk factor for perinatal mortality and other adverse outcomes such as disorders of the amniotic fluid, low birth weight and a low Apgar score.[247] Studies suggest that bleeding in either first or

second trimester of pregnancy is also associated with a 30-60% increased risk of premature delivery.[248,249] Because the exact etiology of vaginal bleeding often cannot be determined,[250] it is clinically relevant to ascertain the role of antidepressants with serotonin activity in the development and/or prolongation of this obstetric complication. Study IV showed that women exposed to either SSRIs/SNRIs (adjusted OR: 0.91; 95% CI: 0.72-1.16) or TCAs/OADs (adjusted OR: 0.83; 95% CI: 0.36-1.92) during the first trimester did not present a higher likelihood of vaginal bleeding complications in early pregnancy compared to non-exposed women. Similarly, exposure to either SSRIs/SNRIs (adjusted OR: 0.81; 95% CI: 0.50-1.31) or TCAs/OADs (adjusted OR: 0.96; 95% CI: 0.26-3.53) during the second trimester did not confer any increased odds of vaginal bleeding complications in midpregnancy. Since pregnancy in itself represents a status of hypercoagulability,[251] such scenario may counteract the inhibiting effects of platelet function by SSRIs and other serotonergic antidepressants. The etiology of vaginal bleeding during pregnancy is often undetermined or thought to occur from local lesions, thus in this last instance, it would be assumed that exposure to antidepressants with serotonin activity might at least prolong the bleeding time. However, this hypothesis was also refuted in study IV where the mean duration of bleeding (in days) in both early and midpregnancy did not differ between non-exposed and antidepressant exposed women.

Study IV also provided relevant insights into the role of non-medicated depressive symptomatology in pregnancy. Women presenting depressive symptoms throughout the pregnancy, precisely at both gestational week 17 and 30, but not medicated with any antidepressants during this time window, presented a significant increased likelihood to experience vaginal blood loss in early (adjusted OR: 1.22, 95% CI: 1.06-1.39) and midpregnancy (adjusted OR: 1.28; 95% CI: 1.07-1.55), as well as recurrent bleeding episodes in early pregnancy (adjusted OR: 1.33; 95% CI: 1.10-1.61). These women were more likely to experience blood loss in medium amount or clots during early pregnancy, or as trace in midpregnancy. The sensitivity analysis on bleeding duration also confirmed that women in the disease-comparison group were more likely to bleed one-two days longer than non-exposed women during early pregnancy. The sensitivity analyses restricted to women with a single participation in the MoBa study showed a significant association between belonging to the disease-comparison group and having a vaginal bleeding with medium/large amounts of blood during midpregnancy (35% increased odds) which was not reflected in the main analysis; however given the similarity in magnitude between the latter

association and that observed for the outcome about any vaginal bleeding, such a discrepancy could simply be ascribed to a heighten accuracy in reporting among women participating only once in the MoBa study.

Several factors could be implicated in the significant association between not medicated depressive symptomatology and vaginal bleeding during gestation: first, women with not medicated depressive symptoms may present higher level of anxiety and stress, potentially leading to different health behaviors and different accuracy and attitudes in reporting. Indeed, the number of ultrasound examinations undertaken during pregnancy by this group of women was significantly higher than that observed in the non-exposed or SSRI/SNRI-exposed groups, possibly reflecting a higher level of apprehension and anxiety for the wellbeing of the unborn child. Second, the higher likelihood of vaginal bleeding among depressed not medicated women might be a sign of threatened abortion; Ross *et al*.[135] pooled results of three studies examining the association between antidepressant exposure and spontaneous abortion yielding an overall borderline significant OR of 1.47 (95% CI: 0.99-2.17); however, the lack of a depressed control group in all three studies made it difficult to disentangle the effect of the medication from that of the underlying maternal illness. Third, since both vaginal bleeding during pregnancy and antenatal depression are considered risk factors for prematurity,[104,105,248] it cannot be excluded that vaginal bleeding during gestation might be an intermediate on the path from depression to prematurity. However, the latter assumption could only be tested in a mediation analysis model. Last, a damaging process of the vascular endothelium triggered by maternal stress, anxiety and depression cannot be ruled out.[252]

Study IV also added to the discordant literature about the association between exposure to antidepressants during gestation and postpartum hemorrhage. Since postpartum hemorrhage is not uncommon and it is a leading cause of maternal morbidity and mortality,[253] identification of risk factors of even moderate magnitude would be of benefit in terms of public health. Recent studies have shown that the overtime changes in maternal characteristics and obstetric practice do not seem to explain the recent increase in postpartum hemorrhage in many developed countries.[254,255] Given this scenario, it is of importance to determine whether exposure to antidepressants near delivery might increase the risk of this outcome. In study IV it was found that women exposed to SSRIs/SNRIs between gestational week 30 and childbirth were not more likely than non-exposed to experience postpartum hemorrhage (adjusted OR: 0.97; 95% CI: 0.57-1.65) overall as well

as in the two delivery mode strata (cesarean delivery / vaginal delivery). These findings were corroborated by additional sensitivity analyses accounting for instrumental intervention (i.e. forceps and/or vacuum), analysis on individual SSRI/SNRI, and classification of antidepressants according to their level of affinity to serotonin transporter. In the postpartum setting, contractions and retractions of the uterine muscle play an important role in securing blood loss,[256] and this process is by far more important than blood clotting. Moreover, SSRI can elicit a contractile effect on the pregnant human myometrium,[257] and therefore working in the opposite direction of postpartum hemorrhage. Nonetheless, tapering or stopping SSRI and SNRI treatment towards the end of pregnancy is often considered as a way to avoid neonatal withdrawal symptoms,[258] and this may prevent identification of any increased risk of postpartum hemorrhage, if existing. Given such a pharmacological scenario, it is not surprising that exposure to SSRIs/SNRIs in the end of pregnancy did not confer any increased risk for postpartum hemorrhage. Although women reporting use of TCAs/OADs between gestational week 30 and childbirth were found to have a significant 3.8-fold increased odds to experience postpartum hemorrhage compared to non-exposed, this measure of association suffered from a very wide confidence interval and the small sample size impeded any further evaluation by mode of delivery. Nonetheless, TCAs are also alpha-1 receptor antagonists, and are thereby able to cause vasodilatation.[144] This proposed mechanism of action can plausibly explain the association between exposure to TCAs and postpartum hemorrhage.

To date, the literature about the association between exposure to SSRIs during gestation and postpartum hemorrhage is still inconclusive: although four studies[149,156-158] have observed positive findings, two,[155] including study IV, have not. In three[149,156,158] out of the four positive studies, exposure was based on prescription claims and prescriptions issued during prenatal care. Beyond the question as to whether receiving or filling a prescription coincides with drug intake, the exposure windows examined in two of these studies,[149,158] specifically early pregnancy and 30 days or six months prior to delivery, may not entirely reflect a pharmacological plausibility. Based upon the elimination half-lives of antidepressants and turn-over time for the platelet population, the antiplatelet effect of SSRIs can be expected to be completely over two weeks after its withdrawal, except for fluoxetine which has an active metabolite (norfluoxetine) with an elimination half-life of weeks.[144] On the basis of these pharmacological properties, study IV employed gestational week 30 – childbirth as exposure window, which is the closest exposure window to

delivery available in the MoBa study, and for which the impact of misclassification has been assessed as minimal.[184]

In the study by Palmsten *et al.*,[156] various exposure windows were examined, most importantly a supply of antidepressants that overlapped with the delivery date; women with a supply of an SSRI, an SNRI or a TCA that overlapped with the delivery date were found to have a significant 1.42-, 1.90- and 1.77-fold increased risk to experience postpartum hemorrhage respectively, compared to non-exposed women with a diagnosis of mood disorder. The larger risk associated with exposure to TCA or SNRI seem to contradict the platelet-serotonin theory, according to which a higher risk estimate would be expected for the SSRI group. However in study IV it was also found that women using TCA/OAD in the end of the pregnancy presented a significant increased likelihood (3.8-fold magnitude) to experience postpartum hemorrhage, even though this result suffered of insufficient statistical power. It could also be assumed that women using TCAs/OADs might be those with more severe depression who probably did not benefit from the first-line therapy with SSRIs, and the association between this drug group and postpartum hemorrhage could be secondary to maternal illness rather than to the drug. However in study IV the rates of history of life-time depression and depressive symptomatology during pregnancy (at two time points) were comparable between the TCA/OAD and the SSRI/SNRI exposed groups, thus refuting the first theory. Since previous studies have found stronger associations between SNRIs or TCAs and preeclampsia than those observed for SSRIs,[147,148] and preeclampsia per se is an important risk factor for postpartum hemorrhage,[259] it cannot be excluded that preeclampsia constitute a possible intermediate on the path between antidepressant exposure and postpartum hemorrhage.

Study IV had the advantage to measure the severity of maternal underlying depressive symptomatology throughout the pregnancy and therefore adjust the multivariate analysis for this important factor which is often lacking in most studies. In fact, in the other studies examining the association antidepressants-postpartum hemorrhage, maternal depressive symptomatology was either not addressed[149,157,158] or based on medical diagnosis,[156] which beyond leading to a potential underascertainment of the disorder, it is certainly not an indicator of severity. Study IV had also the advantage of a unique disease comparison group including women with depressive symptomatology at two time points in pregnancy but not medicated with any antidepressants, which allowed separating the effect attributable to antidepressants from that of the underlying maternal depression. Women in

the disease-comparison group did not have higher odds than non-exposed to experience postpartum hemorrhage in the overall analysis (adjusted OR: 1.14; 95% CI: 0.97-1.34) and in the strata by mode of delivery. The association became instead significant (1.8-fold magnitude) in the sensitivity analysis restricted to women with a single participation in the MoBa regardless of delivery type, although it was not in the stratified analyses by mode of delivery.

5.3 Methodological considerations

The interpretation of the findings discussed in the section above should be made in the context of the following methodological strengths and limitations. The limitation section has been subdivided in sub-sections to facilitate readability; however several of the limitations addressed below pertain to multiple sub-sections and their placement must not be interpreted in strict terms (for instance, many considerations addressed in the sub-section "Information bias" are also of relevance for the sub-section "Reliability and validity of collected data").

5.3.1 The Multinational Medication Use in Pregnancy Study (studies I, III)

The Multinational Medication Use in Pregnancy Study was unique in uniformly collecting information about medication use and related factors from over 9,000 pregnant women and new mothers. The anonymous web-based approach has indeed facilitated the reach of a large proportion of the birthing population in several countries worldwide. Recent epidemiological studies have indicated reasonable validity of web-based recruitment methods.[260,261] It has been shown in several areas of research that the information provided in a web-based questionnaire is equivalent, of quality, and as reliable as that collected via traditional modes.[262-264] Also, missing answers seemed to be lower in web-based than in paper-based questionnaires and sensitive questions can be answered more truthfully in a web-based questionnaire than in a face-to-face interview.[265] Since data are entered electronically, errors in the process of data entry are also expected to be minimal. The growing body of evidence about the widespread utilization of the internet by pregnant women, supported by epidemiological studies indicating a reasonable validity of web-based recruitment methods,[260,261] may enhance utilization of e-epidemiology in pregnancy-related research.

- Selection bias

In the Multinational Medication Use in Pregnancy Study women were invited to participate via banners posted on pregnancy-related websites. The study design implied no probability sampling of the target population; respondents were those women who happened to have internet access, visited the website(s) where the invitation was posted, and decided to participate in the survey. Hence, the possibility of a self-selection bias cannot be excluded. In order to reduce this risk and reach the widest possible segment of the target population, the invitation to participate in the study was posted on 2-3 websites in each participating country, which were selected according to the number of daily users, and on social networks and/or pregnancy forums. Use of social networks and pregnancy forums was endorsed given their widespread use among the pregnant population. A recent study performed in Ireland has in fact shown that 95% of pregnant women attending a large maternity hospital reported to use the internet for pregnancy information, and the type of internet usage mostly included discussion forums (70%) and social networks (67%).[266] Similar findings were observed in another study carried out in Italy.[267] Another qualitative study found that pregnant women turned to the internet and smartphones to fill those knowledge gaps not dealt with during prenatal care visits.[268]

Although the internet penetration rate in households or at work is relatively high among women of childbearing age in Europe, North America and Australia,[269-273] a selection of more educated women and/or women with easier access to the internet cannot be ruled out. However, a recent study[266] has found that even socially disadvantaged women reported high levels of digital media usage during pregnancy, and selection of more educated subjects is not limited to web-based studies but it applies to most epidemiological studies using patients or individuals as source of information.[274] Although the analyses in study I and III were adjusted for educational level, a factor thought to be associated with selection of participants, this may not necessarily translate into adjustment for selection bias.[275] Furthermore, no variable reflecting internet coverage and/or usage across the participating countries was created in the analyses in studies I and III. Women with specific disorders or in need of information about medication use during pregnancy might have been more likely to consult internet websites and therefore participate in this study. However, the majority of websites used for recruiting purposes were general pregnancy-related and not medication-oriented websites. The possibility that the women who decided to participate in

the study differed from the general birthing population in other ways that our analysis could not control for cannot be excluded.

- Response rate and representativeness

The questionnaire was available through various internet websites, social networks and pregnancy forums; by using this kind of approach a conventional response rate cannot be calculated. Since the study was completely anonymous, no information about how many users clicked on the study invitation (for example via the computer IP address) could be retrieved. The recruitment took place via several platforms including websites, social networks and pregnancy forums, and therefore an overlap in website access is plausible; because of this, the click rate could not be calculated. In studies I and III we could however calculate how many women accepted to participate in the study among those who read the study description and answered either 'yes' or 'no' to the question 'Are you willing to participate in the study?', which was equal to 98.6%.

Studies performed in 2004-2005 showed that the response rate for web-based questionnaires was lower than that for postal questionnaires.[276,277] However, such scenario has probably improved in the recent years given the constantly increasing coverage of internet in household, work, smartphones; indeed, internet use is relatively high among individuals aged 25–34 years in Europe, ranging from 48% in Russia to 100% in Iceland. The internet penetration rates in other parts of the world vary, being highest in the USA, Australia, and Canada (80–94%) and lowest in South America (48%).[269-273] A recent study has shown that web-based questionnaires are by far preferred over paper-based questionnaire by responders.[264] The response rate to web-based questionnaires is also thought to very much depend on the context or population as well as on the design used for conducting the web-based study.[278] Since women have been shown to use the internet in a very high extent during pregnancy to seek for pregnancy-related information,[266,279] this population is probably a suitable target group in e-epidemiology. This assumption was certainly corroborated by a recent prospective cohort pilot study[168] targeting women planning a pregnancy in Denmark and following them up; indeed, the questionnaire cycle-specific response rates ranged from 87 to 90% and at 6 months 87% were still under follow-up.

Studies have also attempted to compare the characteristics of the responders to web-based questionnaires versus those of responders to traditional mode of data collection; it has been

shown that factors such as gender, health status, income, age, or education are comparable between the two sets of responders, although responders to web-based questionnaires are more likely to be obese.[280-282] However to date no such validation study has been conducted in the female birthing population, which makes it difficult to corroborate whether the characteristics of women responding to web-based surveys are equivalent to those responding to conventional questionnaires.

The questionnaire in the Multinational Medication Use in Pregnancy Study was also carefully designed to suit the internet administration approach and for improving the completion rate: specific technical features such as multiple page design, routing of questions and progress indicator of completion were applied. A non-monetary incentive (participation in a lottery where the winner would get a gift card) was also used to promote the response rate.

In order to appraise the representativeness of the sample in each participating country, the socio-demographic and life-style characteristics of sample on an individual country level were compared to those of the general birthing population in the same country. This latter battery of information was retrieved from reports of National Statistics Bureaus, Medical Birth Registry Statistics, or previous studies. On average, the women in the study had higher education and were slightly more often primiparous than the general birthing populations in the various countries. The ratio between the number of respondents and the estimated number of live births in the 2-months period was also examined for each country. In specific countries (Australia, Canada, France, Russia, The Netherlands, and the USA) the study sample was a small proportion of the general birthing population; hence the generalizability of our findings for these specific countries should be interpreted with caution.

- Information bias

Information about background sociodemographic and life-style characteristics, pregnancy details and medication use during pregnancy was dependent on the accuracy of the women's reporting and recall. Study I included pregnant women and new mothers, and in the latter instance data were registered retrospectively; hence a risk of recall bias cannot be ruled out. In both studies I and III pregnant women were included in the analysis regardless of time of gestation. Since many ailments requiring pharmacotherapy occur in mid or late pregnancy, inclusion of pregnant women at early gestation in the total material

has somewhat inflated the prevalence of non-users of any medication and OTCs during pregnancy. However, this was tested to be not relevant in relation to the estimates of medication use for chronic disorders (study I).

In order to enhance recall, all questions pertaining to medication use in pregnancy were indication-oriented. As shown in a previous study,[283] adopting prompts and indication-oriented questions over open-ended questions has the benefit to improve recall and accuracy in reporting use of medication during pregnancy.

Recall of OTC medications was aided with a list of five OTC medication categories, along with examples of brand name products of relevance in each country. However it cannot be excluded that information about OTC use might be less accurate than information pertaining to medications used for chronic or long-term disorders.

- Reliability and validity of collected data

The Multinational Medication Use in Pregnancy Study suffered from lack of validity of the self-reported diagnoses. Both short-term illness and chronic disorders were self-reported by the respondents and therefore dependent on the women's perception of illness and accuracy in reporting. This limitation might have biased the observed prevalence estimates in two possible directions: 1) an overestimation of short-term illness such as UTIs is plausible since women may perceive dysuria without ascertainment of bacteriuria in the urine as UTI; women were not specifically enquired whether the UTI was confirmed by a urine test; 2) an underestimation of chronic/long-term disorders such as depression and anxiety for which underreporting is most often seen among individuals who have less severe illness or who have not received treatment.[284] Also, women may ascribe symptoms of depression or anxiety to the pregnancy itself rather than to a probable disorder, and women with severe psychiatric disorders might be less likely to engage in research studies. However, the lack of validity of self-reported diagnosis is not considered to affect the prevalence estimates of medication use, which was in fact the main aim of the Multinational Medication Use in Pregnancy Study.

Multiple psychometric instruments were used in the Multinational Medication Use in Pregnancy Study to measure medication adherence (MMAS-8), maternal symptoms of depression (EPDS), and beliefs about medicines (BMQ-Specific). In study III, the internal consistency of the MMAS-8 was satisfactory among women treated for depression and

other psychiatric disorders (Cronbach's alpha ≥0.7), however it was borderline adequate for anxiety. With respect to the EPDS, we used a cut-off score with high sensitivity and specificity in predicting probable depression.[198] In the Multinational Medication Use in Pregnancy Study, pregnant women were asked to complete the EPDS only once; although it has been shown that a single administration of the EPDS in early pregnancy is likely to detect transient distress for predictable reasons rather than depressive symptomatology, and administration at two time points in pregnancy is indeed considered to be preferable,[204,285] another study found that use of the EPDS early in the second trimester identifies a substantial number of women with potential mental disorders.[286] Since the mean gestational week of the sample in study III was about 21 weeks, and we additionally utilized an adequate cut-off score for probable depression, the measurement of maternal mental health in study III is deemed to be valid. The BMQ-Specific has been shown to have satisfactory psychometric properties in the setting of mental disorders; specifically, the Necessity and Concerns subscales were found to measure independent dimensions, with subsequent reliability of the Necessity-Concerns differential.[121]

The EPDS, BMQ-Specific and MMAS-8 are valid psychometric instruments with good psychometric properties when used in paper-based questionnaires.[120,195,198] However, their validity when administered over the internet has only been tested for the EPDS. Spek *et al*.[287] showed that an internet-administered EPDS has good psychometric properties (Cronbach's alpha = 0.87) comparable to those observed in paper-and-pencil questionnaires;[198] however the equivalency of the cut-off scores employed in paper-based versus web-questionnaires has to be verified. Further, the BMQ-Specific and MMAS-8 have not been validated in the pregnant population.

- Sample size and statistical considerations

In paper I, the study sample obtained in most participating countries was large enough to warrant calculation of prevalence estimates with a precision of 5%. However, less precise estimates were permitted by the study sample in Austria, Iceland and The Netherlands (precision of 9-11%), as well as in Australia, Canada, Croatia, Serbia, Slovenia, and USA (precision of 6-7%). Individual countries were grouped into region in most analyses in order to facilitate readability and presentation of the results. For the very same reason, medications were not presented on individual substance level, but rather on clinically relevant groups.

In paper III, the overall prevalence of low adherence was uncertain due to the small total study sample, but could nevertheless be estimated with a precision of ±8%. The study sample was also small for the individual psychiatric disorders, thus limiting the statistical power of specific sub-analyses. Also, the country-specific samples had to be combined into regions because of low statistical power, thus restraining us from doing country-specific analyses on the relationship between beliefs and adherence. However, a recent meta-analysis[119] in a non-pregnant sample has shown that the association between patient's beliefs and adherence seems to exist across different countries, languages and cultures.

In both studies I and III, several statistical tests were performed with a 95% CI; hence, in one out of 20 tests the statistical significance may have been caused by chance rather than being a true association. The presence of unmeasured factors confounding the associations investigated in studies I and III cannot be ruled out.

5.3.2 The Norwegian Mother and Child Cohort Study and Medical Birth Registry of Norway (studies II and IV)

Several characteristics make the MoBa study unique for pregnancy-related research. The study includes more than 90,000 mother-child pairs recruited between 1999 and 2008 which were prospectively followed-up throughout the pregnancy, and will be followed-up until the children reach the age of eight years. Data collection was carried out prospectively, hence avoiding the risk of recall bias. The prospective design diminishes the risk of differential misclassification of the exposure with subsequent limited risk of biased measures of associations.

The collection of a vast array of health related information, sociodemographic and life-style factors permitted to adjust the multivariate models for several important confounders. Information about the severity of maternal depressive symptomatology during pregnancy and postpartum, as measured via validated psychometric instruments,[200-203] allowed to account for this factor in the multivariate analyses (studies II and IV), and not least to include a properly chosen disease comparison group (study IV) enabling to disentangle the effect attributable to pharmacotherapy from that of the underlying maternal psychiatric illness.

The MBRN is a population-based registry where all information is prospectively collected by healthcare professional during prenatal care and at birth. Beyond providing medically

confirmed records, the MBRN is also unlikely to suffer from selection bias given its population-based characteristic.

- Selection bias

In the MoBa study all pregnant women in Norway were invited to participate in the study through a postal invitation in connection with a routine ultrasound examination offered to all women. Although the study was population-based, the risk of self-selection cannot be ruled out. Nilsen *et al*.[274] have thoroughly examined self-selection in the MoBa and its potential for bias by comparing the MoBa study population with the total Norwegian birthing population. The findings of this study indicate that the youngest women (<25 years), those living alone, mothers with >2 previous births and with previous stillbirth, and women smoking during pregnancy were strongly under-represented in MoBa. On the other hand, women using multivitamins and folic acid supplements were over-represented.[274] Given this scenario, it can be corroborated that the MoBa suffers from a possible self-selection of the healthiest women to the study. Although the prevalence estimates for various exposures, outcomes or maternal characteristics in MoBa could not necessarily be generalized to the target population, Nielsen *et al*. also concluded that the estimates of exposure-outcome associations are not biased due to self-selection.[274] Indeed, the MoBa was not a prevalence study but a prospective cohort study. Nilsen *et al*.[274] compared 23 well-known exposure variables (e.g., maternal smoking, maternal diabetes) and outcome variables (e.g., low birth weight, prematurity) in the MoBa and in the population of all other women giving birth in Norway during the same time period (using data from the MBRN). The researchers found that the magnitude of the association between maternal smoking and low birth weight in the MoBa study, for instance, was similar to that observed for all other women not participating in the MoBa.

The findings of study II pertaining to the prevalence of eating disorders or psychotropic use among women with eating disorders in the time around pregnancy could therefore not necessarily be generalized to the target population. Prevalence estimates of eating disorders in the six months prior and during pregnancy were somewhat lower than point prevalence estimates reported in other population-based studies among young women for AN and BN (AN: 0.09% in the MoBa vs. 2.0%; BN: 0.94% in MoBa vs. 4.6%),[53] but higher for BED (5.0% in MoBa vs. 1.8%).[52,288] However, when the same eating disorder questions were used in studies of the Norwegian Twin panel, they yielded prevalence

estimates and comorbidity profiles similar to those seen in other large population-based samples.[197] However the discrepancy in the prevalence of the eating disorder was most likely secondary to factors other than self-selection, primarily use of different instruments to measure eating disorders and different thresholds to define eating disorders and related behaviors; indeed, in study II the eating disorders subtypes were assessed as broadly defined AN, BN, EDNOS-P and BED. Additional factors such as under-detection of women with eating disorders in pregnancy because of their reluctance to disclose their illness during prenatal care or because of severity of illness or unlikelihood to become pregnant (particularly for women with AN), could also contribute to the above-mentioned discrepancies in prevalence estimates of eating disorders. On the other hand, the magnitude of the associations found between the exposure and outcome variables in studies II and IV can be deemed valid. We cannot, however, rule out that some of these associations could be influenced by selection bias.

- Response rate and representativeness

The MoBa study has a low response rate (40.6% of all women invited),[189] and therefore it cannot be ruled out that women participating in the MoBa possess specific characteristics that separate them from the population they are meant to represent. However, the response rate was high among those who agreed to participate: 95% for Q1, 92% for Q3, and 87% for Q4.[189] It has been shown that women included in the MoBa are less often single or smokers than the non-included counterpart, and therefore represent the healthiest segment of Norwegian birthing population. However this potential for self-selection seems to have little impact on the magnitude of exposure-outcome associations (as described in detail earlier in this section).[274]

The external validity of the results from study II is worth to be addressed. It is plausible that women with eating disorders who participated in MoBa may represent the healthier end of the eating disorder severity spectrum because they had to be well enough to conceive and participate. This especially applies to the AN group; indeed, engagement to participate in the MoBa study among women with severe AN was probably impeded by unfortunate physical conditions and difficulties with fertility and reproduction.[289] In fact, in study II the mean BMI at conception among women with AN was equal to 18.2, indicating cases of mild anorexia. Also, women excluded from the analysis because of missing items for the eating disorder assessment had a more unfavorable profile in terms of age,

education, socioeconomic status and BMI than the included counterpart, implying a plausible exclusion of women with more severe eating disorder symptoms.

In this regard, the risk of attrition bias merits to be addressed. In study II, women completing Q1 but being lost to follow-up at gestational week 30 (i.e., they did not complete Q3) were more likely than women completing both Q1 and Q3 to have symptoms of depression and anxiety around gestational week 17 (SCL-5 cut-off point: 11.5% vs. 6.9%, respectively; $p<0.001$). Similarly, the prevalence of eating disorders was significantly higher ($p<0.001$) among women lost to follow-up than the non-lost counterpart (AN: 0.2% vs. 0.1%), BN (1.5% vs. 1.0%), EDNOS-P (0.3% vs. 0.1%), and BED (6.4% vs. 5.1%). Use of psychotropics before or during the first trimester was higher among the lost to follow-up women than the non-lost counterpart (before pregnancy: 4.6% vs. 3.9%; $p=0.008$; during the first trimester: 2.7% vs. 2.0%; $p<0.001$), but not during the second trimester. The analysis of attrition bias in relation to women lost to follow-up at six months postpartum showed that women completing Q1 and Q3 but not Q4 had a significantly higher burden of depressive symptoms around gestational week 30 compared to women who did complete Q4 (SCL-8 cut-off point: 10.8% vs. 6.8%, respectively; $p<0.001$), however these groups did not differ in terms of use of psychotropics during the third trimester. Overall, it can be substantiated that study II included the healthier end of the eating disorder and mental health severity spectrum; women who completed Q1, Q3 and Q4 had to be well enough to conceive, participate throughout the pregnancy and even after childbirth.

- Information bias

In studies II and IV information about background sociodemographic and life-style characteristics and pregnancy details could originate from the MBRN or the MoBa study. In the former instance, all information is based on medically confirmed records prospectively collected during prenatal care and at birth, and therefore unlikely to suffer from recall or information bias. On the other hand, information retrieved from the MoBa study was dependent on the accuracy of the women's reporting and recall. In studies II and IV, use of medication during pregnancy (as well as prior to and after pregnancy in study II) and life-style characteristics (i.e., smoking during pregnancy, alcohol consumption) was reported by the study participants and therefore susceptible to recall bias. However, a recent study has validated self-reported tobacco use against nicotine exposure assessed by

plasma cotinine in the MoBa and found that the sensitivity and specificity for self-reported daily smoking (using 30 nmol/l as the cut-off concentration) were 82 and 99%, respectively.[290] Although the validity of maternal reporting of medication use during pregnancy has been shown to be satisfactory for medication used for chronic disorders,[185] or for vitamin supplements specifically in the MoBa study,[291,292] a combination of maternal report with pharmacy records or prescription claims, can be considered a better method to ascertain exposure to medication during pregnancy.[186] In most MoBa questionnaires (Q1 and Q3) information about medication use was collected prospectively. Use of medications in the period between gestational week 30 and childbirth was the only information collected retrospectively (in Q4), and may therefore be more susceptible to recall bias. However, a recent validation study between the MoBa and the Norwegian Prescription Database has shown that the impact of non-differential misclassification of the exposure (study IV) on risk associations is minimal for SSRIs.[184] Hence, since in both studies II and IV the main focus was on antidepressants and other psychotropics, the impact of recall bias for these groups of medications can assumed to be low.

In order to enhance recall, all questions pertaining to medication use in MoBa Q1-Q4 were indication-oriented. As shown in a previous study,[283] adopting prompts and indication-oriented questions over open-ended questions has the benefit to improve recall and accuracy in reporting use of medication during pregnancy. Yet, given the limited space provided in the MoBa questionnaires for answering questions pertaining to medication use, a potential under-reporting cannot be excluded. Also, in the MoBa questionnaires it was not possible to ascertain the timing of use of each specific medication when multiple drugs were used for the same indication. In this instance, that is when multiple drugs were used and multiple timings checked, we considered the drugs to be used in all time periods. Information about dosage and duration of pharmacotherapy is not completely accurate in the MoBa.

In study IV, information about two outcome measures, vaginal bleeding episodes during early and midpregnancy, were self-reported by the study participants and therefore reliant on women's attitude and accuracy in reporting, recall and not least perception of the bleeding event. This latter factor might have been particularly relevant in the assessment of the amount of blood loss (i.e., trace versus medium or large blood loss). Information about the outcome measure postpartum hemorrhage originated from the MBRN records; although this was medically confirmed information, a correct estimation of blood loss at

birth is difficult to achieve, and this might have led to a non-differential misclassification of the outcome in study IV. Although records in the MBRN have been shown to be valid for some specific maternal chronic disorders, other conditions or diagnosis at birth seem to be not optimally reported.[293,294]

- Reliability and validity of collected data

Validated psychometric instruments were utilized to measure symptoms of depression and anxiety during pregnancy (studies II and IV) and postpartum (study II), namely the short versions of the SCL-25: SCL-5 and SCL-8.[200,201] These scales significantly correlated with the SCL-25, which is considered a reliable screening instrument for depression and anxiety as defined by the ICD-10.[202] The SCL-5 was estimated to correlate at r=0.92 with the total score from the original instrument, whereas the SCL-8 correlated at r=0.94 with the original total score. The alpha reliability was estimated at 0.85 for the SCL-5 and 0.88 for the SCL-8.[201,203] Strand *et al.*[200] reported sensitivity and specificity for SCL-5 at 82% and 96% with a cut-off of 2.00. The SCL-8 does not include somatic questions from the original scale, due to the special situation of pregnant woman and mothers of infants with regard to lack of sleep and fatigue.

- Sample size and statistical considerations

In study II, the AN and EDNOS-P groups were small, thus limiting the statistical power of several analyses. In study IV there was enough power (80%) for the SSRI/SNRI group to detect a moderately increased risk of bleeding complications during pregnancy and postpartum, however the study was underpowered for the TCA/OAD group and for the individual antidepressants. Also, low power impeded specific analyses based on severity of postpartum hemorrhage. Since bleeding complications are common in pregnancy, an alternative statistical method could have been applied in order to determine RR estimates rather than OR estimates.[295]

In study IV, several statistical tests were performed with a 95% CI; hence, it cannot be excluded that in one out of 20 tests the statistical significance was due to chance rather than to a true association. In order to limit this risk, a more conservative approach was undertaken in study II by adopting a 99% CI.

In study II, utilization of DAGs permitted a proper selection of confounding factors for the multivariate models, thus diminishing the risk of over-adjustment. In paper IV, adjustment for confounding factors was made according to the statistical or clinical relevance of the candidate confounding variables. The variables measuring maternal underlying depressive symptomatology (SCL-5 and SCL-8) were used as continuous variables in the adjusted analyses in both studies II and IV since they are indicators of severity. Other variables such as maternal age and BMI at conception were used as continuous variables in study II, but as categorical variables in study IV. It cannot be excluded this categorization of variables might have caused residual confounding. In both studies, the presence of unmeasured factors confounding the associations investigated cannot be ruled out.

6. Clinical implications and future research

Several of the findings of this thesis have important clinical implications in the setting of obstetrics, psychiatry, primary care and pharmacy care, but they also address knowledge gaps that limit informed clinical decisions on medication use in pregnancy. Awareness that eight out ten women are exposed to at least one medication during pregnancy, and that five out of ten women may inadvertently or not be exposed to medication during the most sensitive period for fetal organogenesis has important clinical implications. Indeed, a large proportion of pregnant women will be in need of tailored evidence-based information about the fetal risk of medication exposures during pregnancy. Efforts should be made to disseminate the available evidence-based information among healthcare providers and make it easily accessible. Strategies should also be put in place in order to promptly translate repeated findings of well-designed studies into prescribing and clinical guidelines. For several disorders, there are no guidelines about pharmacotherapy in pregnancy, and in some instances, they are not conclusive, leaving clinicians with the dilemma as to whether medicate or not women with important illnesses during pregnancy, and balance on their own experience the benefit-risk ratio of pharmacotherapy versus maternal untreated disorder.

An important step forward is the newly published amendment by the FDA entitled '*Pregnancy and Lactation Labelling Final Rule*', which overcomes the obsolete and simplistic pregnancy risk category letter system (i.e., A, B, C, D and X).[296] The new labeling scheme will go into effect in June 2015 and will only affect prescription and

biological drugs, not OTCs. The pregnancy risk categories in letter format will be removed from the Physician Labeling Rule and substituted by information stemming from pregnancy exposure registries about dosing and fetal risks, whenever such information does exist for the medication in question.[296] The purpose of the labeling revision is to provide physicians with updated and technical information about medications in pregnancy in order to identify the safest treatment options, and thereby tailor adequate counselling to pregnant women needing pharmacotherapy in pregnancy. Future studies should definitely evaluate the impact of the FDA labeling revision in the clinical and prescribing practice. It would be interesting to explore whether the new labeling will be able to attenuate the elevated perceived risk of medication exposure among healthcare professionals and thereafter among pregnant women's, and whether it will positively contribute to informed clinical decisions on medication use in pregnancy.

Our findings about the maternal characteristics positively associated with use of the various types of medication in pregnancy, including OTC drugs, may facilitate identification in clinical settings of those women more likely to need information about medication use during pregnancy. In this specific context, the role of community pharmacists is indeed of value. Pharmacists are accessible healthcare providers who have the unique opportunity to counsel pregnant women about preconception care,[297] but also about the teratogenic risk of exposure to OTC medications and optimal management of chronic disorders during pregnancy. Results of a systematic review[298] has unfortunately shown that to date, pharmacists do not actively engage in dispensing teratology information to pregnant women, but they rather refer this population group to their physicians. Hence, adequate professional training and dissemination of more evidence-based information in this field is needed in order to empower the pharmacist's role in the setting of obstetrics.

Yet, evidence about the fetal risk of medication exposures during pregnancy is not always available. To date, few medications have been shown to be major teratogens in human pregnancies, however the risk of minor teratogenicity or of more subtle effects on fetal development still have to be determined for most medication.[13] Thus, in many cases clinicians cannot provide their pregnant patients with clear-cut answers regarding teratogenicity and other adverse pregnancy outcomes, but the decision whether to medicate or not pregnant women is rather based on the severity of the disease in question and on individual risk-benefit evaluations. Well-designed studies with adequate statistical power

are needed to determine the effects of medications on major and minor teratogenicity, but also in relation to other perinatal outcomes (e.g., stillbirth, prematurity, low birth weight) and long-term neurodevelopmental outcomes (e.g., psychomotor, behavioral, cognitive, and language development). Given the vast array of medications used by pregnant women in the different countries and the different burden of the various disorders in pregnant as well as childbearing women, setting research priorities in medication safety in pregnancy is surely challenging; however, the role of severity of the maternal disorders and the potential consequence of no pharmacotherapy for maternal-fetal health may indeed facilitate this decisional process.[299]

Pregnancy may represent an important time window for recognition of potential psychiatric symptomatology such as depression and eating disorders, establishment of their treatment, and not least tailored interventions by healthcare professionals to ensure that needed medications are taken as prescribed. Unfortunately to date, many women with current psychiatric disorder are neither identified nor treated in the pregnancy and postpartum periods.[300] Our findings about the maternal characteristics positively associated with use of psychotropics during pregnancy but also with no use of medications despite the presence of a psychiatric disorder, may assist clinicians in identifying these women and also in tailoring evidence-based counseling about the effect of pharmacotherapy versus that of undertreated maternal psychiatric illness in pregnancy.[104,105,133,134,137,138] This may be of particular relevance in the context of pharmacotherapy discontinuation at conception.

Our findings about the high burden of psychiatric comorbidity, the extensive use of psychotropics in the time around pregnancy, and not least the direct association between specific eating disorders and (incident) use of psychotropics during pregnancy and postpartum deserve attention. Clinicians are encouraged to query female patients about their medication-taking behavior and provide evidence-based counseling about the risk of medication exposure versus the risk of untreated psychiatric illness during pregnancy and postpartum. To date very little is known about the distinct effects of treated versus untreated eating disorders on perinatal outcomes;[110,111] however the detrimental impact of untreated maternal depression, which is highly comorbid with eating disorders, on maternal-fetal health has been documented.[104,105] Future research should attempt to establish whether pharmacotherapy with psychotropics during pregnancy among women with eating disorders may be of benefit in reducing the risk of a relapse of the disorder

itself as well as of depression in the postpartum period, but also in reducing the risk of specific perinatal and long-term neurodevelopmental outcomes.[54] Efforts should be made to not let women with eating disorders or other psychiatric disorders go unrecognized during pregnancy.

Awareness of the high burden of low adherence to psychotropics during pregnancy and that the most severely depressed women are at greater risk of non-adherence may assist clinicians when following-up pregnant patients with psychiatric disorders. Understanding women's beliefs about their psychotropic medications and the perceived risk of antidepressant exposure may assist clinicians in identifying women who are most likely to demonstrate low adherence. Also, since pregnant women overestimate the risk of the medications they take and recall negative information far more often than reassuring information,[7,35] proper risk communication and information framing may represent effective tools in attenuating women's negative beliefs and perceptions, thereby heightening medication adherence during pregnancy.[6,301] Future research should test whether interventions proven to be effective in improving antidepressant adherence in the general population would be so also in the pregnant population.[50] There is also the need to objectively measure adherence to psychotropic medication in pregnancy (i.e., via the plasma concentration of the drug in question) and to estimate the effect of poor medication adherence on important clinical outcomes, namely relapse of the psychiatric disorder at different times during gestation and/or in the postpartum period. Not least, researcher should attempt to develop a feasible and reliable medication adherence scale suited to pregnant women; this scale should be able to measure intentional and unintentional barriers to medication adherence, but also women's hesitancy to follow the prescribed regimen because of fear of teratogenicity.

Although our findings about the risk of vaginal bleeding after gestational exposure to antidepressants were reassuring, they need to be corroborated by future studies. Focus should also be given to the role of not medicated depression in relation to bleeding complications during gestation, and test whether vaginal bleeding may simply represent an intermediate on the path from depression to premature delivery. The controversial findings about the risk of postpartum hemorrhage associated with antidepressants should be settled by further studies. It would be particularly interesting to explore the relationship between bleeding complications postpartum and the maternal plasma concentrations of

antidepressants at the beginning of labor, or even the concentration of these drugs in umbilical cord blood samples.

So far very little research has been done in relation to maternal safety after exposure to antidepressant during gestation. For instance, it is still not elucidated whether use of these medications during pregnancy may increase the risk of cardiovascular disorders such as preeclampsia or gestational hypertension,[145,147,148,150] and for other conditions (e.g. gestational diabetes, weight gain) the literature is very scarce. It is also worth mentioning that to date, there is no evidence about the benefit and effectiveness of pharmacological treatment of depression or eating disorders during pregnancy.[302] No randomized comparative study has evaluated the effectiveness of evidence-based psychiatric treatments during pregnancy, and few observational studies have assessed maternal benefit outcomes of SSRI treatment during pregnancy versus no treatment.[181,303] On top of this, sound research data are needed to understand how pregnancy alters the pharmacokinetics and pharmacodynamics of antidepressants and therefore guide required dose adjustments during pregnancy.[304]

At present, the study size and data availability in the Multinational Medication Use in Pregnancy Study give the opportunity to assess on a multinational level the fetal risk of those medications - on individual substance level - most commonly used by the pregnant population during the first trimester of pregnancy, and add to the current literature so far restricted to individual country level.[26,43] These data material will also consent to explore medication adherence during pregnancy for treatment of other important chronic conditions such as asthma and hypothyroidism. The amount of data available in the MoBa study, along with the possibility to link such data with population-based registries such as the MBRN, the Norwegian Prescription Database and the Norwegian Patient Registry, offer an unique possibility to study the effects of numerous medications on immediate perinatal outcomes and on long-term neurodevelopmental outcomes in children until the age of 8 years. The availability of biological material in the MoBa offers the exceptional possibility to rely on maternal drug concentrations as exposure variable and therefore increase the exposure reliability, but also to explore whether specific perinatal and long-term neurodevelopmental outcomes are associated with epigenetic changes acted by drug exposures during fetal life. Integration of biology and pregnancy-related epidemiology is indeed an important step forward in research, which will probably have an important impact on public health and prevention. Similarly, application of new statistical

methodologies in the field of epidemiology and pregnancy-related research will enable researchers to overcome, at least in those instances where the study design allows doing so, the mere concept of associations and infer causality.

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Medication use in pregnancy: a cross-sectional, multinational web-based study

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ABSTRACT

Objectives: Intercountry comparability between studies on medication use in pregnancy is difficult due to dissimilarities in study design and methodology. This study aimed to examine patterns and factors associated with medications use in pregnancy from a multinational perspective, with emphasis on type of medication utilised and indication for use.

Design: Cross-sectional, web-based study performed within the period from 1 October 2011 to 29 February 2012. Uniform collection of drug utilisation data was performed via an anonymous online questionnaire.

Setting: Multinational study in Europe (Western, Northern and Eastern), North and South America and Australia.

Participants: Pregnant women and new mothers with children less than 1 year of age.

Primary and secondary outcome measures: Prevalence of and factors associated with medication use for acute/short-term illnesses, chronic/long-term disorders and over-the-counter (OTC) medication use.

Results: The study population included 9459 women, of which 81.2% reported use of at least one medication (prescribed or OTC) during pregnancy. Overall, OTC medication use occurred in 66.9% of the pregnancies, whereas 68.4% and 17% of women reported use of at least one medication for treatment of acute/short-term illnesses and chronic/long-term disorders, respectively. The extent of self-reported medicated illnesses and types of medication used by indication varied across regions, especially in relation to urinary tract infections, depression or OTC nasal sprays. Women with higher age or lower educational level, housewives or women with an unplanned pregnancy were those most often reporting use of medication for chronic/long-term disorders. Immigrant women in Western (adjusted OR (aOR): 0.55, 95% CI 0.34 to 0.87) and Northern Europe (aOR: 0.50, 95% CI 0.31 to 0.83) were less likely to report use of medication for chronic/long-term disorders during pregnancy than non-immigrants.

Conclusions: In this study, the majority of women in Europe, North America, South America and Australia used at least one medication during pregnancy. There was a substantial inter-region variability in the types of medication used.

Strengths and limitations of this study

- Uniform data collection of drug utilisation data across all participating countries allows for intercountry comparability of the prevalence of medication use during pregnancy, up to now impeded by differences in study design and methodology.
- The study adds a multinational perspective on over-the-counter medication use during pregnancy to the limited number of studies quantifying the extent of self-medication during pregnancy.
- Lack of validity of the self-reported diagnoses is a limitation since all disorders and related medication use were self-reported by the study participants.
- A web-based survey as a study method impedes calculation of a conventional response rate and may cause selection bias of the target population.

INTRODUCTION

Ethical reasons preclude inclusion of pregnant women in the vast majority of premarketing clinical trials.[1] As a consequence, most medications are placed onto the market without a directly established safety profile in human pregnancy.[2] So far, few medications have been shown to be major teratogens, yet the risk of minor teratogenicity or of more subtle effects on fetal development still have to be determined for most of them.[3] Despite this, medication use during pregnancy is common. Mitchell *et al*[4] found that use of medications, either prescribed or purchased over the counter (OTC), occurred in 88.8% of all pregnancies in the USA. In Europe, prevalence estimates of prescribed medication use vary considerably across countries, ranging from 26% in Serbia to 93% in France.[5–10] Such intercountry variability could, at least in part, be caused by

differences in study design, methodology and exposure ascertainment across studies.[11] Uniform collection of drug utilisation data during pregnancy between countries may overcome such drawbacks, allowing for intercountry comparability of prevalence estimates and shedding light on differences in prenatal care in the various countries.

Prior studies have addressed research priorities in this area such as presenting results on an individual drug level according to the indication of use, quantifying the extent of OTC and prescribed medication use during pregnancy, and taking into account intercountry comparability.[4] Only a few studies have individually examined maternal factors associated with specific types of medication use during pregnancy.[11–14]

The objectives of the current study were to examine patterns of medication use in pregnancy from a multinational perspective, with special emphasis on type of medication utilised, including OTC medications and self-reported indications for use, and to identify maternal background factors potentially associated with medication use for acute/short-term illnesses, medication use for chronic/long-term disorders and OTC medication use during pregnancy.

METHODS

Study design and data collection

This is a multinational, cross-sectional, web-based study. Pregnant women at any gestational week and mothers with children less than 1 year of age were eligible to participate. Member countries of the European Network of Teratology Information Services (ENTIS), the Organization of Teratology Information Specialists (OTIS) in North America, MotherSafe in Australia and European institutions conducting public health research were invited to take part in the project. Of these, 18 countries participated (Australia, Austria, Canada, Croatia, Finland, France, Iceland, Italy, the Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, the UK and the USA). Data originating from some South and Central American countries were also collected through OTIS. Owing to the low number of participants on the individual country level, the region of Central America was excluded and countries in South America were aggregated into one region. Data selection to achieve the final study sample was performed as depicted in figure 1. Participants were categorised according to the reported country of residency and grouped into six regions: Western Europe, Northern Europe, Eastern Europe, North America, South America and Australia.

Data were collected through an anonymous online questionnaire administered by Quest Back (http://www.questback.com) and accessible for a period of 2 months in each participating country within the period 1 October 2011 to 29 February 2012. The questionnaire was open to the public via utilisation of banners (invitations to participate in the study) on national websites and/or social networks commonly visited and consulted by pregnant women and/or new mothers. The complete questionnaire is presented in online supplementary appendix 1. Detailed information about recruitment tools utilised and Internet penetration rates are summarised in online supplementary appendix 2.

The questionnaire was first developed in Norwegian and English and then translated into the other relevant languages. A pilot study was carried out in September 2011 (n=47) which elicited no major change to the questionnaire. Collected data were scrutinised for the presence of potential duplicates (based on reported country of residency, sociodemographic characteristics, date and exact time of questionnaire completion) but none were identified.

Exposure variables

Maternal sociodemographics (ie, region of residency, age, educational level, mother tongue, working status at time of conception, previous children, marital status and unplanned pregnancy) and lifestyle characteristics (ie, smoking status before and during pregnancy and alcohol consumption after awareness of pregnancy) constituted the exposure variables. To assess external validity, we compared sociodemographic and lifestyle characteristics of our study population on an individual country level with those of the general birthing population in the same country. Reports of National Statistics Bureaus or previous national studies were utilised for this purpose. The ratio between the number of respondents and the estimated number of live births in the 2-month period was also examined for each country (see online supplementary appendix 3).

Outcome variables

Use of any medication, medication for acute/short-term illnesses, medication for chronic/long-term disorders and OTC medication use during pregnancy constituted the outcome variables. Participants were first confronted with a list of the most common acute/short-term illnesses (ie, nausea, heartburn, constipation, common cold, urinary tract infections (UTIs), other infections, pain in the neck/back/pelvic girdle, headache and sleeping problems) and the most prevalent chronic/long-term disorders (ie, asthma, allergy, hypothyroidism, rheumatic disorders, diabetes, epilepsy, depression, anxiety, cardiovascular disease and other disorders) and asked whether they suffered/had suffered from these conditions during pregnancy. In case of an affirmative response, women were questioned about medication use for each individual indication as a free-text entry. Use of OTC medications was also recorded. Recall was aided with a list of five OTC medication categories: painkillers, nasal spray/drops, antinauseants, antacids and laxatives, along with examples of brand name products of relevance in each country. It was optional to report timing of exposure for each of the medication use questions (the alternatives were gestational weeks 0–12 (1st

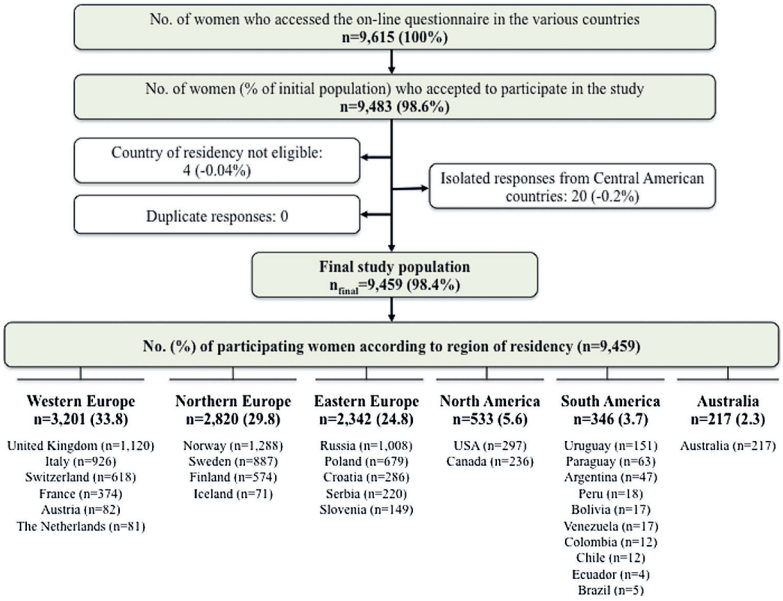

Figure 1 The participant flowchart to achieve the final sample analysed.

trimester), 13–24 (2nd trimester) and 25 to delivery (3rd trimester)).

We defined a medicine as a single product containing one or more active ingredients. We initially identified the main active ingredient(s) and formulation of the reported medicinal products either in the relevant national medicines database or in the 'Martindale' textbook.[15] All recorded medications were coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes at the ATC 5th level (ie, the substance level) whenever possible, otherwise into the 2nd–4th levels as appropriate, in accordance with the WHO ATC index.[16] The OTC status of medications was crosschecked with the prescription policies within each country. Whenever a prescription medication was reported under the OTC question, this record was omitted from the analysis of OTC use but counted in the estimation of total medication use (including prescription and OTC). Iron, mineral supplements, vitamins, herbal remedies and any type of complementary medicine were recorded separately and excluded from the estimation of medication use.

The required sample size calculation for the outcome variables on region and individual country levels is outlined in online supplementary appendix 4. The expected prevalence estimates were set according to the results of previous studies.[5–10 17 18]

Ethics

All participants gave informed consent by answering 'Yes' to the question 'Are you willing to participate in the study?'. All data were handled and stored anonymously.

Statistical analysis

Descriptive statistics were utilised as appropriate. Univariate and multivariate logistic regression analyses were used to examine the association between maternal characteristic and three categorical outcome measures (yes/no): medication use for acute/short-term illnesses; medication use for chronic/long-term disorders; OTC medication use. p Values of <0.05 were considered statistically significant. Data are presented as adjusted ORs (aOR) with 95% CI. The analysed explanatory variables included all maternal sociodemographics and lifestyle characteristics. After fitting the univariate logistic regression model for all explanatory variables, the multivariate model was built and adjusted for all remaining covariates. The Hosmer and Lemeshow[19] test was used to assess goodness of fit of the final multivariate model. Analogue subanalyses on individual region level were performed. In these instances, region of residency was not included in the model. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) V.20.0 (IBM SPSS Statistics).

RESULTS

Population characteristics

A total of 9615 women accessed the online questionnaire, of which 98.6% completed it. The participant flowchart to achieve final study population (n=9459) is depicted in figure 1. A total of 5089 women (53.8%)

were pregnant at the time of completion of the questionnaire, whereas 4370 women (46.2%) had delivered their babies within the previous year. Of the former group, 1095 (21.5%), 1702 (33.4%) and 2291 (45%) women were in the first, second and third trimester of pregnancy, respectively. Of the latter group, 1320 (30.2%), 947 (21.7%) and 2102 (48.1%) had a baby of age ≤16 weeks, 17–28 weeks and ≥29 weeks, respectively. For two women, the time of gestation/baby's age was unknown. Overall, the birthing population in each participating country was reflected quite well by the sample with respect to age, parity and smoking habits (see online supplementary appendix 3). However, there was a difference in terms of educational level; on average, the women in the study had higher education than the general birthing population in each country. In addition, participants in Sweden, Austria, Iceland and Italy were slightly more often primiparous, whereas the responders in Australia, the USA, the Netherlands, Slovenia and Croatia were somewhat older than the general birthing population.

Total medication use

After exclusion of vitamins, mineral supplements and iron, use of at least one medication either prescribed or OTC at any time during pregnancy was reported by 7678 of 9459 women (81.2%). Figure 2 depicts prevalence estimates of total medication use during pregnancy by region and country of residence. The extent of OTC medication use, as well as medication use for acute/short-term illnesses and chronic/long-term disorders, is also outlined. The highest prevalence of total medication use during pregnancy was observed in the Netherlands (95.1%), Iceland (93%) and Finland (92.3%). The overall prevalence estimates of medication use in pregnancy according to timing and drug class (ATC levels 1 and 2) are presented in online supplementary appendix 5. Medications for the nervous system (ATC class N) were most commonly used during pregnancy (57.5%), mostly due to paracetamol (acetaminophen) and its combinations.

A corollary analysis according to pregnancy status showed that pregnant women reported in a significantly lower degree than new mothers any medication use during pregnancy (78.8% vs 84%, p<0.001), as well as OTC medication use (63% vs 71.5%, p<0.001) and medication use for acute/short-term illnesses (66.2% vs 70.9%, p<0.001). In contrast, the difference in medication use for chronic/long-term disorders was not significant (17.4% vs 16.5%, p=0.271). None of the rates differed significantly when women in the third trimester of pregnancy were compared with new mothers.

Medication use according to indication

Headache, heartburn, pain, nausea and UTIs constituted the leading indications for use of medication

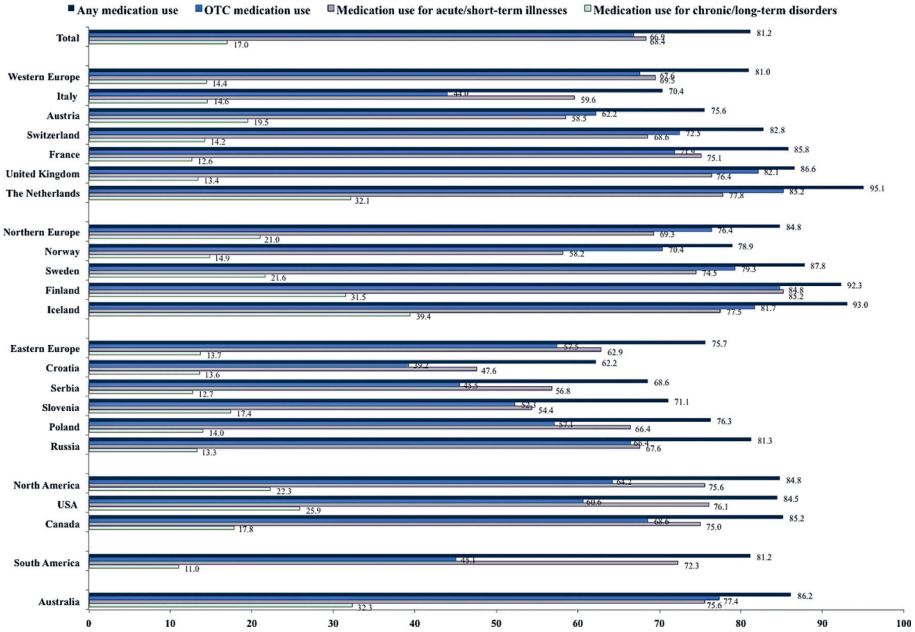

Figure 2 The proportion of respondents (%) reporting use of any medication, over-the-counter (OTC) medication, medication for acute/short-term illnesses and medication for chronic/long-term disorders during pregnancy, according to region and country of residency. The observed estimates do not include vitamins, mineral supplements, iron and herbal or complementary medicine products.

during pregnancy among the acute/short-term illnesses analysed. Hypothyroidism, asthma, allergy and depression were the leading indications for chronic/long-term medication use. Observed prevalence rates of these disorders, overall and by region of residency, are presented in online supplementary appendices 6 and 7, respectively, along with rates of total and specific medication use. Table 1 outlines prevalence estimates of OTC medication use during pregnancy by region and indication for use. Only the most common medication groups reported are presented. Inter-region variations in rates and types of medication used during pregnancy were observed for acute/short-term illnesses (eg, nausea and UTIs), chronic/long-term disorders (eg, asthma and depression) and OTC medications (eg, nasal spray).

Factors associated with medication use

Factors associated with medication use during pregnancy according to type of medication utilised are presented in table 2. Use of chronic/long-term medications during pregnancy was reported in a significantly larger extent by women in Northern Europe (aOR: 1.68, 95% CI 1.46 to 1.94), North America (aOR: 1.80, 95% CI 1.42 to 2.28) and Australia (aOR: 2.76, 95% CI 2.03 to 3.76) compared with women in Western Europe. Older women or housewives, those with low education or with an unplanned pregnancy, were the ones most often reporting use of chronic/long-term medication. Subanalysis on individual region level revealed that women not having the official language of the country of residency as mother tongue were less likely to report chronic/long-term medication use in Western (aOR: 0.55, 95% CI 0.34 to 0.87) and Northern Europe (aOR: 0.50, 95% CI 0.31 to 0.83), but not in the other regions.

DISCUSSION

This is the first web-based study examining patterns and factors associated with medication use during pregnancy on a multinational level. In all regions, approximately 8 of 10 women reported use of at least one medication, either prescribed or OTC, during the course of their pregnancy. This finding is in line with previous research conducted in Europe, North America, South America and Australia,[4 20–25] though our estimates were somewhat higher in some of the Eastern European countries, for example, Serbia, than those observed in a previous study.[5] Different recruitment strategies, that is, web based in our study versus maternity care unit/community pharmacy based in the previous study could explain such discrepancy.

Overall, analgesics, antacids, nasal decongestants/antiallergics and systemic antibiotics were the medication groups dominating the drug utilisation scenario, as also shown by previous research.[4 20–22] However, our study also provides insights into the proportion of medicated women among those suffering from a specific illness during pregnancy across the six regions. We found that approximately 7 of 10 women who reported UTIs were treated with antibiotics during pregnancy. This related to all regions, except Eastern Europe where it was only 4 of 10 women. Since women may perceive dysuria without ascertainment of bacteriuria in the urine as UTI, an over-reporting of the illness could have occurred. Yet, a suboptimal treatment of UTIs during pregnancy in Eastern Europe cannot be ruled out. The intercountry variability in the types of antibiotics used for UTIs could simply be explained by differences in prescribing practice,[26] presence of screening for bacteriuria in early pregnancy or specific antibiotic resistance patterns.

Even though nausea was the condition affecting most women in all six regions, the corresponding proportions of medicated nausea were generally low. This scenario is probably due to two main factors: (1) the predominantly mild character of nausea and the possibility of non-pharmacological management (eg, dietary advices) and (2) the reluctance of general practitioners to prescribe antinauseants even though safety profile assessments are in place.[27 28] As also shown in previous studies,[4 29] use of serotonin antagonists during pregnancy in North America and Australia is increasing compared with the other regions, eliciting the need of sound studies assessing the safety profile of this drug group in pregnancy.

In most regions, the self-reported prevalence of hypothyroidism was somewhat higher than the reported hormone substitution rate. Owing to its known association with adverse pregnancy outcomes,[30] the unexpected finding of potential suboptimal treatment of hypothyroidism during pregnancy deserves attention. It could probably be due to lack of information about hypothyroidism typology and its diagnostic ascertainment in our study.

In our study, depression was self-reported and not based on any psychometric assessment, thus the observed substantial inter-regional variability in the extent of this disorder and related medication use could have certainly been affected by women's attitudes in reporting. Our estimate of medication use for depression in Australia was higher than that observed in a recent study (10.6% vs 2.1%).[31] However, the similarity in self-reported depression itself (11.5% vs 15.6%) suggests that our population might mostly comprise women who did not discontinue their pharmacological therapy once they became pregnant. Our estimates for North America and Western Europe were in line with recent literature showing an increase in antidepressant use in pregnancy during the past years.[4 32] Selective serotonin reuptake inhibitors (SSRIs) were the most widely used antidepressant class. Recent meta-analyses have shown that antidepressants, including SSRIs, do increase the risk of poor neonatal adaptation syndrome, specific cardiovascular malformations and persistent pulmonary hypertension of the newborn.[33–35] However, the clinical impact of the latter two outcomes, in absolute terms, is small and the risk of pharmacotherapy should always be

Table 1 Use of OTC medication at any time during pregnancy by ATC level, indication for use and region (n=9459)*†

OTC medication use, overall and by drug groups	REGION						
	Western Europe n=3201 n (%)	Northern Europe n=2820 n (%)	Eastern Europe n=2342 n (%)	North America n=533 n (%)	South America n=346 n (%)	Australia n=217 n (%)	Total n=9459 n (%)
OTC painkillers, total	*1714 (53.5)*	*1773 (62.9)*	*734 (31.3)*	*284 (53.3)*	*127 (36.7)*	*151 (69.9)*	*4783 (50.6)*
By drug group							
Paracetamol (including combinations) (N02BE)	1655 (51.7)	1735 (61.5)	630 (26.9)	263 (49.3)	87 (25.1)	146 (67.3)	4516 (47.7)
Non-steroidal anti-inflammatory drugs (M01A)	70 (2.2)	182 (6.5)	68 (2.9)	40 (7.5)	59 (17.1)	7 (3.2)	426 (4.5)
Acetylsalicylic acid (including combinations) (N02BA)	7 (0.2)	11 (0.4)	32 (1.4)	2 (0.4)	2 (0.6)	1 (0.5)	55 (0.6)
Metamizole (N02BB02)	–	6 (0.2)	31 (1.3)	1 (0.2)	12 (3.5)	–	50 (0.5)
OTC antacids, total	*1011 (31.6)*	*883 (31.3)*	*583 (24.9)*	*129 (24.2)*	*48 (13.9)*	*76 (35.0)*	*2730 (28.9)*
By drug group							
Antacids (aluminium, salts combinations, antiflatulents)	472 (14.7)	550 (19.5)	508 (21.7)	47 (8.8)	36 (10.4)	54 (24.9)	1667 (17.6)
Alginic acid complex/sucralfate/bismuth (A02BX)	606 (18.9)	421 (14.9)	87 (3.7)	4 (0.8)	1 (0.3)	17 (7.8)	1136 (12.0)
H_2 receptor antagonists (A02BA)	20 (0.6)	20 (0.7)	16 (0.7)	57 (10.1)	10 (2.9)	17 (7.8)	137 (1.4)
Antacids with calcium (A02AC)	23 (0.7)	12 (0.4)	10 (0.4)	69 (12.9)	2 (0.6)	10 (4.6)	126 (1.3)
Proton pump inhibitors (A02BC)	38 (1.2)	52 (1.8)	–	10 (1.9)	2 (0.6)	5 (0.3)	107 (1.1)
OTC nasal sprays/drops, total	*272 (8.5)*	*742 (26.3)*	*451 (19.3)*	*35 (6.6)*	*7 (2.0)*	*14 (6.5)*	*1521 (16.1)*
By drug group							
Sympathomimetic nasal decongestants (R01AA/R01BB)	204 (6.4)	683 (24.2)	365 (15.6)	20 (3.8)	3 (0.9)	4 (1.8)	1279 (13.5)
Nasal corticosteroids (R01AD)	31 (1.0)	49 (1.7)	12 (0.5)	5 (0.9)	2 (0.6)	10 (4.6)	109 (1.2)
Nasal immunostimulants (low-dose interferon) (L03A)	–	–	28 (1.2)	–	–	–	28 (0.3)
OTC laxatives, total	*240 (7.5)*	*227 (8.0)*	*237 (10.1)*	*50 (9.4)*	*8 (2.3)*	*19 (8.8)*	*781 (8.3)*
By drug group							
Osmotically acting laxatives (A06AD)	159 (5.0)	171 (6.1)	197 (8.4)	2 (0.4)	2 (0.6)	8 (3.7)	539 (5.7)
Contact laxatives (A06AB)	28 (0.9)	44 (1.6)	18 (0.8)	7 (1.3)	6 (1.7)	2 (0.9)	105 (1.1)
Enemas (A06AG)	3 (0.1)	25 (0.9)	34 (1.5)	4 (0.8)	–	2 (0.9)	68 (0.7)
Softeners, emollients (A06AA)	8 (0.2)	–	–	38 (7.1)	–	6 (2.8)	52 (0.5)
OTC antinauseants, total	*263 (8.2)*	*273 (9.7)*	*41 (1.8)*	*60 (11.3)*	*28 (8.1)*	*40 (18.4)*	*705 (7.5)*
By drug group							
First generation antihistamines (R06A)	141 (4.4)	256 (9.1)	7 (1.5)	55 (10.3)	5 (1.4)	5 (2.3)	469 (5.0)
Metoclopramide/domperidone/bromopride (A03FA)	113 (3.5)	5 (0.2)	18 (0.8)	2 (0.4)	19 (5.5)	27 (12.4)	184 (1.9)
Total OTC medication use	*2163 (67.6)*	*2155 (76.4)*	*1347 (57.5)*	*342 (64.2)*	*156 (45.1)*	*168 (77.4)*	*6331 (66.9)*

*Countries are grouped into regions as shown in figure 1.
†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron and herbal or complementary medicine products.
Total use estimates of the main OTC categories are presented in italics.
ATC, Anatomical Therapeutic Chemical; OTC, over-the-counter medications.

Table 2 Factors associated with medication use in pregnancy (n=9459)*

	Medication use					
	For acute/short-term illnesses (n=6469)		For chronic/long-term disorders (n=1604)		OTC (n=6331)	
	n (%)	aOR (95% CI)	n (%)	aOR (95% CI)	n (%)	aOR (95% CI)
Region of residency†						
Western Europe	2224 (69.5)	Reference	462 (14.4)	Reference	2163 (67.6)	Reference
Northern Europe	1954 (69.3)	0.96 (0.86 to 1.08)	593 (21.0)	*1.68 (1.46 to 1.94)*	2155 (76.4)	*1.54 (1.36 to 1.74)*
Eastern Europe	1474 (62.9)	*0.69 (0.61 to 0.78)*	322 (13.7)	1.03 (0.87 to 1.21)	1347 (57.5)	*0.60 (0.53 to 0.67)*
North America	403 (75.6)	*1.28 (1.03 to 1.60)*	119 (22.3)	*1.80 (1.42 to 2.28)*	342 (64.2)	*0.81 (0.66 to 0.99)*
South America	250 (82.3)	1.03 (0.79 to 1.34)	38 (11.0)	0.70 (0.48 to 1.01)	156 (45.1)	*0.34 (0.27 to 0.44)*
Australia	164 (75.6)	1.29 (0.93 to 1.79)	70 (32.3)	*2.76 (2.03 to 3.76)*	168 (77.4)	*1.57 (1.12 to 2.20)*
Maternal age (years)						
≤20	232 (70.5)	1.22 (0.93 to 1.60)	761 (14.7)	*0.58 (0.39 to 0.87)*	205 (62.3)	1.05 (0.81 to 1.36)
21–30	3531 (68.2)	Reference	33 (10.0)	Reference	3461 (66.8)	Reference
31–40	2576 (68.6)	0.90 (0.82 to 1.00)	764 (20.4)	*1.44 (1.27 to 1.63)*	2531 (67.4)	*0.85 (0.77 to 0.94)*
≥41	130 (66.3)	0.73 (0.54 to 1.00)	46 (23.5)	*1.61 (1.13 to 2.29)*	134 (68.4)	0.86 (0.62 to 1.19)
Previous children						
No	3082 (65.5)	Reference	735 (15.6)	Reference	2949 (62.6)	Reference
Yes	3387 (71.3)	*1.34 (1.22 to 1.47)*	869 (18.3)	1.08 (0.96 to 1.21)	3382 (71.2)	*1.58 (1.44 to 1.74)*
Marital status						
Married/cohabiting	6066 (68.5)	Reference	1503 (17.0)	Reference	5960 (67.3)	Reference
Single/divorced/others	403 (66.3)	0.91 (0.75 to 1.10)	101 (16.6)	1.06 (0.83 to 1.35)	371 (61.0)	0.91 (0.75 to 1.10)
Working status						
Employed, but not as HCP	3737 (66.8)	Reference	905 (16.2)	Reference	3667 (65.6)	Reference
HCP	934 (74.4)	*1.41 (1.23 to 1.63)*	240 (19.1)	1.13 (0.96 to 1.33)	944 (75.2)	*1.42 (1.23 to 1.64)*
Student	592 (69.1)	1.11 (0.94 to 1.31)	128 (14.9)	1.04 (0.84 to 1.30)	578 (67.4)	1.10 (0.93 to 1.30)
Housewife	608 (72.6)	1.14 (0.96 to 1.35)	170 (20.3)	*1.34 (1.10 to 1.63)*	577 (68.9)	1.05 (0.88 to 1.24)
Job seeker	281 (66.0)	0.96 (0.78 to 1.20)	66 (15.5)	1.03 (0.78 to 1.36)	258 (60.6)	0.85 (0.68 to 1.05)
Other than above	311 (65.2)	0.91 (0.75 to 1.12)	94 (19.7)	*1.29 (1.01 to 1.65)*	302 (63.3)	0.91 (0.74 to 1.12)
Educational level						
Less than high school	331 (72.7)	1.17 (0.93 to 1.49)	92 (20.2)	*1.51 (1.15 to 1.97)*	317 (69.7)	*1.32 (1.04 to 1.67)*
High school	1864 (68.7)	Reference	428 (15.8)	Reference	1779 (65.6)	Reference
More than high school	3574 (68.4)	0.99 (0.89 to 1.11)	916 (17.5)	1.04 (0.91 to 1.20)	3489 (66.8)	1.07 (0.96 to 1.19)
Others, unspecified	700 (65.7)	0.82 (0.70 to 0.96)	168 (15.8)	0.94 (0.77 to 1.16)	746 (70.0)	1.13 (0.97 to 1.33)
Alcohol use after awareness of pregnancy						
No	5270 (67.1)	Reference	1322 (16.8)	Reference	5133 (65.3)	Reference
Yes	1144 (75.7)	*1.59 (1.39 to 1.81)*	270 (17.9)	1.11 (0.95 to 1.29)	1150 (76.1)	*1.95 (1.71 to 2.23)*
Smoking during pregnancy						
No	5835 (68.5)	Reference	1441 (16.9)	Reference	5716 (67.0)	Reference
Yes, but less than before pregnancy	530 (69.0)	1.08 (0.91 to 1.27)	130 (16.9)	1.01 (0.82 to 1.25)	511 (66.5)	1.06 (0.90 to 1.26)
Yes, the same or more than before pregnancy	88 (67.7)	0.95 (0.64 to 1.40)	28 (21.5)	1.19 (0.74 to 1.90)	89 (68.5)	1.21 (0.81 to 1.82)

Continued

Table 2 Continued

	Medication use					
	For acute/short-term illnesses (n=6469)		For chronic/long-term disorders (n=1604)		OTC (n=6331)	
	n (%)	aOR (95% CI)	n (%)	aOR (95% CI)	n (%)	aOR (95% CI)
Planned pregnancy						
Yes	5836 (68.4)	Reference	1427 (16.7)	Reference	5727 (67.2)	Reference
No	616 (68.4)	0.96 (0.82 to 1.12)	173 (19.2)	*1.29 (1.06 to 1.56)*	587 (65.1)	1.00 (0.85 to 1.17)
First language different from the official main language in the country of residency						
No	6089 (68.5)	Reference	1530 (17.2)	Reference	5972 (67.1)	Reference
Yes	363 (67.2)	0.93 (0.76 to 1.12)	71 (13.1)	*0.66 (0.50 to 0.86)*	347 (64.3)	0.89 (0.74 to 1.08)

*Numbers may not add up due to missing values. Missing values are less than 5% of the total. Mineral supplements, vitamins, iron, herbal or complementary medicine products are not included in the medication use estimates.
†Countries are grouped into regions as shown in figure 1.
Statistically significant results (ie, p values <0.05) are presented in italics.
aOR, adjusted OR; HCP, healthcare provider; OTC, over-the-counter medications.

weighted versus the risk of undertreated depression in pregnancy.

In most regions, approximately 60–70% of women reported use of at least one OTC medication during the course of their pregnancies, mostly for pain conditions, heartburn and upper airways disorders, indicating a substantially high rate of self-medication during pregnancy. This estimate aligns with previous research carried out in North America.[17] Of note, self-medication with OTC sympathomimetic nasal decongestants was more extensive in Northern and Eastern Europe than in the remaining regions; this could be explained by the time of the year when the data collection was performed.

Region of residency was an important factor associated with medication use during pregnancy. As also shown by Cleary *et al*,[36] we found that rates of medication use among women originally from Eastern Europe and South America were significantly lower than those observed in Western Europe, North America and Australia. Such geographical differences could be due to culture, variations in prenatal care assistance or access to medications in the various regions and the related costs.

Women working as healthcare providers, consuming alcohol during pregnancy or those already having children were more likely to use short-term and OTC medications, possibly reflecting higher confidence in self-treatment and use of medications in general in the former instance, and less anxiety for the pregnancy outcome in the latter two instances.

Contrary to previous studies indicating an association between higher maternal education and more prevalent use of medication during pregnancy,[14 17 23] we found that lower education was associated with a higher use of OTC medications as well as medication for chronic/long-term disorders (30–50% increased risk). Results of similar magnitude (30% increased risk) were also observed by Olesen *et al*,[37] whereas Stokholm *et al*[38] identified a stronger association (2.3-fold increased risk) between low maternal education and use of antibiotic for respiratory tract infections during pregnancy. One factor negatively associated with chronic/long-term medication use was not having the official language of the country of residency as mother tongue. This tendency was detected in Western and Northern Europe, raising concerns about the potential health risks for immigrant women in these two regions. As shown by Hämeen-Anttila *et al*,[39] 57% of pregnant women have perceived information needs about medications during pregnancy. Thus, identification of potential users or non-users of medication during pregnancy might be of clinical relevance. Indeed, this may allow tailored evidence-based information about medication safety or outcome of suboptimal medication of severe medical conditions in pregnancy.

Strengths and limitations

The main strength is that data collection was performed uniformly across all participating countries, allowing for

intercountry comparison of the prevalence of medication use during pregnancy. By quantifying the extent of self-medication with OTC drugs and medication use according to self-reported indication, it was possible to determine the leading causes for medication use among pregnant women. Categorisation of maternal characteristics positively associated with the various types of medications used during pregnancy enabled us to identify which groups of women are more likely to need information about medication use during pregnancy. The utilisation of an anonymous web-based questionnaire enabled us to reach a large proportion of the birthing population in several countries worldwide. However, we cannot exclude the possibility that the women who decided to participate in the study differed from the general birthing population in other ways that our analysis could not control for. In most of the participating countries, the study sample was large enough to warrant calculation of prevalence estimates with a precision of 5%. However, less precise estimates were permitted by the study sample in Austria, Iceland and the Netherlands (precision of 9–11%), as well as in Australia, Canada, Croatia, Serbia, Slovenia and the USA (precision of 6–7%).

One main limitation of the study is the lack of validity of the self-reported diagnoses. All disorders were self-reported by the participants, and hence dependent on the women's perception of the medical condition. Similarly, information about medication use during pregnancy was dependent on the accuracy of the women's reporting and recall. For new mothers, data were registered retrospectively; hence a risk of recall bias cannot be ruled out. In specific countries (Australia, Canada, France, Russia, the Netherlands and the USA), the study sample was a small proportion of the general birthing population; hence the generalisability of our findings for these specific countries should be interpreted with caution.

The questionnaire was only available through Internet websites; by using this kind of approach, a conventional response rate cannot be calculated and a selection bias of the target population cannot be ruled out. However, recent epidemiological studies indicate reasonable validity of web-based recruitment methods.[40 41] Also, the penetration rate of the Internet either in households or at work is relatively high among women in childbearing age.[42–46] Hence, the degree to which our findings can be extrapolated to the target population is based on the representativeness of the respondents to the general birthing populations in each country. The sample in each country had a somewhat higher educational level than the general birthing populations. Such a limitation might have led to an underestimation of the prevalence of medication during pregnancy. Since many ailments requiring pharmacotherapy occur in mid or late pregnancy, inclusion of women in the first trimester of pregnancy in the total data material has somewhat inflated the prevalence of non-users of medications during pregnancy. Also, women with specific disorders or in need of information about medication use during pregnancy might have been more likely to consult Internet websites, and therefore participate in this study.

CONCLUSIONS

Use of medications for acute/short-term illnesses and chronic/long-term disorders, as well as use of OTC medications, was common during pregnancy. The extent of medicated illnesses and types of medications used for the different indications varied across the six regions. This was especially relevant not only for acute/short-term illnesses such as nausea and UTIs, but also for chronic/long-term disorders such as hypothyroidism or depression. Women with higher age or lower educational level, housewives or women with an unplanned pregnancy were those most often reporting chronic/long-term medication use, as opposed to immigrants residing in Western and Northern Europe who reported the least use of this medication category. Future research should definitely focus on this specific group of women and also address more insights into the outcome of suboptimal medication for severe conditions in pregnancy.

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Appendix 1: Survey questionnaire

Internet questionnaire

Medication use in pregnancy with focus on attitudes, perception of risk and mental health

The Multinational Medication Use in Pregnancy Study

INFORMATION ABOUT YOURSELF

1. In which country do you live? **Country:**_____	**In which region/province do you live?** **Region:** _____
2. Are you pregnant right now? □ Yes	□ No
(If yes in Q2) In which pregnancy week are you? **From 1 to 44** **(If yes in Q2) Is it a multiple pregnancy?** □ No □ Yes (e.g. twins, triplets, etc)	**(If No in Q2) How old is your newborn child (in weeks)?** **0-4 / 5-8 / 9-12 / 13-16 / 17-20 / 21-24 / 25-28 / > 29** **(If No in Q2) Do you breast feed your child?** □ Yes □ No
3. How many children do you already have from before? □ None □ One □ Two □ More than two	
4. What is your marital status? □ Married □ Cohabitant □ Single □ Divorced/Separated □ Other	
5. What is the highest education you have completed? □ Primary school (8-9 years of education) □ High-school (11-13 years of education) □ University □ Other education	
6. What was your work situation when you became pregnant? □ Student □ Housewife □ Health care personnel, i.e., physician, nurse, or pharmacist □ Employed in another sector □ Job seeker □ None of the above	
7. Is English your mother tongue? □ Yes □ No **(If No in Q7 above) What is your mother tongue**? _____	
8. Your age: Years, from 15 to 55	

INFORMATION ABOUT YOUR PREGNANCY

9. (If pregnant) Are you attending any pregnancy/birth preparation course or similar?

□ Yes
□ No, but I am planning to attend
□ No, I am not going to attend it

10. (If pregnant) What are your thoughts about how the experience of giving birth is going to be?

Please indicate your thoughts in a scale from 1 to 6, where **1 corresponds to absolutely terrible and 6 to absolutely fantastic**

Absolutely terrible	1 □	2 □	3 □	4 □	5 □	6 □	Absolutely fantastic

11. Was your pregnancy planned?

□ Yes
□ No, but it was not completely unexpected
□ No, it was not planned

12. Did you contact any healthcare provider due to infertility?

□ Yes
□ No

(If Yes in Q12 above) Did you, in this pregnancy, become pregnant secondarily to infertility treatment?

□ Yes
□ No

13. Have you taken folic acid? (alone or as part of multivitamins)

□ Yes, before pregnancy
□ Yes, before and during pregnancy
□ Yes, only during pregnancy
□ No
□ cannot remember

14. Did you smoke cigarettes before becoming pregnant?

□ Yes, regularly
□ Yes, occasionally
□ No, never

(If yes in Q14 as regularly/occasionally) Do you/did you smoke during pregnancy?

□ Yes, more than before
□ Yes, approximately the same
□ Yes, but less
□ No

(If yes) How many cigarettes (on average) do you/did you smoke per day?

□ < 1
□ 1-5
□ 6-10
□ > 11

15. Did you drink any alcohol after finding out that you were pregnant?

□ Yes

□ No
□ Cannot remember

(If yes) How much did you drink (in units)?
1 alcohol unit is equivalent to:
one 25ml single measure of whisky (ABV 40%),
or a third of a pint of beer (ABV 5-6%)
or half a standard (175ml) glass of red wine (ABV 12%).

□ More than 1-2 units per week
□ 1-2 units per week
□ 1-4 units per month
□ 1-2 units during the pregnancy
□ Can not remember

HEALTH DISORDERS AND MEDICATIONS DURING PREGNANCY

16. Have you experienced any of the disorders listed below during this pregnancy? If you use or have used any medicines in relation to [each health disorder listed] please enter the names of the medicines. In which weeks of pregnancy have you used them?

Health disorder		Medicine	Period of use (pregnancy weeks)
Nausea	□ Yes □ No	(If Nausea ticked) If you use or have used any medicines in relation to nausea, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Heartburn or reflux problems	□ Yes □ No	(If Heartburn ticked) If you use or have used any medicines in relation to heartburn or reflux problem, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Constipation	□ Yes □ No	(If Constipation ticked) If you use or have used any medicines in relation to constipation, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Common cold	□ Yes □ No	(If common cold ticked If you use or have used any medicines in relation to common cold, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Urinary tract infections	□ Yes □ No	(If UTI ticked) If you use or have used any medicines in relation to urinary tract infections, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Other infections	□ Yes □ No	(If other infections ticked) If you use or have used any medicines in relation to other infections, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Pain in neck or back or pelvic girdle	□ Yes □ No	(If pain ticked) If you use or have used any medicines in relation to pain in neck or back or pelvic girdle, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Headache	□ Yes □ No	(If headache ticked) If you use or have used any medicines in relation to headache, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Sleeping problems	□ Yes □ No	(If sleeping problems ticked) If you use or have used any medicines in relation to sleeping problems, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery

17. Have you been on sick leave during this pregnancy?	
□ Yes	□ No

18. (If yes in Q17) What was the reason for it? In which pregnancy weeks have you been on sick leave?

Reason of the sick leave	**Sick leave period (pregnancy week)**
_____ _____	□ week 0-12 □ week 13-24 □ week 25-delivery

19. Below, some common over-the-counter (OTC) medicines are mentioned. Please indicate whether you have used any of them during pregnancy.

Please enter the name of all *X* medicines you have used.
In which pregnancy weeks have you used them?

		Name of the medicine(s) you have used	**Period of use (pregnancy week)**
Pain killers (*e.g. paracetamol*)	□ Yes □ No	(If painkillers ticked) Please enter the name of all pain killers you have used during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Nasal spray/drops (excluding salt water solution) (*e.g. Otrivine, Vicks Sinex decongestant Nasal spray*)	□ Yes □ No	(If nasal spray ticked) Please enter the name of all nasal sprays/drops you have used during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Medication against heartburn (*e.g. Gaviscon or Rennie*)	□ Yes □ No	(If OTC for heartburn ticked) Please enter the name of all medications you have used against heartburn during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Medication against nausea/travel sickness (*e.g. Cetirizine, Sea-Legs)*	□ Yes □ No	(If OTC for nausea ticked) Please enter the name of all medications you have used against nausea during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Medication against constipation (*e.g.Lactulose, Dulcolax)*	□ Yes □ No	(If OTC for constipation ticked) Please enter the name of all medications you have used against constipation during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery

20. Did you take any herbal preparations during pregnancy (e.g. ginger, echinacea, valerian, cranberries)**?**

□ Yes □ No □ Cannot remember

(If yes) Please provide the name of all herbal preparations you have taken during pregnancy**.**
(If yes) What was the reason for taking herbal preparations (health disorder, illness)?
(If yes) In which pregnancy weeks did you take herbal preparations?

Name of herbal preparation used	**Reason for use (health disorder, illness)**	**Period of use (pregnancy week**
_____ _____ _____	_____ _____ _____	□ week 0-12 □ week 13-24 □ week 25- delivery
_____ _____ _____	_____ _____ _____	□ week 0-12 □ week 13-24 □ week 25- delivery

21. (If you used herbal preparations during pregnancy) Who recommended to you to take herbal preparations during pregnancy? (You may tick more than one answer)

□ My own initiative
□ Family/friends
□ Physician
□ Midwife/Nurse
□ Pharmacy personnel
□ Herbal shop personnel
□ Internet
□ Magazines, media, etc.
□ Other (please specify:_____)

22. Did you use homeopathic products during pregnancy?

□ Yes □ No □ Cannot remember

(If yes in Q22 above) What was the reason for use?

_____

A BIT MORE ABOUT MEDICATION USE DURING PREGNANCY

23. Have you deliberately avoided taking an over-the-counter medicine during your pregnancy?

□ Yes □ No □ Cannot remember

(If yes in Q23 above) Which medicine was it?

_____

(If yes in Q23 above) What was the reason for doing so?

_____

_____

24. Have you deliberately chosen not to use a medicine prescribed by a doctor because you were pregnant?

□ Yes □ No □ Can not remember

(If yes in Q24 above) Which medicine was it?

_____

(If yes in Q24 above) What was the reason for doing so?

_____

_____

YOUR NEEDS FOR INFORMATION

25. Did you need information about medicines during the course of your pregnancy?
□ Yes □ No □ Cannot remember

26. (If yes in Q25) Whom did you turn to for information? (*You may tick more than one answer*)
□ Family/friends
□ Physician
□ Midwife/Nurse
□ Pharmacy personnel
□ Herbal shop personnel
□ Drug formulary/information leaflet
□ Poison information centre
□ Teratology information service
□ National center of information on medicines
□ Internet
□ Magazines, media, etc
□ Other (please specify:_____)

27. (if yes in Q25) If you have obtained information from various sources, was such information similar?
□ Yes, completely similar
□ Yes, as a whole (only the wording or detail level was somewhat different)
□ No, part of the information was different
□ No, the information was completely contradictory

28. (If No – last 2 options in Q27) If there were discrepancies among the sources, what did it mean to you? (*You may tick more than one answer*)
□ Nothing
□ I became anxious
□ I decided not to use the medication
□ I sought for a new information source (Which new source have you consulted? _____)
□ I chose to rely on one source and ignore the conflicting one (On which source have you relied? _____Which source have you ignored? _____)

29. How often do you have someone help you read hospital materials?
□ Always
□ Often
□ Sometimes
□ Occasionally
□ Never

30. How confident are you filling out medical forms by yourself?
□ Extremely
□ Quite a bit
□ Somewhat
□ A little bit
□ Not at all

31. How often do you have problems learning about your medical condition because of difficulty understanding written information?
□ Always
□ Often

□ Sometimes
□ Occasionally
□ Never

The following section will pop-up only if the subject has reported to be suffering from a chronic disease

I. MEDICATIONS FOR CHRONIC DISEASES DURING PREGNANCY

If you use or have used medicines for a chronic disease during your pregnancy fill out this part of the questionnaire (I, II, III) and provide some information about those medicines you use daily.

Some chronic diseases are asthma, allergy, hypothyroidism (low thyroid hormone), rheumatic diseases (incl. rheumatoid arthritis, psoriatic arthritis), diabetes (type I or II), epilepsy, depression, anxiety, cardiovascular diseases (incl. hypertension, high cholesterol, and heart diseases)

Do you suffer of any chronic disease? **□ Yes** **□ No**

(If Yes above) Please indicate whether you suffer of any of the following chronic diseases.

		If you use or have used medicines for *X* during your pregnancy, please enter the name of the medicines.	**In which weeks of pregnancy did you use them?**
Asthma	□ Yes □ No	(If Asthma ticked) If you use or have used medicines for asthma during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Allergy	□ Yes □ No	(If Allergy ticked) If you use or have used medicines for allergy during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Hypothyroidism (low thyroid hormone)	□ Yes □ No	(If Hypothyroidism ticked) If you use or have used medicines for hypothyroidism during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Rheumatic disorders (incl. rheumatoid arthritis, psoriatic arthritis)	□ Yes □ No	(If Rheumatic disorders ticked) If you use or have used medicines for rheumatic disorder during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Diabetes (type I or II)	□ Yes □ No	(If Diabetes ticked) If you use or have used medicines for diabetes during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Epilepsy	□ Yes □ No	(If Epilepsy ticked) If you use or have used medicines for epilepsy during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Depression	□ Yes □ No	(If Depression ticked) If you use or have used medicines for depression, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery

		If you use or have used medicines for *X* during your pregnancy, please enter the name of the medicines.	**In which weeks of pregnancy did you use them?**
Anxiety	□ Yes □ No	(If Anxiety ticked) If you use or have used medicines for anxiety during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Cardiovascular diseases (incl. hypertension, high cholesterol, heart diseases)	□ Yes □ No	(If Cardio disease ticked) If you use or have used medicines for cardiovascular diseases during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Others (If Others ticked) (Please specify which other disease(s): _____)	□ Yes □ No	(If Other disease ticked) If you use or have used medicines for your chronic disease during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery

Section II will pop-up only if the subject has reported to be suffering of a chronic disease

II. YOUR VIEWS ABOUT PRESCRIBED MEDICINES

In this section of the survey questionnaire, the **Belief About Prescribed Medicine Questionnaire (BMQ-Specific)** was presented (Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1-24).

Section III will pop-up only if the subject has reported to be suffering of a chronic disease. There will be one single scale for each chronic condition reported

III. QUESTION ABOUT YOUR USE OF MEDICATIONS FOR X DURING PREGNANCY AND/OR POSTPARTUM

In this section of the survey questionnaire, the **8-item Morisky Medication Adherence Questionnaire (MMAS-8)** was presented (*Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Medical care. 1986;24(1):67-74; Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich) 2008;10:348-54*)

Do you have any other comments about your medication use during pregnancy?

_____
_____
_____
_____
_____

YOUR VIEWS ABOUT MEDICATIONS

In this section of the survey questionnaire, the **Belief About Medicine Questionnaire (BMQ-General)** was presented (*Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1-24*).

32. Below are some statements about use of medicines in pregnancy. Please specify how much you agree or disagree with these statements by ticking where appropriate. (*You may only tick once per line*)

	Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
I have a higher threshold for using medicines when I am pregnant than when I'm not pregnant	○	○	○	○	○
Even though I am ill and could have taken medicines, it is better for the foetus that I refrain from using them	○	○	○	○	○
Pregnant women should preferably use herbal remedies than conventional medicines	○	○	○	○	○

YOUR ASSESSMENT OF PREGNANCY RISKS

33. Among 100 healthy women in a healthy environment, how many do you think will give birth to a child with a birth defect?

_____

34. Here below is a list with various medicines, food and other substances.
Please indicate how harmful you think they are for the foetus in a scale from 0 to 10, where 0 corresponds to 'not harmful' and 10 to 'very harmful'.

If you have not heard before about such substance, tick 'unknown substance'.

	Unknown substance	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Paracetamol/acetaminophen	○	○	○	○	○	○	○	○	○	○	○	○
Antibiotics (*e.g. Penicillins*)	○	○	○	○	○	○	○	○	○	○	○	○
Antidepressants	○	○	○	○	○	○	○	○	○	○	○	○
Thalidomide	○	○	○	○	○	○	○	○	○	○	○	○
Swine influenza vaccine	○	○	○	○	○	○	○	○	○	○	○	○
OTC medicines against nausea/travel sickness	○	○	○	○	○	○	○	○	○	○	○	○
Ginger	○	○	○	○	○	○	○	○	○	○	○	○
Cranberries	○	○	○	○	○	○	○	○	○	○	○	○
Blue veined cheese *(e.g. Gorgonzola)*	○	○	○	○	○	○	○	○	○	○	○	○
Eggs	○	○	○	○	○	○	○	○	○	○	○	○
Alcohol during the 1. trimester (*e.g. wine, beer, spirits*)	○	○	○	○	○	○	○	○	○	○	○	○
Smoking (*e.g. cigarettes*)	○	○	○	○	○	○	○	○	○	○	○	○
Dental X-ray	○	○	○	○	○	○	○	○	○	○	○	○

HOW YOU ARE FEELING NOW

In this section of the survey questionnaire, the **Edinburgh Postnatal Depression Scale (EPDS)** was presented (*Cox J, Holden J, Sagovsky R. Detection of postnatal depression. Development of the 10-item edinburgh postnatal depression scale. The British Journal of Psychiatry. 1987 June 1, 1987;150(6):782-6*).

HOW YOU SEE YOURSELF

In this section of the survey questionnaire, the **Big Five Inventory (BFI)** was presented (*John OP, Srivastava S, editors. The big five trait taxonomy: History, measurement, and theoretical perspectives: New York: Guilford; 1999; John OP, Robins RW, Pervin LA. Handbook of personality: Theory and research: The Guilford Press; 2008*).

Appendix 2: Websites used for recruitment and internet penetration rates in each country where data were collected

Country	*Website used for recruitment*	*Internet penetration rates (%)*
EUROPE		
	Western Europe	
Austria	www.schwangerschaft.at; www.schwangerschafts-blog.at; www.fratz.at; www.netdoctor.at; www.babycenter.at; www.baby-boom.at; www.ekiz-dachverband.at; www.babyguide.at	93* [1]
France	www.aufeminin.com (*Including ipad application to website subscribers*)	91* [1]
Italy	*Pregnancy Forums*: www.gravidanzaonline.it; www.forumsalute.it; www.mammole.it; www.pianetamamma.it; www.miobambino.it *Targeted email to pregnancy forum subscribers*: www.gravidanzaonline.it	70* [1]
Switzerland	www.bebe-bebe.com; www.swissmom.ch	84* [2]
The Netherlands	www.lareb.nl; www.gezondzwangerzijn.nl; www.babybytes.nl	98* [1]
United Kingdom	*Targeted email to pregnancy forum subscribers*: www.bounty.com *Pregnancy Forums*: www.pregnancyforum.co.uk; www.pregnancyforum.org.uk	93* [1]
	Northern Europe	
Finland	www.vauva.fi; www.meidanperhe.fi; www.kaksplus.fi	99* [1]
Iceland	*Pregnancy Forums*: www.bland.is	100* [1]
Norway	www.barnimagen.com; www.klikk.no; www.jormorsiri.no; www.tryggmamamedisin.no	99* [1]
Sweden	www.barntotal.se; www.minbebis.com; www.se.babycenter.com; www.socmed.gu.se	99* [1]
	Eastern Europe	
Croatia	www.cybermed.hr	80* [1] (data from 2010)
Poland	www.zzief.umlub.pl *Pregnancy Forums*: www.ebrzuszek.pl; www.babyboom.pl; www.zapytajpolozna.pl; www.planujemydziecko.pl; www.twoja-ciaza.com.pl	84* [1]
Russia	www.babyblog.ru; www.littleone.ru	48* [2]

Country	*Website used for recruitment*	*Internet penetration rates (%)*
	Pregnancy Forums: www.woman.ru; www.9months.ru; www.bemam; www.280dney.ru; www.iampregnant.ru www.pregnancy.org.ua; www.baby.ru; www.mama66.ru; www.spuzom.ru	
Serbia	www.ringeraja.rs	52* [1] (data from 2009)
Slovenia	*Pregnancy Forums*: www.med.over.net	92* [1]
AMERICAS		
	North America	
Canada	www.otispregnancy.org; Facebook page of OTIS; www.babyontheway.com.ca *Pregnancy Forums*: www.babycentre.com.ca; www.thecradle.com; www.talk.sheknows.com; www.parenting.com	94† [3]
USA	www.otispregnancy.org; Facebook page of OTIS; www.justmommies.com *Pregnancy Forums*: www.babyandbump.com www.thecradle.com; www.talk.sheknows.com; www.parenting.com	80§ [4]
	Central America	
Belize	www.otispregnancy.org; Facebook page of OTIS	23[2]
Costa Rica		43[2]
El Salvador		25[2]
Guatemala		16[2]
Honduras		16[2]
Nicaragua		14[2]
Panama		43[2]
	South America	
Argentina	www.otispregnancy.org; Facebook page of OTIS	67[2]
Bolivia		30[2]
Brazil	*Pregnancy Forums*: www.semanaasemana.com;	46[2]
Chile	www.univision.com; www.elembarazo.net	59[2]
Colombia		59[2]
Ecuador		44[2]
Paraguay		24[2]
Peru		37[2]
Uruguay		56[2]

Country	*Website used for recruitment*	*Internet penetration rates (%)*
Venezuela		41[2]
	AUSTRALIA	
Australia	www.mothersafe.org.au; www.bubhub.com.au *Pregnancy Forums*: www.abds.org.au; www.birth.com.au	83[ζ] [5]

[*]Indicates the frequency of internet access - at least once a week, including every day - among individuals aged 25- 34 years. Differences between men and women were relatively small. Slightly more than two thirds of men (70%) and 65% of women used the Internet regularly.
[†]Indicates individuals aged 16-45 years who used the internet for personal use.
[§]Indicates individuals > 18 years old, access from anywhere; household internet for women is equal to 68.1%; higher percentages are observed for people aged 25-54 years.
[ζ]Indicates households with access to the internet at home.

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Appendix 3: Socio-demographic characteristics of the study population and general birthing population on individual country

Appendix 3a: Socio-demographic characteristics in Western European countries (Switzerland, Italy and United Kingdom (UK))

	Study sample in Switzerland n=618	General birthing population in Switzerland LB=80,808[1]	Study sample in Italy n=926	General birthing population in Italy LB=546,606[1]	Study sample in the UK n=1,120	General birthing population in UK* LB=723,165[2]
	(%)	(%)	(%)	(%)	(%)	(%)
No. of respondents/No. live births[¶]	4.6%		1.0%		0.9%	
Mean Age +/- sd	31.6 +/- 4.3	31.4[3]	32.3 +/- 5.0	31.3[4]	30.5 +/- 5.2	29.6[2]
Marital status						
In marriage	80.0	80.7[3]	68.8	75.1[1]	63.3	53.2[2]
Outside marriage	20.0	19.3[3]	31.2	31.5[1]	36.7	46.8[2]
Parity						
No previous children	53.2	-	59.7	48.7[5]	48.0†	41.9[2] †
Educational level						
Less than high school	11.0	11.7[6]	7.0	25.2[6]	0.6	16.5[2]
High school	13.6	49.2[6]	47.2	49.2[6]	27.9	37.2[2]
More than high school	47.2	39.1[6]	44.3	25.6[6]	52.1	46.3[2]
Other	28.2	-	1.5	-	19.3	-
Women smoking before pregnancy	25.1	25.4[7]	34.2	33.3[4]	25.2	25.7[7]
Women smoking during pregnancy	5.5	6.6[8]	10.5	22.7[9]	7.1‡	13.2[10] ‡
Use of alcohol during pregnancy	20.7	29.9[8]	17.9	17.7[9]	28.3	24.0[11] §

Abbreviations: LB: Number of live births per year.

*The figures shown here are statistic estimates for England and Wales. Scotland and Northern Ireland have separate statistical reports. Since more than 85% of the study population in UK were resident in England and about 8% in Wales, we are only showing national statistic data for these two parts of the UK.

¶The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

†Among married women only – as provided by the Statistics Bureau in the UK.

‡Among women resident in England only (as provided by the Statistics Bureau in the UK, data on 4th Quarter of 2011).

§Women reporting at least one occasion during pregnancy of consuming more than four drinks in a day.

Appendix 3b: Socio-demographic characteristics in Western European countries (Austria, France and The Netherlands)

	Study sample in Austria n=82	General birthing population in Austria LB=78,109[1]	Study sample in France n=374	General birthing population in France LB=824,263[1]	Study sample in The Netherlands n=81	General birthing population in The Netherlands LB=180,060[1]
	(%)	(%)	(%)	(%)	(%)	(%)
No. of respondents/No. live births*	0.6%		0.3%		0.3%	
Mean Age +/- sd	30.6 +/- 4.6	30.0[12]	29.6 +/- 4.9	30.1[13]	32.0 +/- 6.4	31.0[14]
Marital status						
In marriage	48.8	59.6[15]	48.9	45.0[1]	69.1	58.2[14]
Outside marriage	51.2	40.4[15]	51.1	55.0[1]	30.8	41.8[14]
Parity						
No previous children	63.4	47.96[15]	52.9	44.2[16]	38.3	46.4[14]
Educational level						
Less than high school	9.8	13.3[6]	1.6	15.4[6]	9.9	15.9[6]
High-school	32.9	64.1[6]	25.1	37.4[6]	66.7	40.2[6]
More than high school	40.2	22.7[6]	57.0	47.2[6]	23.5	43.9[6]
Other	17.1	-	16.3	-	-	-
Women smoking before pregnancy	31.7	32.1[17]	39.3	39.0[16]	34.6	29.5[7]
Women smoking during pregnancy	4.9	-	14.2	28.0[16]	14.8	17.1[18]
Use of alcohol during pregnancy	13.4	-	11.5	52.0[19]	11.1	16-35[14]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3c: Socio-demographic characteristics in Northern European countries (Norway, Finland and Sweden)

	Study sample in Norway n=1,228	General birthing population in Norway LB=60,220[1]	Study sample in Finland n=574	General birthing population in Finland LB=59,961[1]	Study sample in Sweden n=887	General birthing population in Sweden LB=111,770[1]
	(%)	(%)	(%)	(%)	(%)	(%)
No. of respondents/No. live births*	12.2%		5.7%		4.8%	
Mean Age +/- sd	29.0 +/- 4.6	29.8 +/- 5.3[20]	29.0+/-5.1	30.1[21]	29.8 +/- 5.3	30.3[22]
Marital status						
In marriage	39.1	46.0[20]	59.4	57.8[21]	40.7	45.8[1]
Outside marriage	60.9	53.4[20]	40.6	42.0[21]	59.3	54.2[1]
Unknown	-	0.6[20]	-	0.2[21]		
Parity						
No previous children	41.4	42.4[20]	35.5	42.2[21]	63.1	44.9[22]
Educational level						
Less than high school	4.5	14.7[6]	8.2	7.1[6]	5.2	11.1[6]
High-school	28.0	31.4[6]	36.4	44.5[6]	30.0	38.2[6]
More than high school	46.9	53.9[6]	52.6	48.4[6]	60.6	50.6[6]
Other	20.7	-	2.8	-	4.2	-
Women smoking before pregnancy	33.5	36.5[7]	36.7	19.7[7]	25.0	27.2[7]
Women smoking during pregnancy	6.8	7.0[20]	11.7	15.2[21]	5.4	6.5[22]
Use of alcohol during pregnancy	4.1	7.4[23]	13.9	-	7.2	5.9[24]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3d: Socio-demographic characteristics in Northern European countries (Iceland)

	Study sample in Iceland n=71	General birthing population in Iceland LB=4,492[1]
	(%)	(%)
No. of respondents/No. live births*	9.3%	
Age range (in years)		
15-20	11.3	5.1[25]
21-25	16.9	19.3[25]
26-30	42.3	34.2[25]
31-35	15.5	27.3[25]
36-40	12.7	11.7[25]
≥41	1.4	2.4[25]
Marital status		
In marriage	31.0	35.0[25]
Outside marriage	69.0	65.0[25]
Parity		
No previous children	47.9	38.1[25]
Educational level		
Less than high school	25.4	21.4[6]
High-school	18.3	30.5[6]
More than high school	43.7	48.1[6]
Other	12.7	-
Women smoking before pregnancy	40.8	35.5[7]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3e: Socio-demographic characteristics in Eastern European countries (Croatia, Slovenia and Serbia)

	Study sample in Croatia n=286	General birthing population in Croatia LB=41,197[1]	Study sample in Slovenia n=149	General birthing population in Slovenia LB=21,947[1]	Study sample in Serbia n=220	General birthing population in Serbia LB=65,598[1]
	n (%)	**(%)**	**n (%)**	**(%)**	**n (%)**	**(%)**
No. of respondents/No. live births*	4.2%		4.1%		2.0%	
Mean Age +/- sd	29.1 +/- 4.5†	27.7[26]	31.7 +/- 4.5	30.4[27]	29.2 +/- 3.9*	28.7[1,28]
Marital status						
In marriage	83.9	86.7[26]	47.0	43.2[27]	90.1	76.1[28]
Outside marriage	16.1	13.3[26]	53.0	56.8[27]	9.9	23.9[28]
Parity						
No previous children	50.7	46.9[26]	45.6	48.5[27]	46.8	51.1[28,29]
Educational level						
Less than high school	1.0	3.1[26]	2.0	8.5[27]	0.9	15.9[29]
High-school	36.7	52.5[26]	24.8	48.5[27]	33.6	54.9[29]
More than high school	61.2	44.4[26]	69.1	43.0[27]	61.8	29.2[29]
Other	1.0	-	4.0	-	3.6	-
Women smoking before pregnancy	50.0	34.4[26]	32.9	34.4[7]	49.1	29.9[30,31]
Women smoking during pregnancy	18.8	23.1[32]	6.7	9.6-11.2[33]	18.2	18.4[31]
Use of alcohol during pregnancy	12.6	15.5[34]	32.2	-	15.0	-

Abbreviations: LB: Number of live births per year.

* The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

†Mean age for first child (as it is available from the Statistics Bureau reports in Croatia and Serbia).

Appendix 3f: Socio-demographic characteristics in Eastern European countries (Poland and Russia)

	Study sample in Poland n=679	General birthing population in Poland LB=388,416[1]	Study sample in Russia n=1,008	General birthing population in Russia LB=1,796,629[1]
	(%)	(%)	(%)	(%)
No. of respondents/No. live births*	1.0%		0.3%	
Mean Age +/- sd	27.1 +/- 4.1	28.6[35] †	27.7 +/- 4.8	27.4[36]
Marital status				
In marriage	85.0	79.4[35]	85.3	73.9[36]
Outside marriage	15.0	20.6[35]	14.7	26.1[36]
Parity				
No previous children	40.6	50.1[35]	57.9	-
Educational level				
Less than high school	1.9	8.7[35]	1.6	-
High-school	31.1	49.6[35]	9.3	-
More than high school	65.1	41.6[35]	75.1	-
Other	1.9	-	14.0	-
Women smoking before pregnancy	49.2	25.0[37]	46.1	30.8[38]
Women smoking during pregnancy	12.8	22-30[37]	9.6	4.3-6.5[39,40]
Use of alcohol during pregnancy	9.6	15.3[41]	26.0	60.0[42]

Abbreviations: LB: Number of live births per year.

* The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

†Median age of women at birth, not mean age.

Appendix 3g: Socio-demographic characteristics in North American countries (Canada and USA)

	Study sample in Canada n=236 n (%)	General birthing population in Canada[43] LB=377,636 (%)	Study sample in The USA n=297 n (%)	General birthing population in USA[44] LB=3,999,386 (%)
No. of respondents/No. live births*	0.4%		0.04%	
Age range (in years)				
15-19	2.1	3.9[43]	4.7	9.3[44]
20-24	25.0	14.6[43]	18.2	23.8[44]
25-29	30.1	30.2[43]	28.3	28.3[44]
30-34	30.5	32.2[43]	29.3	24.1[44]
35-39	11.0	15.6[43]	15.2	11.6[44]
40-44	1.3	3.1[43]	4.0	2.7[44]
≥45	-	0.2[43]	0.3	0.2[44]
Mean Age +/- sd	28.3 +/- 5.2	29.6[43]	29.3 +/- 6.1	-
Marital status				
In marriage	42.4	60.4[43]	67.0	59.2[45]
Outside marriage	57.6	28.8[43]	33.0	39.9[45]
Unknown	-	10.8[43]	-	0.9[45]
Parity				
No previous children	48.3	43.3[43]	41.1	40.1[44]
Educational level				
Less than high school	1.3	8.4[46]	2.7	17.4[47]
High-school	24.6	-	25.3	24.4[47]
More than high school	67.8	69.6[46]	62.0	58.2[47]
Other	6.4	-	10.1	-
Women smoking before pregnancy	29.2	22.0[48]	28.3	21.5[49]
Women smoking during pregnancy	16.1	13.4[46]	8.1	10.2[50]

	Study sample in Canada n=236 n (%)	General birthing population in Canada[43] LB=377,636 (%)	Study sample in The USA n=297 n (%)	General birthing population in USA[44] LB=3,999,386 (%)
Use of alcohol during pregnancy	16.1	10.5[46]	17.5	15.5[49]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3h: Socio-demographic characteristics in Australia

	Study sample in Australia n=217	General birthing population in Australia[51] LB=301,617
	n (%)	**(%)**
No. of respondents/No. live births*	0.4%	
Mean Age +/- sd	31.1 +/- 5.7	30.7[51]
Marital status		
In marriage	70.5	65.8[51]
Outside marriage	29.5	34.2[51]
Parity		
No previous children	47.9	43.8[51]
Educational level		
Less than high school	0.5	20.6†[52]
High-school	29.0	
More than high school	63.1	56.0[53]
Other	7.4	-
Women smoking before pregnancy	29.1	29.9[54]
Women smoking during pregnancy	14.3	14.5[55]
Use of alcohol during pregnancy	27.2	29.0[56]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

†Refers to the educational levels "high school" and "less than high school" grouped together.

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Appendix 4: Sample size calculation (using 5% precision with 95% confidence interval) for the population survey on region and individual country levels.

	Study sample	**Population size***	**Expected prevalence**				
			Any medication use=80%	*Any medication use=70%*	*OTC medication use=60%*	*Chronic medication use=30%*	*Chronic medication use=15%*
			Required sample size				
Western Europe	3,201	Not known	246	323	369	323	196
United Kingdom	1,120	120,528	245	322	368	322	196
Italy	926	91,101	245	322	367	322	195
Switzerland	618	13,468	241	315	359	315	193
France	374	137,377	245	322	368	322	196
Austria†	82	13,018	241	315	359	315	193
The Netherlands†	81	30,010	244	319	364	319	195
Northern Europe	2,820	Not known	246	323	369	323	196
Norway	1,228	10,037	240	313	356	313	192
Sweden	887	18,628	243	317	362	317	194
Finland	574	9,994	240	313	356	313	192
Iceland†	71	749	185	225	247	225	155
Eastern Europe	2,342	Not known	246	323	369	323	196
Russia	1,008	299,438	246	322	368	322	196
Poland	679	64,736	245	321	367	321	195
Croatia§	286	6,866	237	308	350	308	190
Serbia¶	220	10,933	240	313	357	313	192
Slovenia**	149	3,658	230	297	335	297	186
North America	533	Not known	246	323	369	323	196
USA§	297	666,564	246	323	369	323	196
Canada††	236	62,939	245	321	367	321	195
South America¶¶	346	Not known	246	323	369	323	196
Australia§§	217	50,270	245	321	366	321	195

Sample size calculations were performed in Epi Info ™ 7 available at: Center for DiseaseControl and Prevention (CDC), Epi Info. URL: http://wwwn.cdc.gov/epiinfo/. Accessed 2013 Dec 31.

*The population size indicates the number of live births in the country in two months (corresponds to the period of data collection) (cf. Appendix 3 for annual estimates of live births in each country). For the all regions except Australia, the population size is very large but not known exactly (i.e. infinite population). Infinite population size is therefore assumed in the calculation of the required sample size.

[†]The sample size allows for prevalence estimates with a precision of 9% (expected prevalence=80%), 10% (expected prevalence=70% and 30%), 11% (expected prevalence=60%) and 8% (expected prevalence=15%).
[§]The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=70%, 60% and 30%).
[¶]The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=80%) and 7% (expected prevalence=70%, 60% and 30%).
[**]The sample size allows for prevalence estimates with a precision of 7% (expected prevalence=80%), 8% (expected prevalence=70%, 60% and 30%) and 6% (expected prevalence=15%).
[††]The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=80%, 70% and 30%) and 7% (expected prevalence=60%).
[¶¶]The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=60%).
[§§]The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=80%) and 7% (expected prevalence=70%, 60% and 30%).

Appendix 5: Overall medication use on 1st and 2nd ATC level according to timing of use in pregnancy (n=9,459)*

	Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels	Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
A	**Alimentary tract and metabolism**	**4,275 (45.2)**	**2,786 (29.5)**	**3,390 (35.8)**	**3,160 (33.4)**
A01	Stomatological preparations	62 (0.7)	42 (0.4)	52 (0.5)	46 (0.5)
A02	*Drugs for acid related disorders*	3,242 (34.3)	2,034 (21.5)	2,634 (27.8)	2,615 (27.6)
A03	Drugs for functional gastrointestinal disorders	650 (6.9)	543 (5.7)	512 (5.4)	381 (4.0)
A04	Antiemetics and antinauseants	136 (1.4)	124 (1.3)	114 (1.2)	81 (0.9)
A05	Bile and liver therapy	24 (0.3)	15 (0.2)	17 (0.2)	16 (0.2)
A06	*Laxatives*	978 (10.3)	696 (7.4)	835 (8.8)	735 (7.8)
A07	Antidiarrheals, intestinal antiinflammatory/antiinfective agents	89 (0.9)	61 (0.6)	69 (0.7)	57 (0.6)
A09	Digestives, incl. enzymes	9 (0.1)	7 (0.1)	8 (0.1)	3 (0.0)
A10	Drugs used in diabetes	85 (0.9)	57 (0.6)	58 (0.6)	45 (0.5)
-	Unspecified medications for nausea	6 (0.1)	5 (0.1)	4 (0.0)	3 (0.0)
B	**Blood and blood forming organs**	**148 (1.6)**	**89 (0.9)**	**102 (1.1)**	**79 (0.8)**
B01	*Antithrombotic agents*	135 (1.4)	78 (0.8)	95 (1.0)	72 (0.8)
B02	Antihemorrhagics	5 (0.1)	4 (0.0)	2 (0.0)	3 (0.0)
B05	Blood substitutes and perfusion solutions	7 (0.1)	5 (0.1)	5 (0.1)	2 (0.0)
B06	Other hematological agents	3 (0.0)	2 (0.0)	2 (0.0)	3 (0.0)
C	**Cardiovascular system**	**202 (2.1)**	**132 (1.4)**	**161 (1.7)**	**133 (1.4)**
C01	Cardiac therapy	7 (0.1)	4 (0.0)	5 (0.1)	4 (0.1)
C02	*Antihypertensives*	56 (0.6)	34 (0.4)	42 (0.4)	31 (0.3)
C03	Diuretics	6 (0.1)	5 (0.1)	3 (0.0)	2 (0.0)
C04	Peripheral vasodilators	3 (0.0)	3 (0.0)	3 (0.0)	3 (0.0)
C05	Vasoprotectives	44 (0.5)	24 (0.3)	35 (0.4)	31 (0.3)
C07	*Beta blocking agents*	74 (0.8)	51 (0.5)	59 (0.6)	51 (0.5)
C08	Calcium channel blockers	21 (0.2)	16 (0.2)	18 (0.2)	13 (0.1)
C09	Agents acting on the renin-angiotensin system	4 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
C10	Lipid modifying agents	5 (0.1)	3 (0.0)	4 (0.0)	4 (0.0)
-	Unspecified medications for hypertension	4 (0.0)	3 (0.0)	3 (0.0)	2 (0.0)

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
D	**Dermatologicals**	**162 (1.7)**	**116 (1.2)**	**127 (1.3)**	**103 (1.1)**
D01	*Antifungals for dermatological use*	38 (0.4)	28 (0.3)	33 (0.3)	27 (0.3)
D02	Emollients and protectives	14 (0.1)	11 (0.1)	12 (0.1)	10 (0.1)
D03	Preparations for treatment of wounds and ulcers	4 (0.0)	3 (0.0)	3 (0.0)	3 (0.0)
D04	Antipruritics, incl. antihistamines, anaesthetics, etc.	6 (0.1)	3 (0.0)	5 (0.1)	4 (0.0)
D05	Antipsoriatics	3 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
D06	Antibiotics and chemotherapeutics for dermatological use	21 (0.2)	15 (0.2)	16 (0.2)	13 (0.1)
D07	*Corticosteroids, dermatological preparations*	56 (0.6)	40 (0.4)	39 (0.4)	31 (0.3)
D08	Antiseptics and disinfectants	14 (0.1)	9 (0.1)	10 (0.1)	9 (0.1)
D09	Medicated dressings	5 (0.1)	5 (0.1)	5 (0.1)	3 (0.0)
D10	Anti-acne preparations	4 (0.0)	4 (0.0)	4 (0.0)	2 (0.0)
D11	Other dermatological preparations	1 (0.0)	-	1 (0.0)	1 (0.0)
-	Unspecified medications for skin disorders	5 (0.1)	4 (0.0)	4 (0.0)	3 (0.0)
G	**Genitourinary system and sex hormones**	**488 (5.2)**	**318 (3.4)**	**394 (4.2)**	**303 (3.2)**
G01	*Gynaecological antiinfective and antiseptics*	406 (4.3)	255 (2.7)	337 (3.6)	258 (2.7)
G02	Other gynecologicals	13 (0.1)	10 (0.1)	10 (0.1)	8 (0.1)
G03	Sex hormones and modulators of the genital system	68 (0.7)	55 (0.6)	50 (0.5)	36 (0.4)
G04	Urologicals	12 (0.1)	8 (0.1)	7 (0.1)	8 (0.1)
H	**Systemic hormonal preparations, excl. sex hormones and insulins**	**486 (5.1)**	**304 (3.2)**	**346 (3.7)**	**262 (2.8)**
H01	Pituitary and hypothalamic hormones and analogues	4 (0.0)	4 (0.0)	3 (0.0)	4 (0.0)
H02	Corticosteroids for systemic use	93 (1.0)	64 (0.7)	78 (0.8)	63 (0.7)
H03	*Thyroid therapy*	397 (4.2)	242 (2.6)	273 (2.9)	201 (2.1)
J	**Anti-infective for systemic use**	**1,381 (14.6)**	**874 (9.2)**	**1,107 (11.7)**	**943 (10.0)**
J01	*Antibacterials for systemic use*	1,325 (14.0)	840 (8.9)	1,061 (11.2)	908 (9.6)
J02	Antimycotics for systemic use	23 (0.2)	16 (0.2)	21 (0.2)	17 (0.2)
J05	Antivirals for systemic use	39 (0.4)	27 (0.3)	30 (0.3)	26 (0.3)
J06	Immune sera and immunoglobulins	4 (0.0)	2 (0.0)	3 (0.0)	4 (0.0)
J07	Vaccines	10 (0.1)	5 (0.1)	8 (0.1)	5 (0.1)
L	**Antineoplastic and immunomodulating agents**	**134 (1.4)**	**83 (0.9)**	**117 (1.2)**	**97 (1.0)**

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
L01	Antineoplastic agents	4 (0.0)	3 (0.0)	4 (0.0)	1 (0.0)
L03	*Immunostimulants*	96 (1.0)	58 (0.6)	86 (0.9)	78 (0.8)
L04	Immunosuppressants	34 (0.4)	22 (0.2)	27 (0.3)	18 (0.2)
M	**Musculo-skeletal system**	**571 (6.0)**	**416 (4.4)**	**437 (4.6)**	**380 (4.0)**
M01	*Antiinflammatory and antirheumatic products*	515 (5.4)	378 (4.0)	396 (4.2)	342 (3.6)
M02	Topical products for joint and muscular pain	54 (0.6)	37 (0.4)	41 (0.4)	41 (0.4)
M03	Muscle relaxants	8 (0.1)	8 (0.1)	4 (0.0)	1 (0.0)
M05	Drugs for treatment of bone diseases	1 (0.0)	-	1 (0.0)	-
M09	Other drugs for disorders of the musculo-skeletal system	2 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
-	Unspecified medications for headache	2 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
N	**Nervous system**	**5,441 (57.5)**	**3,638 (38.5)**	**4,247 (44.9)**	**3,449 (36.5)**
N01	Anaesthetics	13 (0.1)	10 (0.1)	7 (0.1)	8 (0.1)
N02	*Analgesics*	5,297 (56.0)	3,562 (37.7)	4,171 (44.1)	3,387 (35.8)
N03	Antiepileptics	76 (0.8)	46 (0.5)	49 (0.5)	42 (0.4)
N05	*Psycholeptics*	210 (2.2)	173 (1.8)	164 (1.7)	138 (1.5)
N06	*Psychoanaleptics*	275 (2.9)	211 (2.2)	213 (2.3)	179 (1.9)
N07	Other nervous system drugs	6 (0.1)	4 (0.0)	5 (0.1)	3 (0.0)
-	Unspecified analgesics/medications for the nervous system	52 (0.5)	38 (0.4)	43 (0.5)	35 (0.4)
P	**Antiparasitic products, insecticides and repellents**	**26 (0.3)**	**20 (0.2)**	**22 (0.2)**	**16 (0.2)**
P01	*Antiprotozoals*	25 (0.3)	20 (0.2)	22 (0.2)	16 (0.2)
P02	Anthelmintics	1 (0.0)	-	-	-
R	**Respiratory system**	**2,609 (27.6)**	**1,878 (19.9)**	**2,047 (21.6)**	**1,702 (18.0)**
R01	*Nasal preparations*	1,547 (16.4)	1,079 (11.4)	1,229 (13.0)	1,046 (11.1)
R02	Throat preparations	167 (1.8)	110 (1.2)	131 (1.4)	122 (1.3)
R03	*Drugs for obstructive airway diseases*	396 (4.2)	269 (2.8)	304 (3.2)	242 (2.6)
R05	Cough and cold preparations	152 (1.6)	103 (1.1)	125 (1.3)	101 (1.1)
R06	*Antihistamines for systemic use*	912 (9.6)	777 (8.2)	740 (7.8)	580 (6.1)
R07	Other respiratory system products	3 (0.0)	2 (0.0)	3 (0.0)	3 (0.0)
-	Unspecified medications of the respiratory system	142 (1.5)	101 (1.1)	118 (1.2)	99 (1.0)

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
S	**Sensory organs**	**45 (0.5)**	**33 (0.3)**	**38 (0.4)**	**28 (0.3)**
S01	*Ophthalmologicals*	33 (0.3)	24 (0.3)	28 (0.3)	23 (0.2)
S02	Otologicals	5 (0.1)	3 (0.0)	4 (0.0)	2 (0.0)
S03	Ophthalmological and otological preparations	3 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
-	Unspecified medications for eye disorders	5 (0.1)	4 (0.0)	5 (0.1)	2 (0.0)
V	**Various**	15 (0.2)	10 (0.1)	11 (0.1)	9 (0.1)
Total medication use (any ATC)		**7,678 (81.2)**	**4,710 (49.8)**	**5,538 (58.5)**	**4,663 (49.3)**

*The most common medication groups within each ATC class are in italics. Exposure timing is defined as follows: 1st trimester (gestational weeks 0-12), 2nd trimester (gestational week 13-24), 3rd trimester (gestational week 25 and up to childbirth).

Appendix 6: Prevalence of acute/short-term illnesses and most common medications used at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

	REGION						
Prevalence of acute/short-term illnesses in pregnancy and related medication use, overall and by drug groups	**Western Europe n=3,201** *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australia n=217** *n (%)*	**Total n=9,459** *n (%)*
Prevalence of headache	1,699 (53.1)	1,657 (58.8)	1,138 (48.6)	373 (70.0)	197 (56.9)	147 (67.7)	5,211 (55.1)
Medication use for headache, total	**1,027 (32.1)**	**1,057 (37.5)**	**522 (22.3)**	**226 (42.4)**	**121 (35.0)**	**109 (50.2)**	**3,062 (32.4)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	994 (31.1)	1,009 (35.8)	372 (15.9)	206 (38.6)	92 (26.6)	101 (46.5)	2,774 (29.3)
Non-steroidal antiinflammatory drugs (M01A)	28 (0.9)	78 (2.8)	37 (1.6)	18 (3.0)	18 (5.2)	2 (0.9)	179 (1.9)
Acetylsalicylic acid (incl. combinations) (N02BA)	7 (0.2)	4 (0.1)	81 (3.5)	1 (0.2)	4 (1.2)	2 (0.9)	99 (1.0)
Opioid analgesics (N02A)	14 (0.4)	46 (1.6)	3 (0.1)	3 (0.6)	-	13 (6.0)	79 (0.8)
Selective serotonin (5-HT_1) agonists (N02CC)	6 (0.2)	22 (0.8)	2 (0.1)	3 (0.6)	-	1 (0.5)	34 (0.4)
Prevalence of heartburn	2,196 (68.6)	1,875 (66.5)	1,425 (60.8)	374 (70.2)	248 (71.7)	141 (65.0)	6,259 (66.2)
Medication use for heartburn, total	**984 (30.7)**	**885 (31.4)**	**525 (22.4)**	**202 (37.9)**	**88 (25.4)**	**72 (33.2)**	**2,756 (29.1)**
By drug group							
Antacids (aluminium, salts combinations, antiflatulents)	384 (12.0)	503 (17.8)	440 (18.8)	51 (9.6)	63 (18.2)	20 (9.2)	1,461 (15.4)
Alginic acid complex/sucralfate/bismuth (A02BX)	569 (17.8)	332 (11.8)	86 (3.7)	4 (0.8)	3 (0.9)	14 (6.5)	1,008 (10.7)
Proton pump inhibitors (A02BC)	77 (2.4)	86 (3.0)	4 (0.2)	13 (2.4)	3 (0.9)	7 (3.2)	190 (2.0)
Antacid with calcium (A02AC)	20 (0.6)	13 (0.5)	10 (0.4)	123 (23.1)	2 (0.6)	9 (4.1)	177 (1.9)
H_2 receptor antagonists (A02BA)	27 (0.8)	27 (1.0)	7 (0.3)	45 (8.4)	5 (1.4)	38 (17.5)	149 (1.6)
Prevalence of pain	2,150 (67.2)	2,067 (73.3)	1,484 (63.4)	369 (69.2)	248 (71.7)	157 (72.4)	6,475 (68.5)
Medication use for pain, total	**533 (16.7)**	**426 (15.1)**	**147 (6.3)**	**110 (20.6)**	**80 (23.1)**	**59 (27.2)**	**1,355 (14.3)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	444 (13.9)	374 (13.3)	65 (2.8)	99 (18.6)	44 (12.7)	55 (25.3)	1,081 (11.4)
Non-steroidal antiinflammatory drugs (M01A)	19 (0.6)	36 (1.3)	21 (0.9)	11 (2.1)	24 (6.9)	3 (1.4)	114 (1.2)
Opioid analgesics (N02A)	39 (1.2)	51 (1.8)	2 (0.1)	4 (0.8)	-	12 (5.5)	108 (1.1)

Prevalence of acute/short-term illnesses in pregnancy and related medication use, overall and by drug groups	REGION						
	Western Europe	**Northern Europe**	**Eastern Europe**	**North America**	**South America**	**Australia**	**Total**
	n=3,201	**n=2,820**	**n=2,342**	**n=533**	**n=346**	**n=217**	**n=9,459**
	n (%)	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***
Prevalence of nausea	2,324 (72.6)	2,244 (79.6)	1,503 (64.2)	409 (76.7)	238 (68.8)	173 (79.7)	6,891 (72.9)
Medication use for nausea, total	**413 (12.9)**	**380 (13.5)**	**140 (6.0)**	**128 (24.0)**	**71 (20.5)**	**39 (18.0)**	**1,171 (12.4)**
By drug group							
First generation antihistamines (R06A)	150 (4.7)	259 (9.2)	21 (0.9)	84 (15.9)	9 (2.6)	4 (1.8)	527 (5.6)
Metoclopramide/domperidone/bromopride (A03FA)	134 (4.2)	69 (2.4)	27 (1.2)	10 (1.9)	45 (13.0)	25 (11.5)	310 (3.3)
Serotonin antagonists (A04AA)	4 (0.1)	8 (0.3)	1 (0.0)	28 (5.3)	1 (0.3)	11 (5.1)	53 (0.6)
Prevalence of UTI	513 (16.0)	327 (11.6)	452 (19.3)	93 (17.4)	92 (26.6)	25 (11.5)	1,502 (15.9)
Medication use for UTI, total	**315 (9.8)**	**221 (7.8)**	**192 (8.2)**	**56 (10.5)**	**63 (18.2)**	**17 (7.8)**	**864 (9.1)**
By drug group							
Unspecified penicillins (J01C-)	94 (2.9)	99 (3.5)	46 (2.0)	16 (3.0)	17 (4.9)	1 (0.5)	273 (2.9)
NOS Antibacterials for systemic use (J01-)	116 (3.6)	85 (3.0)	25 (1.1)	20 (3.8)	14 (4.0)	6 (2.8)	266 (2.8)
Penicillins with extended spectrum +/- beta-lactamase inhibitors (J01CA/J01CR)	85 (2.7)	78 (2.8)	44 (1.9)	14 (2.6)	17 (4.9)	1 (0.5)	239 (2.5)
Nitrofurantoin (J01XE)	7 (0.2)	25 (0.9)	54 (2.3)	10 (1.9)	3 (0.9)	1 (0.5)	100 (1.1)
Cephalosporins (J01D)	20 (0.6)	10 (0.4)	36 (1.5)	2 (0.4)	11 (3.2)	6 (2.8)	85 (0.9)
Total prevalence of any acute/short-term illness	**3,159 (98.7)**	**2,803 (99.4)**	**2,299 (98.2)**	**523 (98.1)**	**341 (98.6)**	**214 (98.6)**	**9,339 (98.7)**
Total medication use for any acute/short-term illness	**2,224 (69.5)**	**1,954 (69.3)**	**1,474 (62.9)**	**403 (75.6)**	**250 (72.3)**	**164 (75.6)**	**6,469 (68.4)**

[‡]Countries are grouped into regions as shown in Figure 1.

[†]Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Abbreviations: UTI: Urinary tract infection; NOS: Not otherwise specified.

Appendix 7: Prevalence of chronic/long-term disorders and most common medications used at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

	REGION						
Prevalence of chronic/long-term disorders in pregnancy and related medication use, overall and by drug groups	**Western Europe n=3,201**	**Northern Europe n=2,820**	**Eastern Europe n=2,342**	**North America n=533**	**South America n=346**	**Australia n=217**	**Total n=9,459**
	n (%)	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***
Prevalence of hypothyroidism	130 (4.1)	118 (4.2)	105 (4.5)	22 (4.1)	11 (3.2)	6 (2.8)	392 (4.1)
Medication use for hypothyroidism, total	**118 (3.7)**	**113 (4.0)**	**96 (4.1)**	**21 (3.9)**	**9 (2.6)**	**6 (2.8)**	**363 (3.8)**
By drug group							
Thyroid hormone, levothyroxine (H03AA01)	117 (3.7)	112 (4.0)	89 (3.8)	21 (3.9)	9 (2.6)	6 (2.8)	354 (3.7)
Prevalence of asthma	163 (5.1)	193 (6.8)	58 (2.5)	43 (8.1)	12 (3.5)	24 (11.1)	493 (5.2)
Medication use for asthma, total	**122 (3.8)**	**133 (4.7)**	**38 (1.6)**	**35 (6.6)**	**8 (2.3)**	**24 (11.1)**	**360 (3.8)**
By drug group							
Inhalant selective beta-2 agonists (R03AC)	94 (2.9)	66 (2.3)	26 (1.1)	32 (6.0)	7 (2.0)	24 (11.1)	249 (2.6)
Adrenergics and other drugs for COPD (R03AK)	33 (1.0)	46 (1.6)	10 (0.4)	3 (0.6)	2 (0.6)	7 (3.2)	101 (1.1)
Inhalant glucocorticoids (R03BA)	28 (0.9)	40 (1.4)	13 (0.6)	12 (2.3)	-	4 (1.8)	97 (1.0)
Systemic selective beta-2 agonists (R03CC)	-	30 (1.1)	-	2 (0.4)	-	-	32 (0.3)
Prevalence of allergy	205 (6.4)	372 (13.2)	163 (7.0)	51 (9.6)	20 (5.8)	23 (10.6)	834 (8.8)
Medication use for allergy, total	**66 (2.1)**	**171 (6.1)**	**65 (2.8)**	**24 (4.5)**	**13 (3.8)**	**17 (7.8)**	**356 (3.8)**
By drug group							
Second generation antihistamines (R06A)	29 (0.9)	104 (3.7)	27 (1.2)	17 (3.2)	4 (1.2)	5 (2.3)	186 (2.0)
Nasal corticosteroids (R01AD)	11 (0.3)	32 (1.1)	17 (0.7)	-	-	7 (3.2)	67 (0.7)
First generation antihistamines (R06A)	13 (0.4)	29 (1.0)	10 (0.4)	9 (1.7)	6 (1.7)	4 (1.8)	71 (0.8)
Prevalence of depression	95 (3.0)	144 (5.1)	29 (1.2)	52 (9.8)	4 (1.2)	25 (11.5)	349 (3.7)
Medication use for depression, total	**61 (1.9)**	**100 (3.5)**	**11 (0.5)**	**29 (5.4)**	**1 (0.3)**	**23 (10.6)**	**225 (2.4)**
By drug group							
SSRI antidepressants (N06AB)	44 (1.4)	82 (2.9)	6 (0.3)	14 (2.6)	-	14 (6.5)	160 (1.7)

Prevalence of chronic/long-term disorders in pregnancy and related medication use, overall and by drug groups	REGION						
	Western Europe	**Northern Europe**	**Eastern Europe**	**North America**	**South America**	**Australia**	**Total**
	n=3,201	**n=2,820**	**n=2,342**	**n=533**	**n=346**	**n=217**	**n=9,459**
	n (%)	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***
SNRIs/mianserin/trazodone/mirtazapine/bupropion	9 (0.3)	11 (0.4)	1 (0.0)	15 (2.8)	-	7 (3.2)	43 (0.5)
Anxiolytics, benzodiazepine (N05BA)	6 (0.2)	2 (0.1)	5 (0.2)	-	-	1 (0.5)	14 (0.1)
Antipsychotics quetiapine/olanzapine (N05AH)	2 (0.1)	4 (0.1)	-	3 (0.6)	-	3 (1.4)	12 (0.1)
Total prevalence of any chronic/long-term disorder	**617 (19.3)**	**831 (29.5)**	**576 (24.6)**	**154 (28.9)**	**51 (14.7)**	**72 (33.2)**	**2,301 (24.3)**
Total medication use for any chronic/long-term disorder	**462 (14.4)**	**593 (21.0)**	**322 (13.7)**	**119 (22.3)**	**38 (11.0)**	**70 (32.3)**	**1,604 (17.0)**

[†]Countries are grouped into regions as shown in Figure 1.

[†]Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Abbreviations: COPD: Chronic obstructive pulmonary disease; SSRI: Selective serotonin re-uptake inhibitors; SNRI: Serotonin–noradrenaline reuptake inhibitors.

II

Medication use before, during, and after pregnancy among women with eating disorders: a study from the Norwegian Mother and Child Cohort Study

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Abstract

Introduction: Little is known about medication use among women with eating disorders in relation to pregnancy.

Aims: To explore patterns and associations between use of psychotropic, gastrointestinal and analgesic medications and eating disorders in the period before, during and after pregnancy.

Method: This study is based on the Norwegian Mother and Child Cohort Study (MoBa). A total of 62,019 women, enrolled at approximately 17 weeks' gestation, had valid data from the Norwegian Medical Birth Registry and completed three MoBa questionnaires. The questionnaires provided diagnostic information on broadly defined anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED) and recurrent self-induced purging in the absence of binge eating (EDNOS-P), along with self-reported use of medication six months before, during, and 0-6 months after pregnancy.

Results: The prevalence of eating disorder subtypes before and/or during pregnancy was: 0.09% AN (n=54), 0.94% BN (n=585), 0.10% EDNOS-P (n=61) and 5.00% BED (n=3104). The highest over-time prevalence of psychotropic use was within the AN (3.7-22.2%) and EDNOS-P (3.3-9.8%) groups. Compared to controls, BN was directly associated with incident use of psychotropics in pregnancy (adjusted RR: 2.25, 99% CI: 1.17-4.32). Having AN (adjusted RR: 5.11, 99% CI: 1.53-17.01) or EDNOS-P (adjusted RR: 6.77, 99% CI: 1.41-32.53) was directly associated with use of anxiolytics/sedatives postpartum. The estimates of use of analgesics (BED) and laxatives (all eating disorders subtypes) were high at all time periods investigated.

Conclusions: Use of psychotropic, gastrointestinal, and analgesic medications is extensive among women with eating disorders in the period around pregnancy. Female patients with eating disorders should receive evidence-based counseling about the risk of medication exposure versus the risk of untreated psychiatric illness during pregnancy and postpartum.

Introduction

Eating disorders are serious mental illnesses primarily affecting women of childbearing age. It is estimated that 0.9%, 1.5%, and 3.5% of the female population experience anorexia nervosa (AN), bulimia nervosa (BN), or binge eating disorder (BED), respectively, over the life time [1]. During pregnancy, up to 7.5% of women may meet the diagnostic criteria for an eating disorder [2]. Few clinical trials have tested pharmacotherapy options for treatment of patients with eating disorders. Although there is no evidence supporting general use of antidepressants or antipsychotics for the treatment of AN, selective serotonin reuptake inhibitor (SSRI) antidepressants seem to moderately reduce the symptoms of BN and BED, but exert little effect on full recovery [3-7]. Previous research in clinical settings has shown that 13% and 49% of women with AN use antipsychotics an antidepressants, respectively [8]. Nevertheless, little is known about the extent of use of psychotropics in a population-based setting.

The use of medication in women with eating disorders has as far as we know not been explored in relation to pregnancy. Inadequate evidence-based counseling about medication safety in pregnancy and negative information framing may led women to discontinue needed medication once pregnant [9]. However, since pharmacotherapy with psychotropics might reduce pregnancy-related exacerbation of eating disorder symptoms such as dieting or vomiting, their effect would probably be beneficial for both mother and fetus rather than detrimental. Since extreme dieting, compensatory behaviors, or psychiatric comorbidity among patients with eating disorders are associated with several painful conditions, including gastrointestinal complaints [10,11], a comprehensive understanding of medication use beyond psychotropics including analgesics and gastrointestinal medication in women with eating disorders, is essential to ensure maternal-fetal health.

Thus, this study investigated patterns of use of psychotropic, analgesic, and gastrointestinal medications before, during, and after pregnancy across eating disorder subtypes, and explored the relationship between eating disorders and use of these specific medications during pregnancy and the postpartum, including whether there was a direct association between eating disorders and medication use or whether the association was indirect, e.g. via an underlying maternal depression and anxiety. We hypothesized a higher extent of medication use in the pregnancy and postpartum periods among women with eating disorders compared to healthy controls.

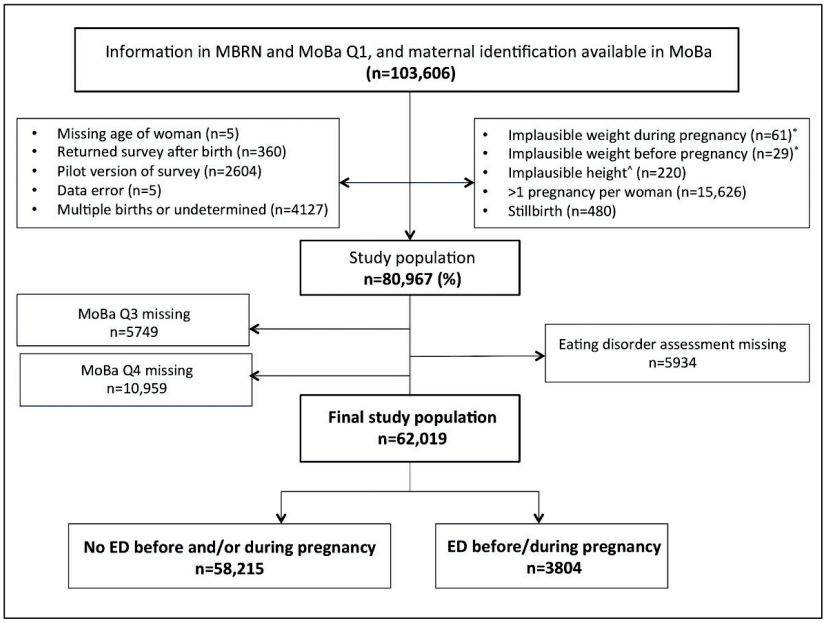
Materials and methods

Study population and data collection

This study is based on the Norwegian Mother and Child Cohort Study (MoBa) and on records in the Medical Birth Registry of Norway (MBRN). MoBa is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health [12]. Participants were recruited from all over Norway from 1999-2008. The women consented to participation in 40.6% of the pregnancies [13]. The cohort now includes 114.500 children, 95.200 mothers and 75.200 fathers. Participants were recruited through a postal invitation in connection with a routine ultrasound examination offered to all pregnant women in Norway at 17-18 weeks of gestation. The current study is based on version 7 of the quality-assured data files released for research including women who delivered between 1999 and 2009. Informed consent was obtained from each participant. The study was approved by The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

The MBRN is based on compulsory notification of all live births, stillbirths and induced abortions and includes information on pregnancy, delivery and neonatal health [14]. Data from MoBa was linked to the MBRN via the women's personal identification number. The analysis population for this study included women who had a record in MBRN, and had answered three self-administered MoBa questionnaires [15]. The first (Q1) and third (Q3) questionnaires were completed in gestational weeks 13-17 and 30, respectively; the fourth questionnaire (Q4), concerning the period from gestational week 30 and onwards, was distributed when the infant was six months old [12,15]. Among those who agreed to participate in the MoBa, the response rate was 95% for Q1, 92% for Q3, and 87% for Q4 [12]. The exclusion criteria and flow-chart to achieve the final population analysis are outlined in Fig. 1.

Fig. 1. Flow-chart to achieve final study population



Conditions may overlap: excluded participants are not mutually exclusive.
*Weight either < 30 Kg or > 300 Kg; ^Height < 100 cm.

Measures

Eating disorder

Q1 included items on eating disorders and disordered eating behaviors designed in accordance with the DSM-IV criteria [16]. These items have previously been used for studies on eating disorders in the Norwegian Institute of Public Health Twin Panel [17,18]. In our analysis population, respondents completed Q1 at a median of 17.1 weeks of gestation (interquartile range 16.0–18.6 weeks). Diagnostic algorithms and hierarchies were constructed to define the presence of eating disorders in the six months prior to pregnancy (retrospective assessment) and during pregnancy. Broadly defined AN was defined as meeting the DSM-IV criteria for AN with the exception of amenorrhea. Our definition of AN is more in accordance with DSM-5 since the amenorrhea criterion is eliminated. It was not possible to classify AN during pregnancy because of the missing body mass index (BMI) criterion due to pregnancy-induced weight gain. The other eating disorder categories

included: broadly defined BN, endorsing at least a weekly frequency of binge eating and either purging (vomiting, laxatives) or non-purging (exercise, fasting) compensatory behaviors; broadly defined BED, at least a weekly frequency of binge eating in the absence of compensatory behaviors; and eating disorder not otherwise specified-purging subtype (EDNOS-P), purging at least weekly in the absence of binge eating. Questions for binge eating included both eating an unusually large amount of food and the feeling of loss of control. The frequency criteria for binge eating and purging in BN, BED, and EDNOS-P differed from the DSM-IV criteria but reflect the new DSM-5 criteria (once a week instead of twice a week). As the symptom profile for many women changed in the interval before pregnancy and during pregnancy, the following diagnostic hierarchy was applied in order to assign only one diagnosis to each woman: AN, BN, EDNOS-P, BED, and no eating disorder. All individuals who met AN criteria before pregnancy were categorized as AN regardless of presentation during pregnancy. Those who met BN criteria either before or during pregnancy and who did not meet AN criteria prior to pregnancy were categorized as BN. If not classified as AN or BN, those who met criteria for EDNOS-P before or during pregnancy and did not endorse binge eating at either time were categorized as EDNOS-P. Similarly, individuals who endorsed BED and did not endorse purging during or before pregnancy were included in the BED group. Group assignment was made only when all responses were available to ensure accurate classification.

Outcome assessment

Self-reported information about type and timing of medication use was available from the MoBa Q1, Q3 and Q4. Respondents were asked to report medication use for numerous chronic, short-term, and pregnancy-related conditions as free entry text, along with the timing of use (six months before pregnancy; first, second and third trimesters; and two time periods postpartum [0-3 and 4-6 months after childbirth]). All medications recorded in Q1, Q3 and Q4 were grouped according to the Anatomical Therapeutic Chemical (ATC)[19] codes, as outlined in S1 Table, into: psychotropics (i.e., antidepressants, antipsychotics, anxiolytics and sedatives), gastrointestinal medications (i.e., antacids, drugs for peptic ulcer and gastro-esophageal reflux disease, laxatives), and analgesics (i.e., opioids, acetaminophen and other antipyretics, and nonsteroidal anti-inflammatory drugs [NSAIDs]). When multiple drugs were used and multiple timings checked, we considered the drugs to be used in all time periods. Our outcome measures (dichotomous 'Yes/No') were: a) medication use at any time "during pregnancy", and "after pregnancy" separately, irrespective of the

respondents's medication use status in the other time periods; b) incident use of medications "during pregnancy only" (i.e., women who started taking the medication in pregnancy and were not using that medication neither before nor after pregnancy) and "postpartum only" (i.e., women who started taking the medication postpartum and were not using that medication neither before nor during pregnancy).

Assessment of maternal mental health

Symptoms of depression and anxiety during pregnancy and postpartum were measured via the short versions of The Hopkins Symptom Checklist-25 (SCL-25): the Symptom Checklist-5 (SCL- 5) in Q1, and the Symptom Checklist-8 (SCL-8) in Q3 and Q4 [20,21]. The scale is considered a reliable screening instrument for depression and anxiety as defined by the ICD-10 [22]. Both SCL-5 and SCL-8 are highly correlated to the SCL-25 [21,23]. For each item of the scales, a score from 1 to 4 can be assigned. Whenever the respondent completed more than a half of the items, imputed values were generated on both instruments via utilization of the estimation-maximization algorithm. Values were imputed for 1.4%, 5.4%, and 8.9% of the study population in SCL-5 (Q1), SCL-8 (Q3), and SCL-8 (Q4), respectively. For all three instruments, the mean score was separately computed. Presence of depressive and anxiety symptoms during pregnancy was defined by a score greater than 2.0 in the SCL-5 and greater than 1.85 in the SCL-8 [20]. The mean scores for the SCL-5 in Q1 and the SCL-8 in Q3 were summed (mean sum score) in order to measure symptoms of depression and anxiety throughout the pregnancy.

Assessment of potential confounders and mediators

Maternal socio-demographics (i.e., age, educational level, socio-economic status, BMI at conception, weight gain during pregnancy, weight decrease after childbirth, illnesses during pregnancy), life-style characteristics (i.e., smoking and alcohol intake during pregnancy) and the degree of maternal depressive and anxiety symptoms during pregnancy (mean sum score of SCL-5 and SCL-8) and postpartum (mean score of the SCL-8) were all analyzed as potential confounders or mediators. Confounding and mediating factors were identified with the aid of directed acyclic graphs (DAGs) using DAGitty version 2.2 (one DAG for each medication-outcome pair) [24]. Our assumptions were: eating disorder status before and/or during pregnancy precedes maternal symptoms of

depression and anxiety during pregnancy; eating disorder status before and/or during pregnancy determines BMI at conception. These assumptions applied to all the eating disorder subtypes.

Statistical analysis

All statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM® SPSS® Statistics). The Pearson chi-square or Fisher exact test, and the Student's t-test were utilized to compare proportions and mean scores between independent groups, respectively. Because of the numerous analyses, we undertook a conservative approach and considered p-values of ≤ 0.01statistically significant.

The Generalized Estimating Equations (GEE) with a Poisson distribution [25] was used to test differences in medication use across the eating disorder subtypes. In the first set of analyses we explored medication use "during pregnancy" and "after pregnancy" separately. In the second set, we assessed incident use of medications "during pregnancy only" and "postpartum only". In the two sets of analyses we carried out the following steps: we first computed crude relative risks (RR) with 99% CI. Then, we entered in Model 1 the minimal sufficient adjustment set of variables (i.e., age, socioeconomic, status and educational level for all medication groups) for estimating the total association between eating disorders and the outcomes of interest. In a sensitivity analysis we included BMI at conception as additional covariate in Model 1 (because of the uncertainty in the direction of the association between BMI and eating disorders); however, the observed results did not differ substantially from the main analyses. In Model 2 we entered the set of confounders from Model 1 plus additional covariates (e.g., maternal depressive and anxiety symptoms, BMI, weight gain in pregnancy) in order to estimate the direct association between eating disorders and the outcomes of interest. Data are presented as crude and adjusted RR if there were at least three cases of women with eating disorders exposed to the specific medication groups.

Results

Population characteristics

A total of 62,019 women were included in this study (Fig. 1). Those excluded from the analysis because of missing eating disorder assessment (n=5,934, 9.6%) were significantly older, had less education, lower socio-economic status, and higher BMI at conception than those included. The

prevalence of eating disorder subtypes before and/or during pregnancy was: 0.09% AN (n=54), 0.94% BN (n=585), 0.10% EDNOS-P (n=61) and 5.00% BED (n=3,104). The remaining 93.87% did not present with any eating disorders (reference group).

Maternal socio-demographics, life-style factors, morbidities, and mental health characteristics across the eating disorder subtypes are outlined in Table 1. Women within the AN, BN, EDNOS-P, and BED groups more frequently had less education and lower socio-economic status than the reference group, and showed significantly higher rates of depressive and anxiety symptoms throughout the pregnancy (Table 1).

Patterns of medication use

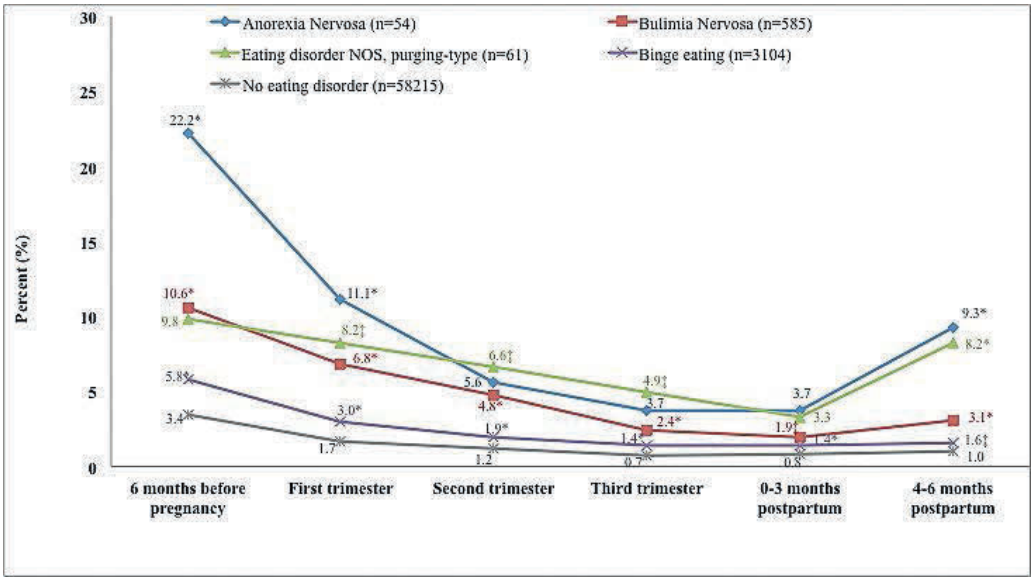
Fig. 2 outlines the extent of psychotropic medication use overtime across the various eating disorder subtypes. Women with AN or EDNOS-P reported the highest rate of psychotropic medication use prior, during and after pregnancy. Use of psychotropics decreased during pregnancy across all eating disorders compared to the period before conception; at 4-6 months postpartum the AN and EDNOS-P groups were characterized by a significant increase in such use (mainly anxiolytics and sedatives) (Fig. 2 and S2 table). The extent of use of the individual psychotropic medications overtime, including regular use at all time periods and across the various eating disorder subtypes is outlined in S2 table. Overall, antidepressants comprised the medication class most widely used before, during, and after pregnancy.

S1 and S2 Figs. outline the extent of use of gastrointestinal drugs and analgesics, respectively, according to timing and across the eating disorder subtypes. Patterns of use for the individual subgroups within gastrointestinal drugs and analgesics are shown in S3 and S4 tables, respectively. Women with any eating disorder were characterized by a high use of gastrointestinal drugs during pregnancy (especially in the second and third trimester) and postpartum. Compared to the reference group, all eating disorder subtypes were characterized by a higher rate of laxative use at some point before, during, or after pregnancy (S3 table).

Even though not always significantly different, use of analgesics was at almost all time points higher among women with AN than the reference counterpart (S2 Fig.). Women with BED were characterized by a significantly higher use of any type of analgesics before, as well as during and

after pregnancy. Also, women with AN, BN or BED were more likely than the reference group to use acetaminophen and other antipyretics at all time periods (S4 table).

Fig. 2: Use of psychotropic medications before, during, and after pregnancy by type of eating disorder[†]



Abbreviations: AN (anorexia nervosa), BN (bulimia nervosa), EDNOS-P (eating disorder not otherwise specified, purging type), BED (binge-eating disorder), ED (eating disorder). [†]Psychotropic medications include antidepressants, antipsychotics, anxiolytics and hypnotics and sedatives. [*]Indicates p-value ≤0.001; [‡]Indicates p-value ≤0.01.

Table 1: Maternal sociodemographics, morbidities and mental health across the eating disorder subtype (n=62,019)[†]

	AN (n=54)	BN (n=585)	EDNOS-P (n=61)	BED (n=3,104)	No ED (n=58,215)
Sociodemographics and life-style factors					
Age (in years)					
(Mean ± sd)	26.8 ± 4.7[*]	29.5 ± 4.7[‡]	28.0 ± 5.3[*]	30.1 ± 4.7	30.0 ± 4.5
BMI at conception[a]					
(Mean ± sd)	18.2 ± 0.6[*]	24.1 ± 4.3	23.7 ± 4.5	25.9 ± 5.1[*]	23.9 ± 4.1
Previous children (%)					
No	37 (68.5)	324 (55.4)	39 (63.9)	1,517 (48.9)[*]	32,226 (55.4)
Yes	17 (31.5)	261 (44.6)	22 (36.1)	1,587 (51.1)	25,989 (44.6)
Marital status (%)					
Married/cohabiting	52 (96.3)	540 (93.6)[*]	51 (85.0)[*]	2,958 (95.8)[*]	56,139 (96.9)
Others	2 (3.7)	37 (6.4)	9 (15.0)	130 (4.2)	1,822 (3.1)
Educational level[b] **(%)**					
Primary/secondary school	28 (57.1)[*]	244 (44.9)[*]	30 (50.0)[‡]	1,292 (43.8)[*]	18,514 (33.5)
University/higher degree	21 (42.9)	299(55.1)	30 (50.0)	1,657 (56.2)	36,691 (66.5)
Minimum household income (%)					
0-499,999 NOK ($0-77,999)	24 (46.2)[*]	114 (21.3)[‡]	17 (32.1)[‡]	632 (21.9)[*]	9,976 (18.3)
500-999,999 NOK ($78,000-155,999)	26 (50.0)	382 (71.4)	33 (62.3)	2,113 (73.1)	40,986 (75.3)
>1 million NOK ($156,000)	2 (3.8)	27 (5.0)	1 (1.9)	102 (3.5)	2,900 (5.3)
Unknown	-	12 (2.2)	2 (3.8)	45 (1.6)	567 (1.0)
Smoking during pregnancy[c] **(%)**					
No	42 (77.8)	457 (78.1)	49 (80.3)	2,456 (79.1)	45,567 (78.3)
Yes	3 (5.6)	47 (8.0)	6 (9.8)	249 (8.0)	4,710 (8.1)
Missing	9 (16.7)	81 (13.8)	6 (9.8)	399 (12.9)	7,938 (13.6)
Alcohol use during pregnancy[d] **(%)**					
No	37 (68.5)	433 (74.0)	49 (80.3)	2,184 (70.4)	41,171 (70.7)
Yes	10 (18.5)	65 (11.1)	5 (8.2)	341 (11.1)	6,340 (10.9)
Missing	7 (13.0)	87 (14.9)	7 (11.5)	579 (18.7)	10,704 (18.4)
Illnesses during pregnancy (%)					
Pelvic girdle/back/shoulder/other pains	45 (83.3)	483 (82.6)[*]	49 (80.3)	2,516 (81.1)[*]	42,937 (73.8)

	AN (n=54)	BN (n=585)	EDNOS-P (n=61)	BED (n=3,104)	No ED (n=58,215)
Headache/migraine	25 (46.3)	261 (44.6)*	24 (39.3)	1,298 (41.8)*	19,937 (34.2)
Gastrointestinal disorders[e]	41 (75.9)	406 (69.4)*	43 (70.5)	2,159 (69.6)*	35,803 (61.5)
Mental health during pregnancy (%)					
Depressive and anxiety symptoms[f]	12 (22.2)*	99 (16.9)*	8 (13.1)*	222 (7.2)*	1,255 (2.2)

Abbreviations: AN (anorexia nervosa), BN (bulimia nervosa), EDNOS-P (eating disorder not otherwise specified, purging type), BED (binge-eating disorder), ED (eating disorder); BMI (body mass index); NOK (Norwegian Kroners).

[a]The BMI is the weight in kilograms divided by the square of the height in meters: underweight: <18.5 kg/m^2; normal weight: 18.5-24.9 kg/m^2; overweight: 25.0-29.9 kg/m^2; obese≥30 kg/m^2.
[b]Primary or secondary education: <10 years (primary) or 10-12 years (secondary) of education; University degree or higher: college or university education.
[c]Indicates smoking until gestational week 30.
[d]Indicates alcohol use at the beginning of pregnancy, until gestational week 17.
[e]Includes heartburn/reflux, duodenal/stomach ulcers, Crohn disease/ulcerative colitis and other gastrointestinal problems.
[f]Indicates scoring over the cut-off point at both gestational weeks 17 (5-items Hopkins symptoms checklist SCL-5≥2) and 30 (8-items Hopkins symptoms checklist SCL8≥1.85).

[†]Numbers may not add up to total because of missing values (<5%). For the variables "smoking" and "alcohol use during pregnancy", missing values were up to 18% and a "missing category" was therefore created. The group "medication users with no ED" is the referent group for all analyses.
*Indicates p-value ≤ 0.001; [‡]Indicates p-value ≤ 0.01.

Association between eating disorders and medication use in pregnancy

Table 2 outlines the measure of association between the eating disorder subtypes and use of specific medication groups during pregnancy. After adjusting for confounding factors (Model 1), women with AN, BN, EDNOS-P, and BED had a significant 5.6-, 4.0-, 3.6- and 1.7-fold increased likelihood, respectively, to use psychotropics during pregnancy. Having BN was directly associated with use of psychotropics during pregnancy (1.8-fold magnitude). In a sub-analysis by psychotropic subgroup, BED was found to be significantly directly associated with use of antidepressants during pregnancy (aRR: 1.45, 99% CI: 1.01-2.08), while BN had such effect on use of anxiolytics and sedatives (aRR: 2.36, 99% CI: 1.26-4.41). Only BN was significantly directly associated with incident use of psychotropics during pregnancy (Model 2, aRR: 2.25, 99% CI: 1.17-4.32).

Women with BN or BED presented a significant 1.3- and 1.2-fold increased likelihood, respectively, for taking gastrointestinal drugs during pregnancy compared to controls (Model 1). However, only the EDNOS-P subtype was significantly directly associated with this outcome (specifically for antacids and laxatives). The BN and BED subtypes presented a significant modest likelihood to use analgesics during pregnancy (Model 1, 11-19% increased risk); however, none of the eating disorder subtypes was directly associated with this outcome (Model 2). In the second set of analysis, women with BED presented a small significant likelihood to be incident users of analgesics during pregnancy (Model 1, aRR: 1.14, 99% CI: 1.02-1.28), although the association was not direct.

Association between eating disorders and medication use postpartum

Table 3 outlines the measure of association between the eating disorder subtypes and use of specific medication groups postpartum. Women with AN, BN, EDNOS-P, and BED presented a significant 9.5-, 2.4-, 7.2- and 1.5-fold increased likelihood, respectively, to use psychotropics in the period 0-6 months after delivery compared to the reference group (Model 1). Only the EDNOS-P subtype was directly associated with this outcome (Model 2, 4.5-fold magnitude). In the sub-analysis on type of psychotropics, AN and EDNOS-P were directly associated with an increased likelihood of using anxiolytics/sedatives postpartum (Model 2, aRR: 5.11, 99% CI: 1.53-17.01; aRR: 6.77, 99% CI: 1.41-32.53, respectively).

In Model 1, BN was significantly associated with a 1.8-fold increased likelihood to take gastrointestinal drugs postpartum compared to controls, and also showed a direct association with this outcome (Model 2, 1.6-fold magnitude). Women with BED, even though in a modest magnitude, were more likely than the reference group to use analgesics postpartum (1.2-fold increased risk); however, the association was not direct. No eating disorder was significantly associated with incident use of gastrointestinal drugs or analgesics postpartum.

Discussion

To our knowledge this is the first population-based study addressing the extent of medication use among women with eating disorders in the period before, during, and after pregnancy. Several of our findings are important for clinical practice. First, knowledge that use of psychotropic medication, especially antidepressants, was common among women with any eating disorder in the preconception period as well as during pregnancy and postpartum may assist clinicians when following-up or counseling female patients with eating disorders. Indeed, women with eating disorders, either pregnant or planning a pregnancy, might be in special need of evidence-based counseling about the benefit-risk ratio of gestational exposure to antidepressants or other psychotropics, and that of untreated psychiatric illness. To date very little is known about the distinct effects of treated versus untreated eating disorders on perinatal outcomes [26,27]; however the detrimental impact of untreated maternal depression, which is highly comorbid with eating disorders, on maternal-fetal health has been documented [28,29].

Second, women with AN or EDNOS-P presented the highest rate of psychotropic drug use at all time periods investigated, which may be due to a high degree of psychiatric comorbidity compared to the other groups of women. Women with AN were also those with the highest extent of regular use (i.e., before, during and after pregnancy) of psychotropics (5.6%), which is not completely unexpected since more than one out of five women with AN presented symptoms of depression and anxiety during pregnancy. Kaye et al.[30] showed in a double-blind placebo-controlled trial that use of fluoxetine may be useful in improving outcome and preventing relapse of patients with AN after weight restoration; since most women with AN are weight restored during the course of the pregnancy, SSRI antidepressants, and in particular fluoxetine, may actually be more beneficial in this setting than before conception.

Table 2: Measure of association between eating disorder subtypes and medication use during pregnancy[†]

		Model 1[*]	Model 2[‡]
Medication group	**Crude RR (99% CI)**	**Adjusted RR (99% CI)**	**Adjusted RR (99% CI)**
Psychotropics			
AN (n=8)	**6.08 (2.62-14.12)**	**5.63 (2.30-13.76)**	1.98 (0.74-5.26)
BN (n=61)	**4.28 (3.11-5.89)**	**4.01 (2.84-5.66)**	**1.81 (1.21-2.71)**
EDNOS-P (n=7)	**4.71 (1.88-11.80)**	**3.63 (1.21-10.85)**	2.77 (0.95-8.08)
BED (n=135)	**1.78 (1.42-2.24)**	**1.71 (1.34-2.17)**	1.09 (0.82-1.44)
No ED (n=1,419)	Referent	Referent	Referent
Gastrointestinal drugs			
AN (n=14)	1.13 (0.63-2.05)	1.30 (0.73-2.33)	1.52 (0.83-2.81)
BN (n=167)	**1.25 (1.05-1.48)**	**1.27 (1.06-1.52)**	1.05 (0.84-1.30)
EDNOS-P (n=20)	1.43 (0.89-2.30)	1.52 (0.93-2.49)	**1.68 (1.09-2.59)**
BED (n=869)	**1.23 (1.13-1.32)**	**1.19 (1.10-1.29)**	1.01 (0.92-1.11)
No ED (n=13,306)	Referent	Referent	Referent
Analgesics			
AN (n=33)	1.24 (0.94-1.64)	1.42 (1.08-1.87)	1.27 (0.92-1.74)
BN (n=338)	**1.17 (1.07-1.28)**	**1.19 (1.08-1.31)**	1.09 (0.98-1.21)
EDNOS-P (n=35)	1.16 (0.88-1.55)	1.09 (0.78-1.53)	1.08 (0.75-1.57)
BED (n=1,760)	**1.15 (1.10-1.20)**	**1.11 (1.06-1.16)**	1.03 (0.98-1.09)
No ED (n=28,733)	Referent	Referent	Referent

[†]Indicates medication use at any point during pregnancy, irrespective of the medication use status before or after pregnancy. The RR is computed when there are at least 3 women exposed to the medication group of interest. Statistically significant results are in bold.

*Model 1: Adjustment done for maternal age (as continuous variable), socioeconomic status and educational level (for all medication groups).
[‡]Model 2: Adjustment done for all covariates in Model 1 with addition of alcohol use during pregnancy, smoking during pregnancy, weight gain during entire pregnancy (as continuous variable), BMI at conception (as continuous variable), depressive and anxiety symptoms throughout the pregnancy (as continuous variable), pain ailments in pregnancy (for analgesics), and gastrointestinal disorders during pregnancy (for gastrointestinal drugs).

Table 3: Association between eating disorder subtypes and use of medication in the postpartum period[†]

		Model 1[*]	Model 2[‡]
Medication group	**Crude RR (99% CI)**	**Adjusted RR (99% CI)**	**Adjusted RR (99% CI)**
Psychotropics			
AN (n=7)	**10.00 (4.02-24.94)**	**9.55 (3.58-25.48)**	2.87 (0.91-9.08)
BN (n=21)	**2.77 (1.58-4.85)**	**2.44 (1.29-4.61)**	0.93 (0.42-2.04)
EDNOS_P (n=5)	**6.33 (2.09-19.16)**	**7.16 (2.41-21.32)**	**4.47 (1.18-16.86)**
BED (n=62)	**1.54 (1.10-2.16)**	**1.46 (1.02-2.10)**	0.87 (0.56-1.35)
No ED (n=754)	Referent	Referent	Referent
Gastrointestinal medications			
AN (n=5)	2.14 (0.71-6.42)	2.43 (0.83-7.18)	1.84 (0.43-7.78)
BN (n=44)	**1.74 (1.19-2.53)**	**1.82 (1.22-2.72)**	**1.63 (1.03-2.58)**
EDNOS_P (n=1)	-	-	-
BED (n=155)	1.16 (0.94-1.42)	1.19 (0.95-1.48)	1.17 (0.92-1.49)
No ED (n=2,520)	Referent	Referent	Referent
Analgesics			
AN (n=24)	1.19 (0.81-1.76)	1.20 (0.79-1.84)	1.16 (0.71-1.90)
BN (n=237)	1.09 (0.95-1.24)	1.12 (0.98-1.29)	0.98 (0.84-1.15)
EDNOS_P (n=20)	0.88 (0.55-1.41)	0.89 (0.53-1.49)	0.77 (0.40-1.48)
BED (n=1,284)	**1.11 (1.05-1.17)**	**1.12 (1.06-1.19)**	1.06 (0.99-1.13)
No ED (n=21,710)	Referent	Referent	Referent

[†]Indicates medication use at any point in the period 0-6 months after delivery, irrespective of the medication use status before or during pregnancy. The RR is computed when there are at least 3 women exposed to the medication group of interest. Statistically significant results are in bold.
[*]Model 1: Adjustment done for maternal age (as continuous variable), socioeconomic status and educational level (for all medication groups).
[‡]Model 2: Adjustment done for all covariates in Model 1 with addition of weight decrease six months after delivery and breastfeeding status, depressive and anxiety symptoms postpartum, and cesarean section (for analgesics).

Third, women with EDNOS-P or AN had a 6.8- and 5.1-fold increased likelihood to be on pharmacotherapy with sedatives/anxiolytics in the postpartum period, even after cancelling out the effect of factors such as weight decrease postpartum or depressive and anxiety symptoms. The substantial physical changes accompanying motherhood may represent a special challenge for women with AN, being characterized by a profound fear of gaining weight and by a distorted perception of body shape. Although about 50% of women with AN or EDNOS-P have been shown to remit at 18 months postpartum [31], little is known about the course of these disorders in the earlier postpartum period. Women with AN or EDNOS-P were found to lose the gestational weight more quickly than controls over the first six months postpartum [32], thus for these women a return to restrictive weight control behaviors and a worsening of the anxiety symptomatology in the early postpartum period, requiring use of sedatives/anxiolytics, cannot be excluded.

Fourth, women with BED were characterized by an extensive use of analgesics before, during and after pregnancy. In the multivariate analysis, though, BED was not directly associated with analgesic use during pregnancy or postpartum, suggesting that other factors, namely depressive and anxiety symptoms, pain ailments, BMI, weight change during pregnancy and postpartum, rather than the binging behavior, might constitute the driving factors for using analgesics.

Lastly, our study revealed that use of laxatives is high among women with any eating disorders not only before pregnancy, but also during pregnancy and the postpartum, raising concerns about the impact of this practice on their own health and that of their unborn children.

Our observed rates of use of psychotropics in the preconception period were lower than those found in three previous studies among women with AN (53%), BED (18%), or all eating disorders (96.7%)[8,33,34]; different recruitment strategies, that is, population-based recruitment in the present study versus clinical research recruitment in others, country-specific therapeutic traditions and access to special care in different countries, could probably explain these discrepancies. Factors such as pregnancy planning might have also deflated our estimates; because of fear to harm the unborn child and elevated risk perception of medication exposure, many women may discontinue their needed pharmacotherapy during pregnancy or when attempting to conceive [35,36].

Compared to controls, BN was directly associated with use and incident use of pychotropics during pregnancy (1.8- and 2.3-fold, respectively). Since antidepressants have shown some

effects in reducing the binge-eating and vomiting behaviors and fluoxetine is the only medication approved for treatment of BN [37], this finding is expected. On the other hand, incident use of psychotropics might also represent a proxy of increased severity of a pre-existing or an incident case of BN. A previous study[38] using the same data source found that the most common pattern for BN was remission or partial remission of symptoms from the pre-pregnancy period to early pregnancy, and incident cases were rare. Given this scenario, we cannot exclude the possibility that pharmacotherapy with psychotropics might have contributed, at least to some extent, to remission of symptoms among women with BN. Also, women with BN might have sought specialist care and treatment once pregnant for the well-being of the fetus. Two previous studies have for example shown that use of dietary supplements and nutritional intake during pregnancy were similar among women with and without eating disorders [39,40], underscoring how these women do their utmost to ensure the well-being of the developing fetus.

The extent of use of gastrointestinal medication observed in our study was high across all the eating disorders and raises several concerns. In particular, women with BED were more often users of gastrointestinal medications during pregnancy (antacids, laxatives, and drugs for gastroesophageal reflux disease [GERD]) and postpartum (drugs for GERD), though not prior to pregnancy, suggesting a possible augmentation in severity or frequency of bingeing episodes during these periods, or more intense pregnancy-related bothers in the gastrointestinal tract secondary to the binge. Prior research using the MoBa cohort [38] has in fact shown that most women with BED experienced continuation of symptoms rather than remission during pregnancy compared to the period before conception, and incident cases were not uncommon. In our multivariate model, though, no direct associations between BED and use of gastrointestinal medications during pregnancy and postpartum were found, implying the importance of indirect factors, namely depressive and anxiety symptoms, weight gain or decrease, BMI and gastrointestinal concerns, on these associations. EDNOS-P, on the other hand, was directly associated with use of gastrointestinal medications during pregnancy (mostly antacids), which may be secondary to regurgitation episodes or to an intensification of purging behavior (i.e., vomiting) during pregnancy or, as shown by Torgersen et al., to the higher odds for these women to experience pregnancy-related vomiting [41].

In line with prior research showing an association between moderate to severe pain and eating disorders [42], we found that use of analgesics before, during and after pregnancy was high across all eating disorder subtypes. However, the multivariate analysis showed that when

accounting for factors such as depressive and anxiety symptoms, pain disorders and weight increase or decrease, none of the eating disorders were directly associated with any analgesic use neither during nor after pregnancy. The higher extent of use of NSAIDs in the third trimester among women with AN, BN or EDNOS-P, however, deserves attention. Women should be advised against use of NSAIDs in the third trimester since use of NSAIDs after week 32 has been associated with premature closure of the ductus arteriosus, oligohydramnios, and inhibition of labor [43].

Frequent follow-ups and support with treatment by a multidisciplinary team including obstetricians, psychiatrists, and therapists is of critical importance for women with eating disorders, especially in a vulnerable phase of life such as pregnancy and motherhood. The high burden of psychiatric comorbidity and the extensive medication use among these women deserves attention: clinicians are encouraged to query female patients about their medication-taking behavior and provide evidence-based counseling about the risk of medication exposure versus the risk of untreated psychiatric illness during pregnancy and postpartum. Sub-optimal treatment of maternal psychiatric illness might lead to adverse outcomes such as a relapse of the disorder, poor life-style or inadequate compliance with prenatal care, which are all harmful factors for both mother and child. In moderate to severe cases of psychiatric illness pharmacotherapy may be necessary [44].

Strengths and Limitations of the Study

The MoBa study encompasses several strengths and limitations. Data collection was carried out prospectively, avoiding the risk of recall bias. Use of medications in the period from gestational week 30 to childbirth was the only information collected retrospectively (in Q4), and may therefore suffer of recall bias. However, the impact of misclassification of use of SSRIs (the most common psychotropics in our sample) in late pregnancy on risk estimates was assessed as minimal [45]. The collection of a vast array of health-related and sociodemographic information enabled us to take into account several potential confounders and mediators. The utilization of DAGs permitted a proper selection of confounding factors for the multivariate models, thus diminishing the risk of over-adjustment. Symptoms of depression and anxiety were measured at two time points in pregnancy and at six months postpartum via utilization of validated instruments, i.e. the SCL-5 and SCL-8, which are reliable screening tools [20-23].

On the other hand, our study has several limitations that should be considered when interpreting the results. Assessment of broadly defined eating disorders was based on women´s self-report, however the questions posed to the study participants were consistent with diagnostic criteria [16]. Other psychometric instruments (e.g., the SCOFF questionnaire) could have been used to identify individuals with eating disorders; however, the eating disorder hierarchy employed in our study has been widely used [31,32,38,39,46]. The MoBa study has a low response rate (40.6% of all women invited), with a possible self-selection of the healthiest women to the study. On the other hand, among those who accepted the invitation, the response rate is high [12]. A previous study [13] has thoroughly examined self-selection and its potential for bias by comparing the MoBa study population with the total Norwegian birthing population, and concluded that although the prevalence estimates could not necessarily be generalized, the measures of associations tested were valid in the MoBa study. We cannot, however, rule out that some of the association found here could be influenced by selection bias.

It is plausible that women with eating disorders who participated in MoBa may represent the healthier end of the eating disorder severity spectrum because they had to be well enough to conceive and participate, especially women with AN. Furthermore, in this specific study women were included in the analysis only if they had completed Q1, Q3 and Q4; hence, a risk of attrition bias cannot be ruled out. Indeed, the burden of eating disorder before and/or during pregnancy as well as the severity of the underlying depressive symptomatology around gestational week 17 were significantly higher among women lost to follow-up at gestational week 30 compared to the non-lost counterpart. Further, women excluded from the analysis because of missing items for the eating disorder assessment had a more unfavorable profile than the included counterpart, implying a plausible exclusion of women with more severe eating disorder symptoms. Our sample was small for the AN and EDNOS-P groups, limiting the statistical power of most analyses.

Information on medication dosage is not available in the MoBa study and data about duration of exposure is not always adequate. Information about type and timing of medication use is self-reported, thus dependent on the accuracy of the women's reporting. However, the validity of self-reported use of antidepressants in the MoBa study has been found to be reliable [45]. Symptoms of depression and anxiety were measured by two self-assessment instruments; although such measurements cannot replace a clinical interview and are not designed to measure perinatal mood specifically, they provide a reliable measure of the severity of these psychiatric

conditions [20,22]. Lastly, we cannot rule out the presence of unmeasured factors confounding the association between eating disorders and medication use, and therefore cannot conclude with regard to whether the associations found reflect causal relationships.

Future studies should evaluate the distinct effect of treated and untreated eating disorders on perinatal outcomes and should focus on how obstetricians, psychiatrists, pharmacists, and midwives can form multidisciplinary teams to ensure that women with eating disorders in pregnancy receive the care and support they need for themselves and their children during this important phase of life.

Conclusions

Our study indicated that psychotropics, especially antidepressants, are widely used by women with eating disorders in the period before, during, and after pregnancy. In particular, women with AN or EDNOS-P were those most often taking psychotropics, which could partly be related to the high psychiatric comorbidity. Women with BN were more likely than healthy controls to initiate pharmacotherapy with psychotropics during pregnancy, even after accounting for the effect of indirect factors. Similarly, AN or EDNOS-P were directly associated with incident use of anxiolytics/sedatives over the six month period after childbirth. While women with BED were characterized by an extensive use of analgesics before, during and after pregnancy, use of laxatives was high among women with any eating disorder at all time periods investigated.

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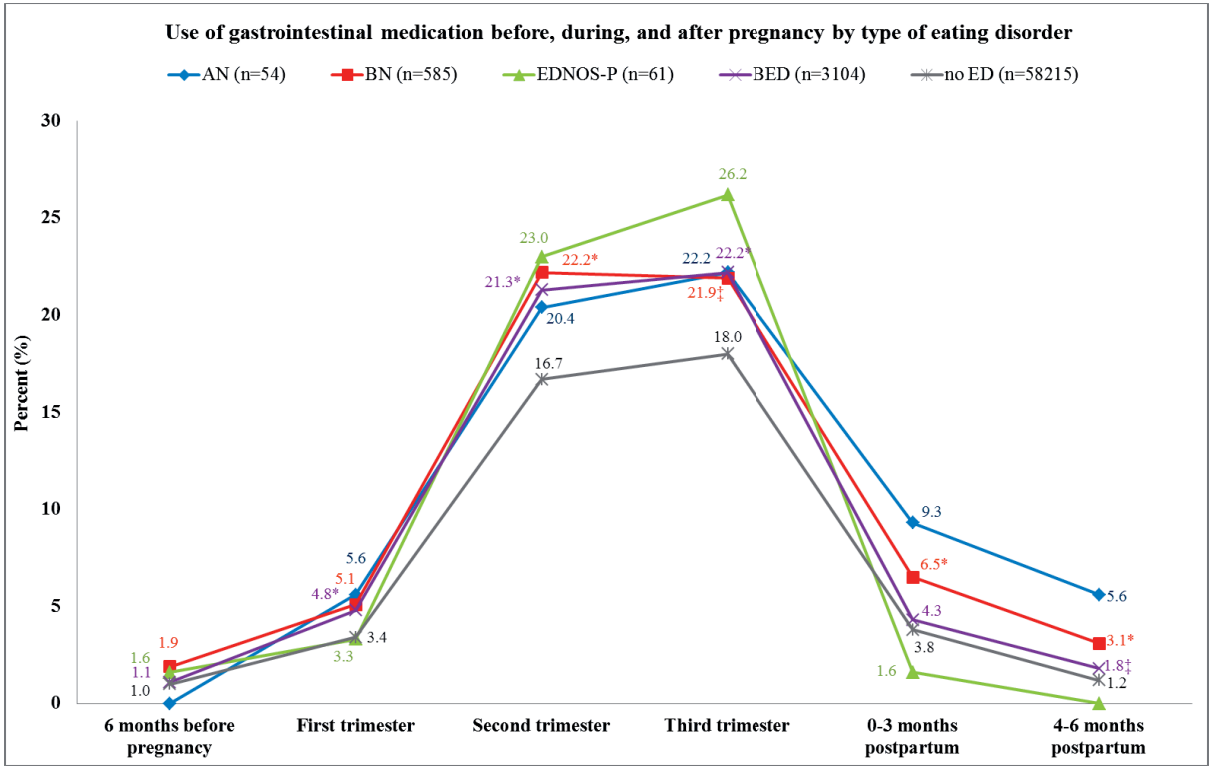
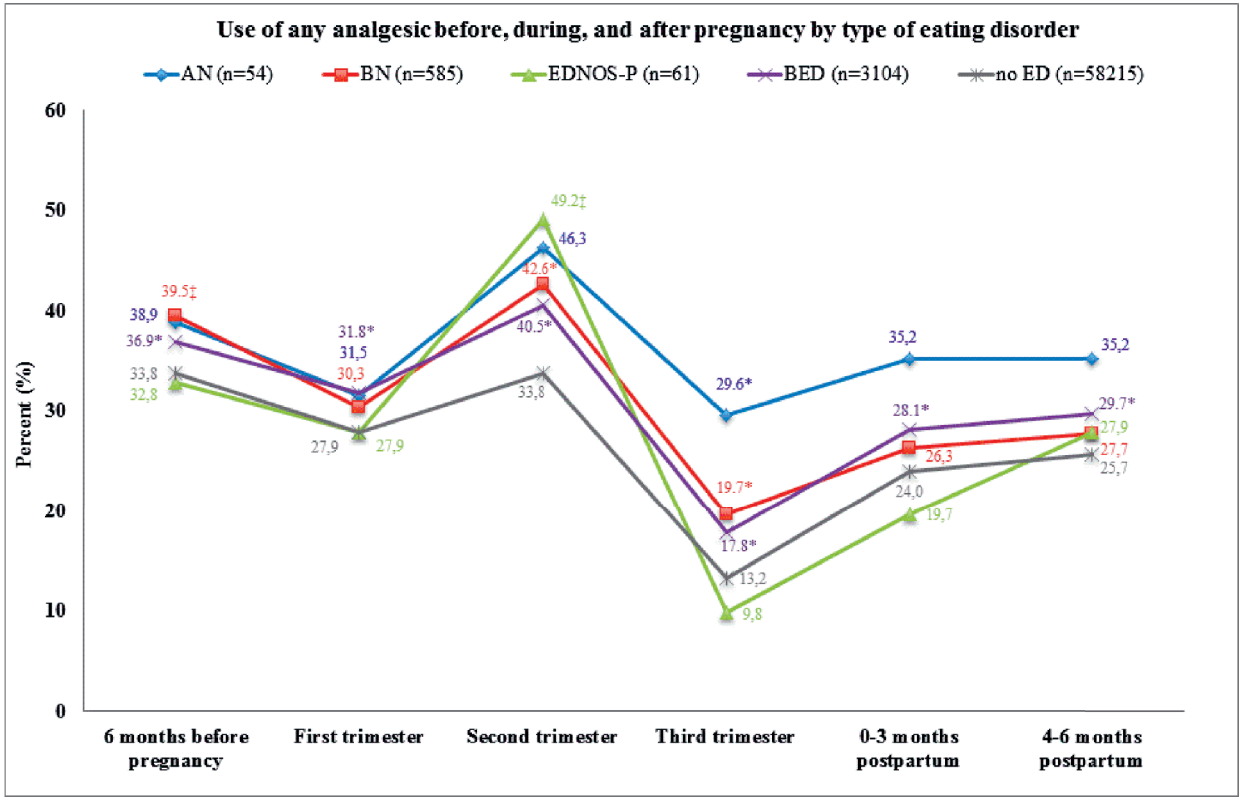
E-Figure 1: Use of gastrointestinal medications before, during, and after pregnancy by type of eating disorder†



Abbreviations: AN (anorexia nervosa), BN (bulimia nervosa), EDNOS-P (eating disorder not otherwise specified, purging type), BED (binge-eating disorder), ED (eating disorder). †Gastrointestinal medications include antacids, drugs for peptic ulcer and gastroesophageal reflux disease, and laxatives. *Indicates p-value ≤0.001; ‡Indicates p-value ≤0.01.

E- Figure 2: Use of analgesic medications before, during, and after pregnancy by type of eating disorder†



Abbreviations: AN (anorexia nervosa), BN (bulimia nervosa), EDNOS-P (eating disorder not otherwise specified, purging type), BED (binge-eating disorder), ED (eating disorder). †Analgesics comprise centrally acting analgesics (i.e. opioids and antipyretics) and NSAIDs. *Indicates p-value ≤ 0.001; ‡Indicates p-value ≤ 0.01.

E-table 1: Categorization of the medications groups included in the analyses according to the ATC classification system

Medication group	ATC code
Psychotropics	
Antidepressants	N06AA, N06AB, N06AX
Antipsychotics	N05A
Anxiolytics and sedatives	N05BA, N05BB, N05BE, N05CF, N05CD
Gastrointestinal drugs	
Antacids	A02AC, A02AD, A02AH
Drugs for peptic ulcer and GERD	A02BA, A02BB, A02BC, A02BX
Laxatives	A06AA, A06AB, A06AC, A06AD, A06AG, A06AH, A06AX
Analgesics	
Opioids	N02A
Acetaminophen and other antipyretics	N02B
Antiinflammatory and antirheumatic products, non-steroids (NSAIDs)	M01AB, M01AC, M01AE, M01AG, M01AH, M01AX

Abbreviations: ATC: Anatomical Therapeutic Chemical; GERD: Gastroesophageal reflux disease.

E-table 2: Use of psychotropic medication subgroups before, during, and after pregnancy by type of eating disorder[†]

Psychotropic medication group	AN (n=54)	BN (n=585)	EDNOS-P (n=61)	BED (n=3104)	No ED (n=58215)
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Antidepressants					
Before pregnancy	**9 (16.7)**[*]	**46 (7.9)**[*]	**6 (9.8)**[‡]	**156 (5.0)**[*]	1474 (2.5)
First trimester	**5 (9.3)**[*]	**24 (4.1)**[*]	**5 (8.2)**[*]	**66 (2.1)**[*]	469 (0.8)
Second trimester	**3 (5.6)**[‡]	**15 (2.6)**[*]	**3 (4.9)**[‡]	**33 (1.1)**[*]	254 (0.4)
Third trimester	1 (1.9)	**9 (1.5)**[*]	2 (3.3)	**28 (0.9)**[*]	185 (0.3)
Any time during pregnancy	**7 (13.0)**[*]	**33 (5.6)**[*]	**5 (8.2)**[*]	**86 (2.8)**[*]	586 (1.0)
0-3 months postpartum	-	**9 (1.5)**[*]	1 (1.6)	**25 (0.8)**[*]	236 (0.4)
4-6 months postpartum	2 (3.7)	**13 (2.2)**[*]	2 (3.3)	**35 (1.1)**[*]	359 (0.6)
Before, during and after pregnancy	1 (1.9)	**7 (1.2)**[*]	1 (1.6)	**17 (0.5)**[‡]	159 (0.3)
Anxiolytics and sedatives					
Before pregnancy	**5 (9.3)**[*]	**21 (3.6)**[*]	1 (1.6)	34 (1.1)	572 (1.0)
First trimester	1 (1.9)	**11 (1.9)**[*]	-	16 (0.5)	257 (0.4)
Second trimester	-	**8 (1.4)**[‡]	1 (1.6)	17 (0.5)	207 (0.4)
Third trimester	-	**6 (1.0)**[‡]	1 (1.6)	**19 (0.6)**[*]	160 (0.3)
Any time during pregnancy	1 (1.9)	**23 (3.9)**[*]	2 (3.3)	**46 (1.5)**[*]	494 (0.8)
0-3 months postpartum	1 (1.9)	2 (0.3)	1 (1.6)	20 (0.6)	218 (0.4)
4-6 months postpartum	**3 (5.6)**[‡]	7 (1.2)	**3 (4.9)**[‡]	22 (0.7)	257 (0.4)
Before, during and after pregnancy	1 (1.9)	-	**-**	3 (0.1)	44 (0.1)
Antipsychotics					
Before pregnancy	1 (1.9)	**5 (0.9)**[‡]	1 (1.6)	9 (0.3)	137 (0.2)
First trimester	1 (1.9)	**9 (1.5)**[‡]	-	19 (0.6)	344 (0.6)
Second trimester	-	7 (1.2)	-	13 (0.4)	294 (0.5)

Psychotropic medication group	**AN (n=54)**	**BN (n=585)**	**EDNOS-P (n=61)**	**BED (n=3104)**	**No ED (n=58215)**
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Third trimester	1 (1.9)	1 (0.2)	-	4 (0.1)	79 (0.1)
Any time during pregnancy	2 (3.7)	**12 (2.1)**‡	-	24 (0.8)	481 (0.8)
0-3 months postpartum	1 (1.9)	1 (0.2)	-	4 (0.1)	51 (0.1)
4-6 months postpartum	1 (1.9)	2 (0.3)	-	3 (0.1)	60 (0.1)
Before, during and after pregnancy	-	1 (0.2)	-	-	18 (0.03)

Abbreviations: AN (anorexia nervosa), BN (bulimia nervosa), EDNOS-P (eating disorder not otherwise specified, purging type), BED (binge-eating disorder), ED (eating disorder).

†The "No eating disorder" group is the reference group for all analyses.

*Indicates p-value ≤0.001; ‡Indicates p-value ≤0.01.

E-table 3: Use of gastrointestinal medication subgroups before, during, and after pregnancy by type of eating disorder[†]

Gastrointestinal medication group	AN (n=54)	BN (n=585)	EDNOS-P (n=61)	BED (n=3104)	No ED (n=58215)
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Antacids					
Before pregnancy	-	2 (0.3)	-	5 (0.2)	81 (0.1)
First trimester	-	7 (1.2)	1 (1.6)	40 (1.3)	551 (0.9)
Second trimester	2 (3.7)	37 (6.3)	7 (11.5)	**266 (8.6)**[*]	3536 (6.1)
Third trimester	6 (11.1)	43 (7.4)	9 (14.8)	**284 (9.1)**[*]	3923 (6.7)
Any time during pregnancy	6 (11.1)	49 (8.4)	10 (16.4)	**348 (11.2)**[*]	4805 (8.3)
0-3 months postpartum	-	**5 (0.9)**[‡]	-	14 (0.5)	135 (0.2)
4-6 months postpartum	-	**6 (1.0)**[‡]	-	11 (0.4)	124 (0.2)
Before, during and after pregnancy	-	**-**	-	-	6 (0.01)
Drugs for peptic ulcer and GERD					
Before pregnancy	-	5 (0.9)	-	29 (0.9)	453 (0.8)
First trimester	1 (1.9)	7 (1.2)	1 (1.6)	**57 (1.8)**[*]	654 (1.1)
Second trimester	6 (11.1)	67 (11.5)	6 (9.8)	**344 (11.1)**[*]	5258 (9.0)
Third trimester	6 (11.1)	74 (12.6)	6 (9.8)	**394 (12.7)**[*]	6315 (10.8)
Any time during pregnancy	7 (13.0)	92 (15.7)	8 (13.1)	**473 (15.2)**[*]	7503 (12.9)
0-3 months postpartum	-	2 (0.3)	-	**19 (0.6)**[‡]	184 (0.3)
4-6 months postpartum	-	-	-	**19 (0.6)**[‡]	173 (0.3)
Before, during and after pregnancy	-	-	-	2 (0.1)	27 (0.05)
Laxatives					
Before pregnancy	-	**5 (0.9)**[*]	1 (1.6)	1 (0.03)	76 (0.1)
First trimester	2 (3.7)	**21 (3.6)**[*]	-	67 (2.2)	936 (1.6)
Second trimester	5 (9.3)	**42 (7.2)**[*]	3 (4.9)	**154 (5.0)**[‡]	2247 (3.9)

Gastrointestinal medication group	**AN (n=54)**	**BN (n=585)**	**EDNOS-P (n=61)**	**BED (n=3104)**	**No ED (n=58215)**
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Third trimester	4 (7.4)	**35 (6.0)**[*]	5 (8.2)	107 (3.4)	1738 (3.0)
Any time during pregnancy	6 (11.1)	**61 (10.4)**[*]	6 (9.8)	**215 (6.9)**[‡]	3279 (5.6)
0-3 months postpartum	5 (9.3)	**31 (5.3)**[‡]	1 (1.6)	112 (3.6)	1945 (3.3)
4-6 months postpartum	**3 (5.6)**[‡]	**12 (2.1)**[*]	-	30 (1.0)	406 (0.7)
Before, during and after pregnancy	**-**	**-**	-	-	12 (0.02)

Abbreviations: AN (anorexia nervosa), BN (bulimia nervosa), EDNOS-P (eating disorder not otherwise specified, purging type), BED (binge-eating disorder), ED (eating disorder); GERD: Gastroesophageal reflux disease. Drugs for GERD include H2-receptor antagonists, prostaglandins, proton pump inhibitors, and other drugs for GERD (i.e., sucralfate and alginic acid).

[†]The "No eating disorder" group is the reference group for all analyses.

[*]Indicates p-value ≤0.001; [‡]Indicates p-value ≤0.01.

E-table 4: Use of any analgesic subgroups before, during, and after pregnancy by type of eating disorder[†]

Analgesic medication group	AN (n=54)	BN (n=585)	EDNOS-P (n=61)	BED (n=3104)	No ED (n=58215)
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Opioids					
Before pregnancy	3 (5.6)	**20 (3.4)**[‡]	1 (1.6)	**90 (2.9)**[*]	1065 (1.8)
First trimester	2 (3.7)	10 (1.7)	1 (1.6)	**45 (1.4)**[*]	505 (0.9)
Second trimester	3 (5.6)	**12 (2.1)**[‡]	3 (4.9)	**48 (1.5)**[‡]	592 (1.0)
Third trimester	1 (1.9)	6 (1.0)	-	**32 (1.0)**[‡]	378 (0.6)
Any time during pregnancy	4 (7.4)	19 (3.2)	3 (4.9)	**100 (3.2)**[*]	1215 (2.1)
0-3 months postpartum	1 (1.9)	9 (1.5)	1 (1.6)	52 (1.7)	697 (1.2)
4-6 months postpartum	1 (1.9)	9 (1.5)	1 (1.6)	**64 (2.1)**[*]	644 (1.1)
Before, during and after pregnancy	1 (1.9)	1 (0.2)	-	**14 (0.5)**[*]	108 (0.2)
Acetaminophen and other antipyretics					
Before pregnancy	20 (37.0)	190 (32.5)	19 (31.1)	**952 (30.7)**[‡]	16555 (28.4)
First trimester	16 (29.6)	167 (28.5)	15 (24.6)	**906 (29.2)**[*]	14998 (25.8)
Second trimester	25 (46.3)	**241 (41.2)**[*]	**29 (47.5)**[‡]	**1210 (39.0)**[*]	19040 (32.7)
Third trimester	**16 (29.6)**[*]	**112 (19.1)**[*]	6 (9.8)	**533 (17.2)**[*]	7352 (12.6)
Any time during pregnancy	32 (59.3)	**326 (55.7)**[*]	34 (55.7)	**1676 (54.0)**[*]	27500 (47.2)
0-3 months postpartum	18 (33.3)	144 (24.6)	10 (16.4)	**813 (26.2)**[*]	12859 (22.1)
4-6 months postpartum	18 (33.3)	148 (25.3)	13 (21.3)	**829 (26.7)**[*]	13480 (23.2)
Before, during and after pregnancy	**12 (22.2)**[‡]	**84 (14.4)**[‡]	5 (8.2)	**425 (13.7)**[*]	6322 (10.9)
NSAIDs					
Before pregnancy	9 (16.7)	86 (14.7)	7 (11.5)	**417 (13.4)**[‡]	6799 (11.7)
First trimester	4 (7.4)	29 (5.0)	2 (3.3)	**166 (5.3)**[‡]	2489 (4.3)
Second trimester	1 (1.9)	22 (3.8)	4 (6.6)	**121 (3.9)**[*]	1559 (91.3)

Analgesic medication group	**AN (n=54)**	**BN (n=585)**	**EDNOS-P (n=61)**	**BED (n=3104)**	**No ED (n=58215)**
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Third trimester	2 (3.7)	5 (0.9)	1 (1.6)	**59 (1.9)**[*]	554 (1.0)
Any time during pregnancy	5 (9.3)	53 (9.1)	4 (6.6)	**296 (9.5)**[*]	4057 (7.0)
0-3 months postpartum	3 (5.6)	34 (5.8)	3 (4.9)	**179 (5.8)**[‡]	2767 (4.8)
4-6 months postpartum	5 (9.3)	44 (7.5)	5 (8.2)	**213 (6.9)**[*]	3108 (5.3)
Before, during and after pregnancy	1 (1.9)	12 (2.1)	-	37 (1.2)	639 (1.1)

Abbreviations: AN (anorexia nervosa), BN (bulimia nervosa), EDNOS-P (eating disorder not otherwise specified, purging type), BED (binge-eating disorder), ED (eating disorder), NSAIDs (nonsteroidal anti-inflammatory drugs). Antipyretics include acetylsalicylic acid, acetaminophen alone or as a combination product.

[†]The "No eating disorder" group is the reference group for all analyses.

[*]Indicates p-value ≤0.001; [‡]Indicates p-value ≤0.01.

III

Research Article

PATTERNS AND FACTORS ASSOCIATED WITH LOW ADHERENCE TO PSYCHOTROPIC MEDICATIONS DURING PREGNANCY—A CROSS-SECTIONAL, MULTINATIONAL WEB-BASED STUDY

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Background: *No previous studies have explored how closely women follow their psychotropic drug regimens during pregnancy. This study aimed to explore patterns of and factors associated with low adherence to psychotropic medication during pregnancy.* **Methods:** *Multinational web-based study was performed in 18 countries in Europe, North America, and Australia. Uniform data collection was ensured via an electronic questionnaire. Pregnant women were eligible to participate. Adherence was measured via the 8-item Morisky Medication Adherence Scale (MMAS-8). The Beliefs about Prescribed Medicines Questionnaire (BMQ-specific), the Edinburgh Postnatal Depression Scale (EPDS), and a numeric rating scale were utilized to measure women's beliefs, depressive symptoms, and antidepressant risk perception, respectively. Participants reporting use of psychotropic medication during pregnancy (n = 160) were included in the analysis.* **Results:** *On the basis of the MMAS-8, 78 of 160 women (48.8%, 95% CI: 41.1–56.4%) demonstrated low adherence during pregnancy. The rates of low adherence were 51.3% for medication for anxiety, 47.2% for depression, and 42.9% for other psychiatric disorders. Smoking during pregnancy, elevated antidepressant risk perception (risk≥6), and depressive symptoms were associated with a significant 3.9-, 2.3-, and 2.5-fold increased likelihood of low medication adherence, respectively. Women on psychotropic polytherapy were less likely to demonstrate low adherence. The belief that the benefit of pharmacotherapy outweighed the risks positively correlated (r = .282) with higher medication adherence.* **Conclusions:** *Approximately one of two pregnant women using psychotropic medication demonstrated low adherence in pregnancy. Life-style factors, risk perception, depressive symptoms, and individual beliefs are important factors related to adherence to psychotropic medication in pregnancy. Depression and Anxiety 0:1–11, 2015.*

Key words: *adherence; pharmacotherapy; antidepressants; depression; anxiety; pregnancy*

INTRODUCTION

Psychiatric disorders, most commonly depression and anxiety, may develop among women of childbearing age.[1–3] Antenatal depressive and anxiety disorders, which are strongly coexistent, occur in as many as 13 and 8.5% of women, respectively.[2,4,5] Psychiatric disorders frequently require pharmacological treatment, even in pregnancy.[6] About 1–8% of women use antidepressants during pregnancy,[7–9] with selective serotonin reuptake inhibitors (SSRIs) being the preferred therapeutic choice for antenatal depressive and anxiety disorders.[3] Pharmacological treatment is however a special challenge among pregnant women since both effective treatment of the mother and prevention of harmful effects to the unborn child have to be assured.

Even though untreated depression or anxiety may pose harm to both mother and fetus and impair mother–child bonding,[10–12] women's overestimation of the teratogenic risk of medication, fear of harming the unborn child, and negative attitudes toward medication may negatively affect adherence to a needed pharmacotherapy.[13,14] Pregnancy has been described to be the driving factor for discontinuation of antidepressant therapy,[15] nevertheless, no previous studies have explored how closely pregnant women follow their psychotropic regimens in the context of ongoing use. Prior research has however indicated that overall 36–59% of women were poor adherers to their chronic regimens during pregnancy.[16,17]

Since medication discontinuation or suboptimal drug therapy of the underlying psychiatric disorder may lead to a relapse of the disorder over the course of the pregnancy and to adverse pregnancy outcomes,[10,11,18] more insight into the extent of and risk factors for low adherence during pregnancy is warranted. This study aimed to investigate the level of adherence to psychotropic medication during pregnancy for treatment of depression, anxiety, and other psychiatric disorders, and to explore whether maternal sociodemographics, mental health, women's beliefs, and risk perception are related to medication adherence during pregnancy.

MATERIALS AND METHODS

STUDY DESIGN AND DATA COLLECTION

This is a multinational, cross-sectional, web-based study performed in 18 countries in Western, Northern, and Eastern Europe; North America; and Australia. Pregnant women at any gestational week were eligible to participate. Data were collected via an anonymous electronic questionnaire (http://www.questback.com), accessible online for a period of 2 months in each participating country between October 1, 2011 and February 29, 2012. The complete questionnaire is presented elsewhere.[19] The questionnaire was open to the public via utilization of banners on national websites and/or social networks commonly visited by pregnant women. Websites were selected on the basis of the number of daily users. Information about recruitment tools utilized and Internet penetration rates in each participating country are described in details elsewhere.[17]

The questionnaire was first developed in Norwegian and English and then translated into other relevant languages. A pilot study in Finland, Italy, Norway, and Sweden elicited no major changes. Data from the pilot study were not included in the analysis. Collected data were scrutinized for the presence of potential duplicates but none were identified.

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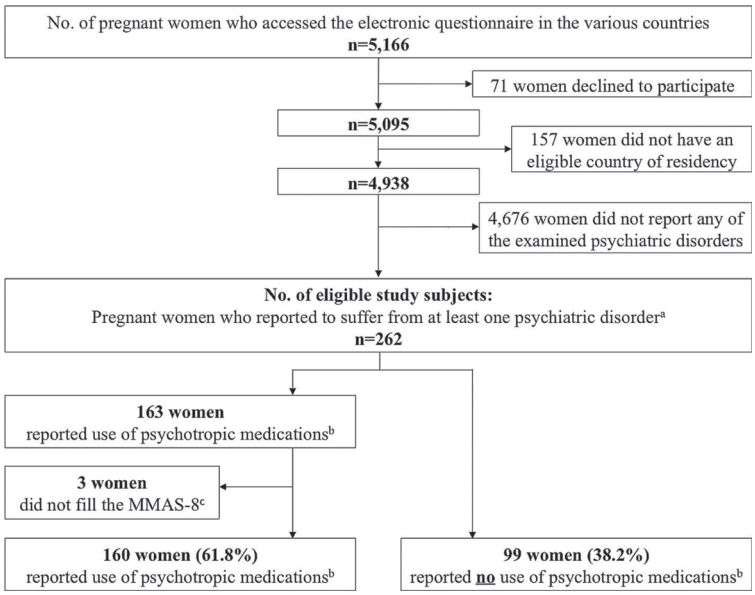

Figure 1. Participant flow-chart to achieve final analysis sample.
[a]Psychiatric disorders include depression, anxiety and other psychiatric disorders (i.e. bipolar, panic and personality disorders).
[b]Psychotropic medications include antidepressats, antipsychotics, anxiolytics, hypnotics and sedatives, antiepileptics and sedating antihistamines.
[c]MMAS-8 indicates the 8-item Morisky Medication Adherence Scale.

PSYCHOTROPIC MEDICATION USE

Participants were presented with a list of chronic disorders, including depression and anxiety. A free-text field was also available, where any other condition not previously listed could be specified. Women were then asked about medication use for each individual chronic disorder as free-text entry. All recorded medications were coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes in accordance with the World Health Organization (WHO) ATC index.[20] Pregnant women reporting depression, anxiety, or other psychiatric disorders (i.e., bipolar, panic, or personality disorders) were considered to be suffering from a psychotropic disorder and thus selected for the data analysis. Women reporting use of antidepressants (ATC N06A), antipsychotics (ATC N05A), anxiolytics (ATC N05B), hypnotics and sedatives (ATC N05C), antiepileptics (ATC N03A), or sedating antihistamines (ATC R06A) for the treatment of any psychiatric disorder were classified as psychotropic medication users (Fig. 1).

MEDICATION ADHERENCE

Adherence to medication was measured via the 8-item Morisky Medication Adherence Scale (MMAS-8).[21] The MMAS-8 is a structured, self-reported medication adherence measure with a satisfactory internal consistency (Cronbach's alpha reliability) of .83.[21–23] The MMAS-8 consists of seven yes/no items and one 5-point Likert scale. Each item measures specific medication-taking behavior, for example, "problems remembering to take the medication," "complexity of the therapeutic regimen," "feeling hassled about sticking to the treatment plan," and "stopping the regimen because the medication make the patient feel worse."[21] The predictive validity of the MMAS-8 has been examined through associations with blood pressure control among hypertensive patients (correct classification for high/medium adherence was 80.3%).[21] The participants completed one MMAS-8 for each self-reported psychiatric disorder. Validated translated versions of the original English MMAS-8 were available in eight languages other than English. For the remaining six languages, translation into the relevant language and back translation to English was done by two independent native speakers and/or translators. Professor DE Morisky approved the construct validity of all translated and/or adapted items of the MMAS-8 (Professor DE Morisky, personal e-mail communication).

For each disorder-specific MMAS-8, the sum score (range 0–8) was calculated and then trichotomized into low (sum score < 6), medium (sum score 6 or 7), and high (sum score $= 8$) adherence.[21] Imputed values were generated when respondents completed at least six of the

eight items on the MMAS-8 (≥75% completion), using the estimation–maximization algorithm.[24] Values were imputed for 1.9% of the study population.

MATERNAL SOCIODEMOGRAPHIC AND MEDICAL FACTORS

Maternal sociodemographics included time of gestation, previous children, marital status, folic acid use before and/or during pregnancy, unplanned pregnancy, country of residency, age, employment status at time of conception, educational level, mother tongue, smoking status during pregnancy, and alcohol consumption after awareness of pregnancy. Assessment of the study's external validity was done by comparing sociodemographic and life-style characteristics of the sample on an individual country level with those of the general birthing population in the country, as described in detail elsewhere.[17]

Maternal mental health was measured via the Edinburgh Postnatal Depression Scale (EPDS), a screening questionnaire for symptoms of depression during pregnancy and postpartum. The EPDS is a self-rating 10-item scale validated for major and minor depression in clinical settings and with satisfactorily Cronbach's alpha reliability (.87).[25] Each question was scored 0–3, producing a total score of 0–30. The cut-off for probable depression was set to 13.[25] Validated translated versions of the original EPDS were available for eight languages other than English.[26] For the Serbian version, translation and back translation were carried out by two independent linguistic experts and any discrepancies between the back-translated and original EPDS were settled. For the remaining five languages, we utilized translated versions used in previous studies.[27–30]

MEASUREMENT OF BELIEFS AND RISK PERCEPTION

Women's beliefs about medicines were explored via the Beliefs about Prescribed Medicines Questionnaire (BMQ-specific) that comprises two subscales: the BMQ-Necessity (five items) and BMQ-Concerns (five items).[31,32] Respondents indicated their degree of agreement with each statement on a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = uncertain, 4 = agree, and 5 = strongly agree). Individual item scores were added, giving a total score of 5–25. Higher scores indicate stronger beliefs in the concepts represented by the subscales. The belief variables were used as continuous in the analysis. The necessity–concerns differential was also calculated. Validated versions of the translated BMQ-specific subscales were used whenever available.[31],[33–38] For seven languages, translation of the original version and back translation were carried out by two independent linguistic experts; any discrepancies between the back-translated and original version were settled. Imputed values were generated when respondents completed at least four of the five items on each subscale, using the estimation–maximization algorithm.[24] Values were imputed for 2.5% of the study population.

Three statements were additionally used to explore women's beliefs about medication use during pregnancy: (1) "I have a higher threshold for using medicines when I am pregnant than when I am not pregnant," (2) "Even though I am ill and could have taken medicines, it is better for the fetus that I refrain from using them," (3) "Pregnant women should preferably use herbal remedies than conventional medicines." Respondents could indicate their degree of agreement with each statement on a 5-point Likert scale (0 = strongly disagree, 1 = disagree, 2 = uncertain, 3 = agree, 4 = strongly agree). The belief variables were used as continuous (score range 0–4) in the analysis.

The perceived risk of antidepressant exposure during pregnancy was measured via a numeric scale ranging from 0 (not harmful to the fetus) to 10 (very harmful to the fetus). Exposure to antidepressants was not considered to increase the risk for congenital anomalies in the offspring (3–6%).[39]

ETHICS

This study was carried out in compliance with the Helsinki Declaration. Informed consent was given by the participants by ticking the answer "yes" to the question "Are you willing to participate in the study?" Regional Ethics Committee in Norway, region Southeast, approved the study. Ethical approval or study notification to the relevant national Ethics Boards was achieved in specific countries as required by national legislation. All data were handled and stored anonymously.

STATISTICAL ANALYSIS

The Pearson chi-square and McNemar tests were used to compare proportions between independent and dependent groups, respectively. Student's *t*-test and one-way analysis of variance (ANOVA) with post hoc testing (Bonferroni correction) were utilized to compare mean scores among two or more groups, respectively. The Spearman's rank correlation coefficient was used to explore the correlation within the medication adherence sum scores and beliefs about medications. A *P*-value of < .05 was considered statistically significant.

Factors associated with medication adherence during pregnancy (dichotomous variable: low versus medium/high adherence) were explored via the Generalized Estimating Equations (GEE).[40] The GEE was used to take into account clustering on region of residency. Data are presented as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). A two-tailed *P*-value of < .05 was considered statistically significant. The multivariate GEE model was built as follows: candidate variables were selected based on a univariate *P*-value < .15; variables having no role (*P*-value > .05) or yielding a change smaller than 15% in the beta coefficients of the

retained variables were removed. Continuous variables were checked for linearity in the logit link. Because of nonlinearity, the variable antidepressant risk perception was categorized according to the nonlinearity midpoints (risk 0–3; 4–5; ≥6). The final multivariate model included statistically significant independent variables (smoking during pregnancy, number of psychotropic medications, EPDS score, and antidepressant risk perception) and potential confounders (i.e., week of gestation, educational level, and employment status).

Internal consistency was assessed via reliability analysis.[41] All statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM® SPSS® Statistics).

RESULTS

POPULATION CHARACTERISTICS

Five thousand one hundred sixty-six pregnant women accessed the electronic questionnaire and 5,095 (98.6%) completed it. Women with no eligible country of residency were excluded, leaving 4,938 participants. Among these, 262 (5.3%) pregnant women reported at least one psychiatric disorder and 163 of these reported use of psychotropic medications. Three of 163 women did not fill the MMAS-8 (<75% completion) and were excluded from the analysis, leading to a final study population of 160 and 99 women reporting use and nonuse, respectively, of psychotropic medications during pregnancy. Women with missing information in the MMAS-8 (<75% completion, $n = 3$) were more often of immigrant status compared to women who did fill the MMAS-8 (66.7 vs. 4.4%; $P = .008$). The mean gestational week at time of questionnaire completion was 20.9 (standard deviation: 10.5, range: 4–40). Data selection to achieve the final study sample is outlined in Fig. 1.

Of the 259 women with a psychiatric disorder, 160 (61.8%) reported treatment with psychotropic medications during pregnancy. Maternal characteristics and beliefs about medications according to medication use are shown in Tables 1 and 2, respectively. Most participants (200/259; 77.2%) were European residents, with 16.6% North American and 6.2% Australian residents, respectively. Women who used psychotropic medications differed significantly from nonusers in region of residency, age, parity, alcohol use after awareness of pregnancy, and pregnancy planning (Table 1). Women who did not use psychotropic medications most strongly believed that the necessity of medications did not outweigh their concerns and that despite being ill, it was better for the fetus to refrain from taking medications (Table 2).

Antidepressants (mainly SSRIs) were the most commonly used medication group (144/259; 55.6%). Specific estimates of psychotropic medication use are outlined in Supporting Information Table 1. The sample contained 53 women with concomitant psychiatric disorders, specifically depression/anxiety/other psychiatric disorders ($n = 4$), depression/other psychiatric disorders ($n = 2$), and depression/anxiety ($n = 47$). The majority of participants using psychotropic medication (120/160, 75.0%) were on monotherapy, whereas 18.7, 4.4, and 1.9% were treated with two, three, or four psychotropic medications, respectively.

ADHERENCE

Of the 160 psychotropic medication users, 78 (48.8%; 95% CI: 41.1–56.4%) demonstrated low adherence during pregnancy. The level of medication adherence by type of psychiatric disorder is outlined in Table 3. The rates of low adherence were 51.3% for anxiety, 47.2% for depression, and 42.9% for other psychiatric disorders. In corollary analyses, we observed no significant interdisorder difference (chi-square test, P-value = .392) in the rates of medication adherence among women concomitantly treated for depression (low: 42.6%; medium: 46.8%; high: 10.6%) and anxiety (low: 53.2%; medium: 38.3%; high: 8.5%). Among women treated for a single psychiatric disorder ($n = 107$), no significant difference in the mean adherence sum score was found across the three disorder groups (mean scores for depression/anxiety/other psychiatric disorders: 5.54/5.58/6.03, respectively; ANOVA test, $P = .792$). Also, the level of medication adherence did not significantly vary by trimester of pregnancy (mean scores for first/second/third trimester: 5.74/5.43/5.40, respectively; ANOVA test, $P = .624$).

FACTORS ASSOCIATED WITH LOW ADHERENCE

In the multivariate analysis, smoking during pregnancy, psychotropic monotherapy, elevated risk perception of antidepressants, and depressive symptoms during pregnancy were significantly associated with low adherence. The corresponding measures of association are shown in Table 4.

The association between medication adherence and the BMQ-Necessity and BMQ-Concerns by type of psychiatric disorder is outlined in Table 5. Overall, there was a positive correlation between increasing level of adherence to psychotropic medication and perception that the benefit of pharmacotherapy outweighed the risks ($r = .282$; $P < .001$).

DISCUSSION

This is the first study to explore adherence to prescribed psychotropic medication in pregnancy using a validated instrument. The study is also novel in providing insight into the effect of pregnant women's beliefs, perceptions of teratogenic risk, and depressive symptoms on adherence to psychotropic medications during pregnancy. Several findings are important for clinical practice. First, many women did not adhere to psychotropic medication during pregnancy; this may raise concerns about suboptimal control of the underlying maternal psychiatric disorder. Second, understanding women's beliefs about their psychotropic medications may

TABLE 1. Characteristics of the study population according to psychotropic medication use during pregnancy[a] (*n* = 259)

Maternal characteristics	Total study population (*n* = 259)	Use of psychotropic medication (*n* = 160)	No use of psychotropic medication (*n* = 99)	Use versus no use of psychotropic medication
	n (%)	*n* (%)	*n* (%)	*P*-value
Depressive symptoms[b]				
No	124 (49.8)	78 (50.6)	46 (48.4)	.733
Yes	125 (50.2)	76 (49.4)	49 (51.6)	
EPDS score (mean ± *SD*)	12.8 ± 5.9	12.5 ± 6.0	13.3 ± 5.6	.288
Gestational week (mean ± *SD*)	21.1 ± 10.4	20.9 ± 10.5	21.4 ± 10.5	.729
Region of residency[c]				
Western Europe	68 (26.3)	42 (26.2)	26 (26.3)	**.008**
Northern Europe	106 (40.9)	70 (43.8)	36 (36.4)	
Eastern Europe	26 (10.0)	9 (5.6)	17 (17.2)	
North America	43 (16.6)	25 (15.6)	18 (18.2)	
Australia	16 (6.2)	14 (8.8)	2 (2.0)	
Maternal age (years)				
≤20	10 (3.9)	3 (1.9)	7 (7.1)	**.001**
21–30	132 (51.0)	71 (44.4)	61 (61.6)	
≥31	117 (45.2)	86 (53.8)	31 (31.3)	
Previous children				
No	129 (49.8)	71 (44.4)	58 (58.6)	**.026**
Yes	130 (50.2)	89 (55.6)	41 (41.4)	
Marital status				
Married/cohabiting	221 (85.3)	137 (85.6)	84 (84.8)	.864
Single/divorced/others	38 (14.7)	23 (14.4)	15 (15.2)	
Folic acid use[d]				
Yes	241 (94.1)	147 (93.0)	94 (95.9)	.340
No	15 (5.9)	11 (7.0)	4 (4.1)	
Working status				
Employed, but not as HCP	119 (58.8)	70 (43.8)	49 (49.5)	.803
HCP	34 (13.1)	23 (14.4)	11 (11.1)	
Student	23 (8.9)	15 (9.4)	8 (8.1)	
Housewife	36 (13.9)	25 (15.6)	11 (11.1)	
Job seeker	19 (7.3)	11 (6.9)	8 (8.1)	
Other than above	28 (10.8)	16 (10.0)	12 (12.1)	
Highest educational level				
Lower than high school	32 (12.4)	20 (12.5)	12 (12.1)	.970
High school	73 (28.2)	44 (27.5)	29 (29.3)	
Higher than high school	122 (47.1)	77 (48.1)	45 (45.5)	
Others, unspecified	32 (12.4)	19 (11.9)	13 (13.1)	
Alcohol use after awareness of pregnancy				
No	209 (80.7)	121 (75.6)	88 (88.9)	**.009**
Yes	50 (19.3)	39 (24.4)	11 (11.1)	
Smoking before pregnancy				
No	139 (53.9)	87 (54.7)	52 (52.5)	.731
Yes	119 (46.1)	72 (45.3)	47 (47.5)	
Smoking during pregnancy				
No	215 (83.3)	130 (81.8)	85 (85.9)	.390
Yes	43 (16.7)	29 (18.2)	14 (14.1)	

(*Continued*)

assist clinicians in identifying women who are most likely to demonstrate low adherence. Third, knowledge that the most severely depressed women and those on psychotropic monotherapy are at greater risk of nonadherence may assist clinicians when following-up pregnant patients with psychiatric disorders.

Of the women with psychiatric disorders included in the study, 61.8% were taking psychotropics, suggesting a significant psychiatric morbidity. This factor would however only affect the representativeness of the results pertaining to the total study population (including users and nonusers of psychotropics), but not the comparison between these two groups or within the group of psychotropic medication users. The observed rates of low medication adherence during pregnancy were high across the different psychiatric disorders (42.9–51.3%).

TABLE 1. Continued

Maternal characteristics	Total study population ($n = 259$)	Use of psychotropic medication ($n = 160$)	No use of psychotropic medication ($n = 99$)	Use versus no use of psychotropic medication
	n (%)	*n* (%)	*n* (%)	*P*-value
Completely unplanned pregnancy				
Yes	38 (14.7)	29 (18.2)	9 (9.1)	**.044**
No	220 (85.3)	130 (81.8)	90 (90.9)	
Immigrant status[e]				
No	247 (95.4)	153 (95.6)	94 (94.9)	.802
Yes	12 (4.6)	7 (4.4)	5 (5.1)	

HCP, health-care provider; EPDS, Edinburgh Postnatal Depression Scale; *SD*, standard deviation.
Statistically significant results (i.e., *P* values < .05) are presented in bold.
Numbers may not add up to total due to missing values (<4%).
[a]Psychotropic medications include antidepressants, antipsychotics, anxiolytics, hypnotics and sedatives, antiepileptics, and sedating antihistamines.
[b]Defined as having a score ≥13 on the EPDS.
[c]Western Europe includes Austria, France, Italy, Switzerland, The Netherlands, and United Kingdom; Northern Europe includes Finland, Iceland, Norway, and Sweden; Eastern Europe includes Croatia, Poland, Russia, Serbia, and Slovenia; North America includes USA and Canada.
[d]Indicates folic acid use before and/or during pregnancy.
[e]Women having the first language different from the official main language in the country of residency.

The results are however in line with prevalence estimates of nonadherence in the general nonpregnant population with psychiatric disorders (40–53%),[42,43] but higher than what we previously found among women with somatic illness during pregnancy, using the same methodology.[17] The suboptimal treatment of psychiatric disorders in pregnant women is, however, of additional concern due to the potential risks of maternal–fetal health. Indeed, maternal depression during pregnancy may increase the risk of poor perinatal outcomes, such as premature delivery, low birth weight, and decreased breastfeeding initiation.[10,44] However, contradictory findings about the safety of antidepressants during pregnancy have so far posed significant challenges on practicing clinicians when assessing the risk of untreated depression versus the risk of pharmacotherapy.[45]

In the current study, we found that women's beliefs about medications were a powerful determinant of low adherence. Women's perception that the benefit of pharmacotherapy outweighed the risks and that herbal remedies should be preferred to conventional medications

TABLE 2. Beliefs about medications according to psychotropic medication use during pregnancy[a] ($n = 259$)

	Total study population ($n = 259$)	Use of psychotropic medication ($n = 160$)	No use of psychotropic medication ($n = 99$)	Use versus no use of psychotropic medication
Beliefs about medication	Mean score ± *SD*	Mean score ± *SD*	Mean score ± *SD*	*P*-value
BMQ-specific[b]				
Necessity	15.84 ± 5.55	17.36 ± 5.06	13.28 ± 5.42	**<.001**
Concerns	13.95 ± 4.28	14.02 ± 3.96	13.85 ± 4.79	.763
Necessity–concerns differential	1.87 ±6.81	3.33 ± 6.71	-0.57 ± 6.28	**<.001**
Pregnancy-specific beliefs[c]				
Statement 1	2.84 ± 1.45	2.79 ± 1.40	2.91 ± 1.53	.539
Statement 2	2.63 ± 1.27	2.48 ± 1.24	2.87 ± 1.28	**.018**
Statement 3	1.77 ± 1.24	1.70 ± 1.25	1.89 ± 1.21	.238

BMQ, Belief about Medicine Questionnaire; *SD*, standard deviation.
Statistically significant results (i.e., *P* values < .05) are presented in bold. Missing values are <5%.
[a]Psychotropic medications include antidepressants, antipsychotics, anxiolytics, hypnotics and sedatives, antiepileptics, and sedating antihistamines.
[b]The BMQ-specific questionnaire comprises the BMQ-Necessity and BMQ-Concerns subscales (score range: 5–25). Higher scores indicate stronger beliefs in the concepts represented by the subscales. The necessity–concerns differential is the difference between the BMQ-Necessity and BMQ-Concerns scores (positive scores indicate that the patient perception of the benefits of medication outweigh the risks, whereas a negative score indicates the converse). The BMQ-specific is copyrighted (©Professor Robert Horne).
[c]Statement 1: "I have a higher threshold for using medicines when I am pregnant than when I am not pregnant," Statement 2: "Even though I am ill and could have taken medicines, it is better for the foetus that I refrain from using them," Statement 3: "Pregnant women should preferably use herbal remedies than conventional medicines." Higher scores indicate stronger agreement with the statements.

TABLE 3. Women's level of adherence to psychotropic medications according to type of psychiatric disorder ($n = 160$)

Psychiatric disorder	No. of subjects[a] n	Cronbach's α	Adherence sum score[b] Mean ± *SD*	Low adherence n (%)	Medium adherence n (%)	High adherence n (%)
Depression	127	.73	5.51 ± 2.08	60 (47.2)	48 (37.8)	19 (15.0)
Anxiety	76	.64	5.32 ± 1.92	39 (51.3)	29 (38.2)	8 (10.5)
Other psychiatric disorders[c]	14	.79	6.23 ± 2.07	6 (42.9)	2 (14.3)	6 (42.9)
Total	160	-	5.52 ± 1.96	78 (48.8)	57 (35.6)	25 (15.6)

MMAS-8, 8-Item Morisky Medication Adherence Scale; *SD*, standard deviation.
[a]Number of subjects exceeds 160 due to overlapping psychiatric disorders and related medication use.
[b]MMAS-8 sum score can range from 0 to 8.
[c]Other psychiatric disorders include bipolar disorder, panic disorder, and personality disorders.

TABLE 4. Multivariate adjusted OR for low adherence to psychotropic medication[a] ($n = 160$)

Variable	Adjusted OR (95% CI)	*P*-value
Smoking during pregnancy		
No	Reference	
Yes	3.87 (1.86–8.02)	<.001
Number of psychotropic medications		
= 1	Reference	
>1	0.32 (0.17–0.60)	<.001
Depressive symptoms during pregnancy[b]		
No	Reference	
Yes	2.53 (1.37–4.67)	.003
Antidepressant risk perception score		
0–3	Reference	
4–5	1.28 (1.01–1.63)	.045
≥6	2.33 (1.38–3.93)	.001

[a]Smoking during pregnancy, number of psychotropic medication, symptoms of depression, and antidepressant risk perception were the only significant independent variables retained in the final multivariate model. Adjustment was done for clustering on region of residency, educational level, employment status, and gestational week.
[b]Depressive symptoms were considered to be present whenever the EPDS score was ≥13.

during pregnancy could in fact explain 28 and 26% of the variance in adherence to psychotropic medications, respectively. Since medication adherence represents a composite and multifaceted medication-taking behavior affected by several practical and perceptual factors, such correlation estimates can be deemed noteworthy and of importance in clinical settings. In the current study, elevated risk perception of antidepressants was associated with low medication adherence, possibly reflecting women's fear that the needed medication might harm the fetus. Since pregnant women overestimate the risk of the medications, and recall negative information far more often than reassuring information,[13,46] proper risk communication and information framing may represent effective tools in attenuating women's negative beliefs and perceptions, thereby heightening medication adherence during pregnancy.[47,48]

Among the risk factors explored, we found that maternal depression in pregnancy was associated with a significant 2.5-fold increased likelihood of low adherence to psychotropic medication during pregnancy compared to absence of depression. The lack of a temporal component in this cross-sectional study unfortunately impedes any substantiation of the relationship between low adherence to psychotropic medications and depressive symptoms, that is, whether low adherence led to poorer mental health or the converse. In alignment with prior research in the general nonpregnant population,[49] we found that women on monotherapy demonstrated poorer adherence than those on polytherapy; a more severe or longer history of psychiatric disorders in the latter group, leading to better knowledge of the medications that are regularly taken, and not least higher awareness of the correct administration schedule could explain such a finding. Future research should test whether interventions proven to be effective in improving antidepressant adherence in the general nonpregnant population[50] would be so also in the pregnant population.

STRENGTHS AND LIMITATIONS

An important strength of the study is the use of a validated self-reported questionnaire of medication adherence, the MMAS-8. The internal consistency of the MMAS-8 was satisfactory among women treated for depression and other psychiatric disorders (Cronbach's $\alpha \geq .7$), however, it was borderline adequate for anxiety. Validated instruments with reliable psychometric properties were also utilized to measure women's beliefs about medications and maternal mental health. With respect to the latter instrument, we used a cut-off score with high sensitivity and specificity in predicting probable depression.[26] Restriction to pregnant women only diminished the risk for recall bias. Data collection was conducted uniformly in all participating countries via utilization of an anonymous electronic questionnaire that

TABLE 5. Correlation between beliefs about medications and adherence to psychotropic medications during pregnancy ($n = 160$)

Beliefs about medication	Medication adherence sum score (MMAS-8)			
	Depression ($n = 127$)	Anxiety ($n = 76$)	Other psychiatric disorders ($n = 14$)	Total ($n = 160$)
	Spearman rank correlation coefficient			
BMQ-specific				
Necessity	**.190**[a]	.108	.057	**.208**[b]
Concerns	**−.206**[a]	−.037	−.500	**−.213**[b]
Necessity–concerns differential	**.262**[b]	.099	**.588**[a]	**.282**[c]
Pregnancy-specific beliefs				
Statement 1	−.091	−.003	.137	−.003
Statement 2	−.144	−.092	.004	−.130
Statement 3	**−.237**[b]	−.184	−.293	**−.243**[b]

MMAS-8, 8-Item Morisky Medication Adherence Scale.

Statistically significant results (i.e., P values < .05) are presented in bold.

[a]Indicates P values < .05.

[b]Indicates P values < .01.

[c]Indicates P values < .001.

Number of subjects exceeds 160 due to overlapping psychiatric disorders and related medication use.

The BMQ-specific questionnaire comprises the BMQ-Necessity and BMQ-Concerns subscales (score range: 5–25). Higher scores indicate stronger beliefs in the concepts represented by the subscale. The necessity–concerns differential is the difference between the BMQ-Necessity and BMQ-Concerns subscale (positive scores indicate that the patient perception of the benefits of medication outweigh the risks, whereas a negative score indicates the converse). The BMQ-specific is copyrighted (©Professor Robert Horne).

Statement 1: "I have a higher threshold for using medicines when I am pregnant than when I am not pregnant," Statement 2: "Even though I am ill and could have taken medicines, it is better for the foetus that I refrain from using them," Statement 3: "Pregnant women should preferably use herbal remedies than conventional medicines."

enabled us to potentially reach a large proportion of the birthing population.

One limitation of the study is the lack of medically confirmed diagnoses. The psychiatric disorders were self-reported by the participants and hence dependent on the woman's perception of the medical condition; the overall prevalence of psychiatric disorders observed in the current study might in fact be an underestimation of the true prevalence. We could however measure underlying maternal depression via the EPDS, which has been validated against clinical interview,[25] even though two measurements from each subject separated in time would have been preferable.[26] Information about medication use during pregnancy was also dependent on the accuracy of the woman's reporting. The overall prevalence of low adherence is uncertain due to the small total study sample, but could nevertheless be estimated with a precision of ±8%. The study sample was also small for the individual psychiatric disorders, thus limiting the statistical power of specific subanalyses. We did not have information about history of psychiatric disorders and prior treatments, ongoing nonpharmacological therapies, as well as the time of onset of the disorders, that is, prior to or during pregnancy. Due to the small study sample, individual countries had to be combined into regions, thus restraining us from doing country-specific analyses on the relationship between beliefs and adherence. In a recent meta-analysis in a nonpregnant sample,[51] it was found that the association between patient's beliefs and adherence seems to exist across different countries, languages, and cultures. The questionnaire was only available through Internet websites that did not permit calculation of a conventional response rate. However, recent epidemiological studies indicate reasonable validity of web-based recruitment methods.[52,53] Also, the penetration rate of the Internet, either in households or at work, is relatively high among women of childbearing age.[54–57] Hence, the degree to which our findings can be extrapolated to the target population is based on the representativeness of the respondents to the general birthing populations in each country. On average, the women in the study had higher education and were slightly more often primiparous than the general birthing populations in the various countries. Women with lower level of education might have been less likely to participate in the present study, whereas immigrant women more often did not complete the utilized adherence measure. These limitations should be borne in mind when considering the representativeness of the study.

CONCLUSION

In our study, we found that low adherence to psychotropic medication regimens is common during

pregnancy, raising concern about suboptimal control of the underlying maternal psychiatric disorder. Individual beliefs and risk perception are important factors determining adherence to psychotropic medication in pregnancy. Adequate counseling and proper teratogenic risk communication will potentially attenuate women's negative beliefs about medication and heighten medication adherence during pregnancy. Knowledge that women being prescribed psychotropic medications are at risk of nonadherence during pregnancy may assist clinicians when following-up pregnant patients with psychiatric disorders.

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Supplementary Table 1: Medications used at any time during pregnancy by psychiatric disorder (n=259)*

Medication	Type of psychiatric disorder							
	Depression		Anxiety		Other psychiatric disorders		Total	
	n	%†	*n*	%†	*n*	%†	*n*	%†
Self-reported psychiatric disorder	191	-	169	-	19	-	259	**-**
Any psychotropic medication use	127	66.5	76	45.0	14	73.7	**160**	**61.8**
Antidepressants							**144**	**55.6**
Sertraline	28	14.7	13	7.7	1	5.3	32	12.4
Citalopram	24	12.6	7	4.1	2	10.5	27	10.4
Fluoxetine	18	9.4	3	1.8	1	5.3	18	6.9
Escitalopram	13	6.8	4	2.4	2	10.5	16	6.2
Venlafaxine	14	7.3	6	3.6	2	10.5	15	5.8
Paroxetine	4	2.1	3	1.8	1	5.3	7	2.7
Bupropion	6	3.1	-	-	1	5.3	7	2.7
Duloxetine	4	2.1	1	0.6	-	-	4	1.5
Others	3	1.6	2	1.2	-	-	4	1.5
Trazodone	2	1.0	1	0.6	-	-	3	1.2
Unspecified antidepressants	3	1.6	-	-	-	-	3	1.2
Mirtazapine	2	1.0	-	-	-	-	2	0.8
Amitriptyline	2	1.0	2	1.2	-	-	2	0.8
Anxiolytics							**34**	**13.1**
Diazepam	1	0.5	6	3.6	-	-	6	2.3
Lorazepam	1	0.5	6	3.6	-	-	6	2.3
Alprazolam	1	0.5	4	2.4	2	10.5	6	2.3
Oxazepam	1	0.5	4	2.4	-	-	5	1.9
Bromazepam	1	0.5	2	1.2	-	-	3	1.2
Hydroxyzine	1	0.5	3	1.8	-	-	3	1.2

Medication	Type of psychiatric disorder							
	Depression		Anxiety		Other psychiatric disorders		Total	
	n	%†	*n*	%†	*n*	%†	*n*	%†
Unspecified anxiolytics	1	0.5	3	1.8	-	-	3	1.2
Prazepam	1	0.5	2	1.2	-	-	2	0.8
Others	-	-	1	0.6	-	-	1	0.4
Antipsychotics							**13**	**5.0**
Quetiapine	6	3.1	2	1.2	4	21.1	7	2.7
Risperidone	2	1.0	-	-	1	5.3	3	1.2
Others	1	0.5	1	0.6	1	5.3	2	0.8
Antiepileptics							**12**	**4.6**
Clonazepam	3	1.6	2	1.2	1	5.3	6	2.3
Lamotrigine	3	1.6	-	-	3	15.8	5	1.9
Others	-	-	-	-	2	-	2	0.8
Hypnotics and sedatives							**4**	**1.5**
Zopiclone	1	0.5	2	1.2	-	-	3	1.2
Others	2	-	1	0.6	-	-	2	0.8
Systemic antihistamines							**3**	**1.2**
Promethazine	-	-	3	1.8	-	-	3	1.2

Other antidepressants include mianserin, fluvoxamine, nortriptyline and trimipramine; other anxiolytics include etifoxine; other antipsychotics include lithium and aripiprazole; other antiepileptics include gabapentin and pregabalin; other hypnotics and sedatives include lormetazepam, zolpidem and temazepam.

*Only medications/medication groups reported by at least two women are specified. Number of subjects may exceed total by indication because some women used more than one medication. Psychiatric disorders include: depression, anxiety and other psychiatric disorders.

†Women who self-reported each of the psychiatric disorders constitute the denominator of the percentage calculations.

IV

Risk of Vaginal Bleeding and Postpartum Hemorrhage After Use of Antidepressants in Pregnancy

A Study From the Norwegian Mother and Child Cohort Study

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Abstract: This study aimed to examine obstetric bleeding outcomes after exposure during pregnancy to selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic (TCAs), and other antidepressants (OADs).

The Norwegian Mother and Child Cohort Study and the Medical Birth Registry of Norway constituted the data source for the present study. We included 57,279 pregnant women, of which 1.02% reported use of antidepressants during pregnancy, mostly SSRIs/SNRIs (0.92%). We categorized exposure according to antidepressant use in pregnancy (SSRIs/SNRIs, n = 527; TCAs/OADs, n = 59; nonexposed, nondepressed, n = 55,411) with inclusion of a disease comparison group (nonexposed, depressed, n = 1282). We used logistic regression to estimate adjusted odds ratio (aOR) and 95% confidence interval (CI) for vaginal bleeding outcomes in pregnancy and postpartum hemorrhage.

Compared with nonexposed subjects, first trimester exposure to SSRIs/SNRIs or TCAs/OADs did not confer any increased risk of vaginal bleeding in early pregnancy (aOR, 0.91; 95% CI, 0.72–1.16 and aOR, 0.83; 95% CI, 0.36–1.92, respectively). No increased risk for vaginal bleeding in midpregnancy was observed among users of SSRIs/SNRIs (aOR, 0.81; 95% CI, 0.50–1.31) or TCAs/OADs (aOR, 0.96; 95% CI, 0.26–3.53) in second trimester. Exposure to SSRIs/SNRIs during gestational week 30 to childbirth did not confer any increased risk of postpartum hemorrhage after vaginal (aOR, 0.90; 95% CI, 0.47–1.74) or cesarean (aOR, 1.47; 95% CI, 0.51–4.22) delivery. Women in the disease comparison group presented a significant moderate increased risk of vaginal bleeding in early pregnancy (aOR, 1.22; 95% CI, 1.06–1.39) and midpregnancy (aOR, 1.28; 95% CI, 1.07–1.55) but not postpartum.

Among this Norwegian cohort of pregnant women, use of antidepressants in pregnancy was not associated with any obstetrical bleeding outcome.

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Symptoms of depression are common in pregnancy[1] and up to 8% of women use antidepressants during this phase of life.[2,3] Although untreated depression may pose harm to both mother and fetus,[4] there have been concerns about the safety of antidepressant use during pregnancy, not least for the selective serotonin reuptake inhibitors (SSRIs). Recent research findings suggest SSRIs or antidepressants with high affinity to the serotonin transporter to be implicated in bleeding-related outcomes from the gastrointestinal tract among nonpregnant subjects.[5] The pharmacological plausibility behind the association SSRI-bleeding resides within the critical role played by serotonin in hemostasis.[6] However, little is known about bleeding outcomes from other sites than the gastrointestinal tract, such as the female genital tract.[7]

Vaginal bleeding is common in pregnancy and its clinical significance depends on the gestational week and the bleeding characteristic.[8] Nonetheless, postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality.[9] To the best of our knowledge, no previous studies have investigated the relationship between use of SSRIs and other antidepressants, and vaginal bleeding throughout pregnancy. On the other hand, a single nested case-control study[10] examined the association SSRIs-PPH and detected no increased risk among women exposed to SSRIs (odds ratio [OR], 1.30; 95% confidence interval [CI], 0.98–1.72) when compared with non-SSRIs. Because of the severity of PPH and because vaginal bleeding is a marker of an at-risk pregnancy, we aimed to investigate the putative association between obstetric bleeding outcomes and exposure to SSRIs and other antidepressants during pregnancy.

MATERIALS AND METHODS

Study Population and Data Collection

Data from the Norwegian Mother and Child Cohort Study (MoBa) and records in the Medical Birth Registry of Norway (MBRN) provided the data used in this study. MoBa is a population-based prospective cohort study described in details elsewhere.[11] Pregnant women from Norway were recruited to the study through a postal invitation in connection with the routine ultrasound examination offered to all pregnant women at 17 to 18 weeks of gestation. At an assessment of the MoBa study in 2009, the participation rate was 43.5% of all women invited.[12] In the present study, information from MoBa was retrieved from 3 self-administered questionnaires.[13] The first (Q1) and third (Q3) questionnaires were completed in pregnancy weeks 13 to 17 and 30, respectively, whereas the fourth

questionnaire (Q4) was distributed when the infant was 6 months old (covering the period from gestational week 30 and onward).[11,13] Among those who agreed to participate in the MoBa, the response rate was 95% for Q1, 92% for Q3, and 87% for Q4.[11] The MBRN is based on compulsory notification of all live births, stillbirths, and induced abortions and includes information on pregnancy, delivery, and neonatal health.[14] Data from MoBa were linked to the MBRN via the women's personal identification number. The Regional Committee for Ethics in Medical Research, Region South, and the Norwegian Data Inspectorate approved the MoBa study. Informed consent was obtained from each participant.

We used the MoBa quality assured data file released for research (version 4) including 72,934 women who delivered between 1999 and 2006. We included women who had both a record in MBRN and had answered MoBa Q1, Q3, and Q4 (n = 59,577). We excluded multiple pregnancies (n = 2004), users of unspecified medication for depression (n = 269), and users of SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) together with tricyclic antidepressants (TCAs) or other antidepressants (OADs) (n = 25). The final study population comprised 57,279 pregnant women and their live born babies. Women could participate in the MoBa for more than 1 pregnancy, with each of them being counted as individual mother-child pair.

Exposure Assessment

Information about type and timing of antidepressant use was retrieved from Q1, Q3, and Q4.[13] Drug exposure was classified and grouped according to the Anatomical Therapeutic Chemical (ATC) Classification System.[15] We defined antidepressant exposure as exposure to a drug belonging to the ATC group N06A, subdivided into SSRIs (ATC code N06AB), SNRIs (ATC codes N06AX16 and N06AX21), TCAs (ATC code N06AA), and OADs (ATC codes N06AX03, N06AX06, N06AX11, N06AX12, and N06AX18). In each questionnaire, women could report use of 1 or more medicinal products for specifically named indications (eating disorders, depression, anxiety, and other mental health problems), along with the corresponding periods of exposure. Exposure to each antidepressant was classified as follows: 6 months before pregnancy, gestational weeks 0 to 4, 5 to 8, and 9 to 12 (Q1); gestational weeks 13 to 16, 17 to 20, 21 to 24, 25 to 28, 29+ (until completion of Q3); last part of pregnancy (gestational week 30 to childbirth) (Q4). Exposure by gestational week was then aggregated into trimesters and total use during pregnancy. In those instances where multiple medications had been reported for the same indication for use and several exposure windows have been recorded, it was assumed that every medication has been taken at each time interval.

Exposure was categorized into 4 groups: the exposed group 1, defined as exposure to SSRIs/SNRIs during pregnancy (n = 527); the exposed group 2, defined as reported use of TCAs or OADs during pregnancy (n = 59); the disease comparison group, defined as no exposure to antidepressants but presence of depressive symptoms at both gestational weeks 17 and 30 (n = 1282); the nonexposed group, defined as no reported use of antidepressants during pregnancy and no presence of depressive symptoms at gestational weeks 17 and/or 30 (n = 55,411).

Assessment of Maternal Mental Health

To define the disease comparison group, the short versions of The Hopkins Symptom Checklist-25 (SCL-25) that is, the Symptom Checklist-5 (SCL-5) and the Symptom Checklist-8 (SCL-8), were used.[16,17] The SCL-5 and SCL-8 were included in Q1 and Q3, respectively, and detected depressive symptoms at gestational weeks 17 and 30. The SCL-25 is a psychometric scale designed to screen for symptoms of depression in population survey[16] and is considered a reliable screening instrument for depression as defined by the *International Classification of Diseases, Tenth Revision*.[18] Both SCL-5 and SCL-8 are highly correlated to the SCL-25.[19,20] Presence of depression was defined by a score greater than 2.0 in the SCL-5 and greater than 1.85 in the SCL-8.[16]

Outcome Assessment

Information on bleeding outcomes during pregnancy was retrieved from Q1 and Q3. In here, women could report details about 2 bleeding episodes; if such episodes differed in typology (trace versus large/medium amount of blood loss), we based our analysis on woman's most severe bleeding experience. The outcomes "bleeding in early pregnancy" and "bleeding in midpregnancy" were defined as any occurrence of vaginal bleeding during the first and second trimester of pregnancy, respectively. Bleeding type was subdivided into trace of blood or spotting, moderate/large amount of blood loss or clots, and occurrence of multiple episodes. The outcome "postpartum hemorrhage," defined as blood loss greater than 500 mL, stems from the MBRN records, and is medically confirmed information. All outcome variables concerning maternal vaginal bleeding were dichotomized as "yes/no."

Assessment of Potential Confounders

Maternal age, parity, marital status, educational level, prepregnancy body mass index (BMI), smoking during pregnancy, and a history of abortions were assessed as potential confounders. Factors related to maternal health before and/or during pregnancy (ie, congenital heart defects, placenta previa, abruption placentae, history of obstetric bleeding) and comedications in pregnancy (ie, nonsteroidal anti-inflammatory drugs and antithrombotics) were also assessed as potential confounders. These variables were categorized as shown in Supplemental Table A (Supplemental Digital Content 1, http://links.lww.com/JCP/A217). The degree of the underlying maternal depression during pregnancy was also assessed as a potential confounding factor. The sum scores for the SCL-5 at gestational week 17 (from Q1) and the SCL-8 at gestational week 30 (from Q3) were used for such purpose and used as continuous variables.

Statistical Analysis

The Pearson χ^2 test was used to identify any association between the exposure groups and maternal characteristics, medical factors, and comedications during pregnancy. A P value of less than 0.05 was considered statistically significant. Univariate and multivariate logistic regression analysis was used to estimate the impact of each exposure group on obstetric bleeding outcomes. Data are presented as adjusted OR (aOR) with 95% CI if there were at least 3 exposed cases. Subanalysis on individual antidepressants and by pregnancy week exposure was also conducted. Forward purposeful selection of covariates was carried out.[21] Goodness of fit of the final multivariate model was assessed by using the Hosmer and Lemeshow test.[21] All final models included adjustment for the level of maternal depression as a continuous variable. By definition, the final model for the same bleeding outcomes in the disease comparison group did not include adjustment for the level of maternal depression. The Predictive Analytics SoftWare PASW version 20 for Windows (SPSS, Chicago, IL) was used in all analysis.

RESULTS

Population Characteristics

All women in the study population (n = 57,279) gave birth to a live-born child. Of these, 587 (1.02%) reported

TABLE 1. Association (aOR, 95% CI) Between Exposure Groups and Vaginal Bleeding in Early and Midpregnancy (n = 57,279)*

		Any Type of Bleeding		Trace of Blood		Medium Blood Loss or Clots		>1 Episode	
		n (%)		n (%)		n (%)		n (%)	
		11,456 (20.0)		6869 (12.0)		4136 (7.2)		4704 (8.2)	
Vaginal Bleeding in Early Pregnancy	**n**	**n (%)**	**aOR[†] (95% CI)**	**n (%)**	**aOR[‡] (95% CI)**	**n (%)**	**aOR[§] (95% CI)**	**n (%)**	**aOR[‖] (95% CI)**
Nonexposed in pregnancy	55,411	11,037 (19.9)	Reference	6631 (12.0)	Reference	3974 (7.2)	Reference	4524 (8.2)	Reference
Disease comparison	1282	293 (22.9)	**1.22 (1.06–1.39)**	158 (12.3)	1.10 (0.92–1.30)	121 (9.4)	**1.32 (1.09–1.60)**	130 (10.1)	**1.33 (1.10–1.61)**
Nonexposed (first trimester)	55,533	11,066 (19.9)	Reference	6654 (12.0)	Reference	3980 (7.2)	Reference	4535 (8.2)	Reference
SSRIs/SNRIs (first trimester)	427	90 (21.1)	0.91 (0.72–1.16)	54 (12.6)	0.96 (0.72–1.30)	31 (7.3)	0.80 (0.55–1.17)	35 (8.2)	0.81 (0.57–1.16)
TCAs/OADs (first trimester)	37	7 (18.9)	0.83 (0.36–1.92)	3 (8.1)	0.61 (0.19–2.01)	4 (10.8)	1.26 (0.44–3.61)	4 (10.8)	1.16 (0.41–3.34)
		Any Type of Bleeding		**Trace of Blood**		**Medium or Large Blood Loss**		**>1 Episode**	
		n (%)		**n (%)**		**n (%)**		**n (%)**	
		5395 (9.4)		**3495 (6.1)**		**1798 (3.1)**		**1580 (2.8)**	
Vaginal Bleeding in Midpregnancy	**n**	**n (%)**	**aOR[¶] (95% CI)**	**n (%)**	**aOR[#] (95% CI)**	**(%)**	**aOR** (95% CI)**	**n (%)**	**aOR[††] (95% CI)**
Nonexposed in pregnancy	55,411	5176 (9.3)	Reference	3355 (6.1)	Reference	1724 (3.1)	Reference	1512 (2.7)	Reference
Disease comparison	1282	158 (12.3)	**1.28 (1.07–1.55)**	98 (7.6)	**1.24 (1.00–1.55)**	56 (4.4)	1.20 (0.89–1.61)	49 (3.8)	1.33 (0.98–1.81)
Nonexposed (second trimester)	55,750	5212 (9.3)	Reference	3379 (6.1)	Reference	1735 (3.1)	Reference	1522 (2.7)	Reference
SSRIs/SNRIs (second trimester)	222	22 (9.9)	0.81 (0.50–1.31)	15 (6.8)	0.92 (0.53–1.62)	7 (3.2)	0.70 (0.32–1.55)	9 (4.1)	1.20 (0.59–2.42)
TCAs/OADs (second trimester)	25	3 (12.0)	0.96 (0.26–3.53)	3 (12.0)	1.80 (0.50–6.43)	—	—	—	—

In all models, the disease comparison group is adjusted for all confounders as SSRI/SNRI and TCA/OAD groups, except for maternal depressive symptoms ("SCL-5" at gestational week 17).

Statistically significant results (ie, when the aOR with its entire 95% CI is above 1.00) are presented in bold.

*The nonexposed group is the reference group in all models. The disease comparison group includes women using no antidepressants during pregnancy but with symptoms of depression at both gestational weeks 17 and 30.

[†]Adjusted for maternal age, parity, BMI, educational level, NSAID and antithrombotic use, smoking, previous abortions and/or miscarriages, and depressive symptoms.

[‡]Adjusted for maternal age, parity, BMI, educational level, NSAID use, smoking, previous abortions/miscarriages, and depressive symptoms.

[§]Adjusted for maternal age, marital status, BMI, NSAID and antithrombotic use, smoking, previous abortions/miscarriages, and depressive symptoms.

[‖]Adjusted for parity, BMI, smoking, previous abortions/miscarriages, educational level, and depressive symptoms.

[¶]Adjusted for maternal age, marital status, BMI, smoking, placenta previa, bleeding episode in first trimester, and depressive symptoms.

[#]Adjusted for maternal age, marital status, BMI, smoking, bleeding episode in first trimester, and depressive symptoms.

**Adjusted for maternal age, educational level, BMI, placenta previa, bleeding episode in first trimester, and depressive symptoms.

[††]Adjusted for maternal age, BMI, placenta previa, bleeding episode in first trimester, history of previous abortion/miscarriage, and depressive symptoms.

antidepressant use during pregnancy, mostly SSRIs/SNRIs (0.92%) (cf. Supplemental Table B, Supplemental Digital Content 2, http://links.lww.com/JCP/A216). Maternal characteristics, comorbidities, and comedications by antidepressant treatment status are shown in Supplemental Table A (Supplemental Digital Content 1, http://links.lww.com/JCP/A217). Overall, 5.9% and 6.3% of the final study population presented depressive symptoms at weeks 17 and 30, respectively. Interestingly, women in the disease comparison group presented a significantly higher ($P < 0.001$) mean score for SCL-5 and SCL-8 (2.48 and 2.31) than women medicated with either SSRIs/SNRIs (1.82 and 1.73) or TCAs/OADs (1.78 and 1.83).

Vaginal Bleeding in Early and Midpregnancy

Of all women in the study population, 20.0% and 9.4% reported occurrence of vaginal bleeding in early and midpregnancy, respectively. The aORs for vaginal bleeding outcomes are shown in Table 1. Compared with nonexposed, use of SSRIs/SNRIs during first and second trimester was not associated with any increased risk of vaginal bleeding of any kind in early (aOR, 0.91; 95% CI, 0.72–1.16) and midpregnancy (aOR, 0.81; 95% CI, 0.50–1.31), respectively. Analog findings were observed in the analysis of specific bleeding type outcomes (Table 1). Exposure to TCAs/OADs during first or second trimester did not confer any significant increased risk of vaginal bleeding in neither early nor midpregnancy, respectively, although the analysis for this exposure group is underpowered (Table 1). Subanalysis by gestational week and individual antidepressants did not show different findings than those observed for exposure by trimester or for the main drug groups SSRIs/SNRIs and TCAs/OADs. Compared with nonexposed, women in the disease comparison group were associated with a statistically significant increased risk of bleeding of any kind in early (aOR, 1.22; 95% CI, 1.06–1.39) as well as midpregnancy (aOR, 1.28; 95% CI, 1.07–1.55) (Table 1).

Postpartum Hemorrhage

In our study population, 8242 women (14.4%) experienced PPH. The aORs for PPH, overall and stratified by type of delivery, are shown in Table 2. Compared with nonexposed subjects, exposure to SSRIs/SNRIs during gestational week 30 to childbirth did not confer any increased risk of PPH (aOR, 0.97; 95% CI, 0.57–1.65) and upon stratification by type of delivery. Exposure to TCAs/OADs during gestational week 30 to childbirth was associated with a 3.75-fold increased risk. Due to low statistical power, no stratification by type of delivery could be carried out and therefore this association cannot be further examined. Subanalysis on individual drug level did not reveal different findings than those observed for the main drug group SSRIs/SNRIs. We had no power to investigate the role of individual TCAs/OADs in relation to PPH. Women in the disease comparison group did not present any increased risk of PPH overall (aOR, 1.14; 95% CI, 0.97–1.34) and upon stratification by type of delivery.

DISCUSSION

The findings of this large prospective cohort study are reassuring: use of neither SSRIs/SNRIs nor TCAs/OADs during the first and second trimesters seems to be implicated in vaginal bleeding outcomes during pregnancy. However, our study also provides relevant insights about the role of nonmedicated depression in pregnancy. We found that women with depressive symptoms but not medicated with any antidepressants presented an increased risk of vaginal blood loss in early and midpregnancy. Interestingly, these women present more severe symptoms of depression than the treated counterpart, suggesting a potential involvement of the maternal underlying depression in vaginal bleeding outcomes. Nonetheless, they may present higher level of anxiety and stress, as indicated by their higher rate of utilization of ultrasound in pregnancy, potentially leading to different health behaviors and accuracy in reporting. Also, in light of previous research findings,[22] it can be speculated that the higher rates of vaginal bleeding observed in the disease comparison group could be simply recognized as signs of threatened abortion.

In the present study, we also found that exposure to SSRIs/SNRIs as a group during gestational week 30 to childbirth did not confer any increased risk of PPH. The results for the SSRIs/SNRIs as a group are, nevertheless, in line with previous findings,[10] although the impact of individual antidepressants on PPH has not been previously addressed. In the postpartum setting, processes other than clotting may prevail in securing blood

TABLE 2. Association (aOR, 95% CI) Between Exposure Groups and Postpartum Hemorrhage (n = 57,279)*

		Any Type of Delivery		Stratum 1: Cesarean Section		Stratum 2: Vaginal Delivery	
		n (%)		n (%)		n (%)	
		8242 (14.4)		2607 (4.6)		5635 (9.8)	
Postpartum Hemorrhage (>500 mL Blood Loss at Delivery)	**n**	**n (%)**	**aOR† (95% CI)**	**n (%)**	**aOR† (95% CI)**	**n (%)**	**aOR† (95% CI)**
Nonexposed in pregnancy	55,411	7937 (14.3)	Reference	2485 (4.5)	Reference	5452 (9.8)	Reference
Disease comparison	1282	211 (16.5)	1.14 (0.97–1.34)	84 (6.6)	1.18 (0.89–1.58)	127 (9.9)	1.05 (0.86–1.28)
Nonexposed (week 30-childbirth)	55,862	8009 (14.3)	Reference	2515 (4.50)	Reference	5494 (9.83)	Reference
SSRIs/SNRIs (week 30-childbirth)	123	18 (14.6)	0.97 (0.57–1.65)	6 (4.88)	1.47 (0.51–4.22)	12 (9.76)	0.90 (0.47–1.74)
TCAs/OADs (week 30-childbirth)	12	4 (33.3)	**3.75 (1.09–12.94)**	2 (16.67)	—	2 (16.67)	—

In all models, the disease comparison group is adjusted for all confounders as SSRI/SNRI and TCA/OAD groups, except for maternal depressive symptoms ("SCL-8" at gestational week 30).

Statistically significant results (ie, when the aOR with its entire 95% CI is above 1.00) are presented in bold.

*The nonexposed group is the reference group in all models. The disease comparison group includes women using no antidepressants during pregnancy but with symptoms of depression at both gestational weeks 17 and 30.

†Adjusted for maternal age, parity, BMI, educational level, smoking, coagulation defects, history of previous abortion/miscarriage, placental abruption, placenta previa, and maternal depressive symptoms.

loss.[23,24] Nonetheless, tapering or stopping SSRI and SNRI treatment toward the end of pregnancy is often considered as a way to avoid neonatal withdrawal symptoms,[25] and this may prevent identification of any increased risk of PPH, if existing. We also tried to regroup all antidepressants according to the level of affinity to serotonin transporter, as done in previous studies,[5] and could not identify any relationship antidepressants-obstetrical bleeding. The difficulties involved in objectively estimating the amount of blood loss after delivery, as well as the variability in the definition and diagnosis of PPH among countries, are factors that should be taken into account when evaluating our results.

Strengths and Limitations of the Study

The MoBa study material encompasses several inherent strengths and limitations. Data collection was carried out prospectively, avoiding the risk of recall bias. Exposure to antidepressants in gestational week 30 to childbirth was collected retrospectively (in Q4), and may therefore suffer of inaccuracy and recall-bias. However, all women reporting antidepressant use in Q4 did it also in Q3. The collection of a vast array of health-related and sociodemographic information enables us to adjust for several potential confounders, including maternal level of depression at 2 time points during pregnancy and concomitant medication use. Moreover, inclusion of a disease comparison group enables us to compare and distinguish between underlying maternal illness and pharmaceutical treatment.

The study has several limitations that should be considered when interpreting the results. First, the MoBa study has a low response rate (43% of all women invited), with a possible self-selection of the healthiest women to the study. On the other hand, among those who accepted the invitation, the response rate is high.[11] The prevalence of antidepressant use in our cohort was slightly lower than in the Norwegian Prescription Database.[26] However, our estimates may in fact be considered more representative of the actual use of antidepressants among pregnant women in Norway because not all prescribed antidepressants are actually taken during pregnancy. A previous study[12] has thoroughly examined self-selection and its potential for bias by comparing the MoBa study population with the total Norwegian birthing population. The authors concluded that although the prevalence estimates could not necessarily be generalized, the estimates of exposure-outcome associations were valid in the MoBa study.

Second, nondifferential misclassification of the exposure status, especially in the last part of pregnancy, may have occurred. However, the impact of misclassification of exposure to SSRIs in late pregnancy on risk estimates was addressed by a recent study and assessed as minimal.[27] To ascertain the accuracy of reporting in Q4, we also compared the prevalence of antidepressant use postpartum in our cohort (based upon data from Q4) with that reported by Engeland et al,[26] which includes data on all antidepressants prescribed to women in Norway after delivery. We did observe complete concordance (0.7% vs 0.7%). Information on antidepressant dosage is not available in the MoBa study and information about duration of exposure is not always adequate.

Third, information about exposure to antidepressants and bleeding outcomes in early and midpregnancy are self-reported, thus dependent on the accuracy of the women's reporting. Fourth, depression was measured by 2 self-assessment instruments; although such measurements cannot replace a clinical interview, they provide a reliable measure of the severity of depression.[16,18] Finally, although this study included more than 57,000 women, we still had low statistical power to detect moderate but nevertheless clinically significant increases in the occurrence of specific bleeding outcomes in midpregnancy as well as PPH for all exposure groups. Also, we were limited by low statistical power in subanalyses on the individual antidepressant level and for the TCA/OAD group.

To conclude, in this study, we identified no overall increased risk of vaginal bleeding in pregnancy or PPH among women exposed to antidepressants. On the other hand, women not medicated with antidepressants but with depressive symptoms present a moderately increased risk of vaginal bleeding in early and midpregnancy. This information will assist women and their health care providers when discussing treatment options for depression during pregnancy.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Supplemental Table A: Exposure to antidepressants according to timing of use (pregnancy weeks) (n=57,279)

Antidepressants	Q1				Q3					Q4		
	6 months < pregnancy	Week 0-4	Week 5-8	Week 9-12	Week 13-16	Week 17-20	Week 21-24	Week 25-28	Week >29	Last part of pregnancy[¶]	Total during pregnancy	
	No.	*No.*	*No.*	*No.*	*No.*	*No.*	*No.*	*No.*	*No.*	*No.*	*No.*	*(%)*
SSRIs/SNRIs[*]	**1223**	**400**	**234**	**172**	**190**	**143**	**150**	**147**	**139**	**123**	**527**	**0.92**
Citalopram	464	130	80	64	68	44	46	47	45	46	**178**	**0.31**
Sertraline	232	70	46	37	39	29	29	28	26	21	**94**	**0.16**
Escitalopram	146	70	35	17	21	16	18	18	18	16	**87**	**0.15**
Paroxetine	191	59	40	36	37	24	24	25	22	22	**81**	**0.14**
Venlafaxine	96	43	21	12	15	10	10	10	10	11	**53**	**0.09**
Fluoxetine	135	41	19	13	20	21	24	20	19	9	**60**	**0.10**
Fluvoxamine	14	1	1	-	-	-	-	-	-	-	**2**	**0.00**
Duloxetine	1	1	1	-	-	-	-	-	-	-	**1**	**0.00**
TCAs/OADs[*]	**153**	**33**	**19**	**15**	**20**	**17**	**18**	**17**	**17**	**12**	**59**	**0.10**
Amitriptyline	31	9	6	3	7	5	5	3	3	2	**17**	**0.03**
Clomipramine	13	5	4	4	2	3	3	3	3	3	**7**	**0.01**
Other TCAs[†]	9	2	1	1	1	1	1	2	2	1	**4**	**0.01**
Other ADs[‡]	101	17	8	7	10	8	9	9	9	7	**32**	**0.06**
Total ADs[§]	**1355**	**433**	**253**	**187**	**210**	**160**	**168**	**164**	**156**	**135**	**587**	**1.02**

[*]The total numbers for SSRI/SNRI and TCA/OAD exposure during pregnancy are lower than the sum of the individual antidepressants because some subjects have used more than one antidepressant of the same drug group and they are only counted once here.

[†]Other TCAs include trimipramine, nortriptyline and doxepin.

[‡]Other ADs include mirtazapine, mianserin, nefazodone, reboxetine and bupropion.

[§]Total AD exposure includes also antidepressant use where timing during pregnancy is unknown and "unspecified" medications for depression (referring to the truncated ATC code "N06A-").

[¶]Last part of the pregnancy comprises the period from the 30th gestational week and onwards up to childbirth.

Abbreviations: SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin–norepinephrine reuptake inhibitors; ADs: antidepressants; TCAs: tricyclic antidepressants; OADs: other antidepressants.

Supplemental Table B: Maternal characteristics, illnesses and co-medications by antidepressant use in pregnancy (n=57,279)*

Maternal characteristics, illnesses and co-medication	**No ADs & no depression during pregnancy** *(Non-exposed group)*	**No ADs & depression during pregnancy** *(Disease comparison group)*	**SSRIs/SNRIs during pregnancy** *(Exposed group 1)*	**TCAs/OADs during pregnancy** *(Exposed group 2)*
	No. (%) **55,411 (100.0)**	**No. (%)** **1,282 (100.0)**	**No. (%)** **527 (100.0)**	**No. (%)** **59 (100.0)**
Age (years) †‡§				
< 20	438 (0.8)	49 (3.8)	9 (1.7)	-
20-29	24,316 (43.9)	627 (48.9)	234 (44.4)	20 (33.9)
30-39	29,622 (53.5)	587 (45.8)	269 (51.0)	33 (55.9)
≥40	1,035 (1.9)	19 (1.5)	15 (2.8)	6 (10.2)
Parity ‡				
No previous live birth	24,606 (44.4)	560 (43.7)	266 (50.5)	28 (47.5)
≥1	30,801 (55.6)	722 (56.3)	261 (49.5)	31 (52.5)
Education[a] †‡§				
Primary	1,254 (2.4)	112 (9.4)	24 (4.8)	5 (8.5)
Secondary	17,971 (34.1)	592 (49.9)	227 (45.6)	28 (47.5)
Tertiary – short	22,396 (42.5)	309 (26.1)	181 (36.3)	16 (27.1)
Tertiary – long	11,023 (20.9)	173 (14.6)	66 (13.3)	10 (16.9)
Marital status †‡§				
Married/cohabiting	53,618 (97.0)	1,133 (88.8)	463 (88.2)	52 (88.1)
Other	1,639 (3.0)	143 (11.2)	62 (11.8)	7 (11.9)
BMI at the beginning of pregnancy[b] †‡§				
Underweight	854 (1.6)	26 (2.1)	12 (2.4)	5 (8.8)
Normal weight	30,988 (57.4)	657 (53.2)	256 (50.7)	30 (52.6)
Overweight	15,556 (28.8)	359 (29.1)	154 (30.5)	19 (33.3)
Obese	6,595 (12.2)	192 (15.6)	83 (16.4)	3 (5.3)
Smoking during pregnancy[c] †‡§				
No	49,624 (90.9)	972 (77.9)	399 (76.9)	45 (76.3)
Yes, sometimes	2,606 (4.8)	112 (9.0)	51 (9.8)	4 (6.8)
Yes, daily	2,361 (4.3)	164 (13.1)	69 (13.3)	10 (16.9)
History of abortion[d] †§				

Maternal characteristics, illnesses and co-medication	No ADs & no depression during pregnancy *(Non-exposed group)*	No ADs & depression during pregnancy *(Disease comparison group)*	SSRIs/SNRIs during pregnancy *(Exposed group 1)*	TCAs/OADs during pregnancy *(Exposed group 2)*
	No. (%) 55,411 (100.0)	**No. (%) 1,282 (100.0)**	**No. (%) 527 (100.0)**	**No. (%) 59 (100.0)**
Yes	17,909 (32.3)	530 (41.3)	185 (35.1)	30 (50.8)
No	37,502 (67.7)	752 (58.7)	342 (64.9)	29 (49.2)
Type of delivery[e] †‡§				
Vaginal	48,017 (86.7)	1,067 (83.2)	434 (82.4)	44 (74.6)
Caesarean section	7,394 (13.3)	215 (16.8)	93 (17.6)	15 (25.4)
Number of ultrasound examinations[f] †§				
None	656 (1.2)	11 (0.9)	2 (0.6)	-
1-3	44,397 (80.1)	906 (70.7)	409 (77.6)	40 (67.8)
4-6	8,046 (14.5)	265 (20.7)	84 (15.9)	9 (15.3)
≥7	2,312 (4.2)	100 (7.8)	31 (5.9)	10 (16.9)
Depressive symptoms[g]				
At gestational week 17 †‡§	1,895 (3.5)	1,282 (100.0)	196 (37.5)	23 (40.4)
At gestational week 30 †‡§	2,109 (3.8)	1,282 (100.0)	186 (35.7)	22 (37.9)
Life-time history of depression †‡§	17,079 (30.8)	1,049 (81.8)	469 (89.0)	47 (79.7)
Maternal illnesses				
Placenta previa ‡	110 (0.2)	3 (0.2)	4 (0.8)	-
Abruptio placentae	180 (0.3)	8 (0.6)	2 (0.4)	-
Congenital heart defect/disease[h]	616 (1.1)	20 (1.6)	5 (0.9)	1 (1.7)
Co-medications during pregnancy				
Antithrombotic agents[i] †	464 (0.8)	22 (1.7)	1 (0.2)	1 (1.7)
NSAIDs[j] †‡§	4,647 (8.4)	183 (14.3)	79 (15.0)	13 (22.0)

* Numbers may not add up due to missing values. Missing values are less than 6% of the total.

[a]Primary: <10 years of education; secondary: 10-12 years; tertiary short=college education; tertiary long=university education.
[b]The body mass index is the weight in kilograms divided by the square of the height in meters: underweight: <18.5 kg/m2; normal weight: 18.5-24.9 kg/m2; overweight: 25.0-29.9 kg/m2; obese≥30 kg/m2.
[c]Defines as smoking at any time during pregnancy, from conception to gestational week 30.
[d]Defined as a history of spontaneous or induced abortion in previous pregnancies.
[e]Includes elective, emergency and unspecified caesarean section.
[f]Number of ultrasound examinations up to gestational week 30.
[g]Defined as SCL-5 score ≥2 and SCL-8 ≥1.85 at gestational week 17 and 30, respectively. By definition 100% of the women in the disease comparison group had depression at weeks 17 and 30. Defined as a Kendlers Life time major depression scale score of 3 or more of 6 depressive symptoms of duration of more than 2 weeks.

[h]Defined as for the ICD-10 codes for coagulation defects D65-D69.
[i]Antithrombotic agents comprise medications with ATC code B01A.
[j]NSAIDs comprise medications with ATC codes M01A and N02BA.

[†]p-value <0.05 Pearson chi-square test or Fisher exact test; disease comparison group versus non-exposed group.
[‡]p-value <0.05 Pearson chi-square test or Fisher exact test; SSRIs/SNRIs during pregnancy (exposed group 1) versus non-exposed group.
[§]p-value <0.05 Pearson chi-square test or Fisher exact test; TCAs/OADs during pregnancy (exposed group 2) versus non-exposed group.

Abbreviations: SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin–norepinephrine reuptake inhibitors; ADs: antidepressants; TCAs: tricyclic antidepressants; OADs: other antidepressants.

APPENDIX 1:

MoBa questionnaires Q1, Q3 and Q4

den norske **Mor & barn undersøkelsen**

Questionnaire 1

This questionnaire will be processed by a computer. It is therefore important that you follow these instructions:

- Please use a blue or black ballpoint pen.
- Put a cross in the box that is most relevant like this:
- Should you put a cross in the wrong box correct it by filling in the box completely like this:
- In the large green boxes write a number or a capital letter

  It is important that you only write in the white area of each box like this:

  Number: 0 1 2 3 4 5 6 7 8 9 Letter: A B C D
- When filling in a single figure in boxes containing two or more squares, please use the square to the right. Example: 5
- A number of questions in this questionnaire concern the week of pregnancy. For example, fill in week 5 for something that occurred 5 weeks after your last period.
- Specific information concerning, for example, medication or profession should be written in the boxes or on the lines provided. Please write clearly in CAPITAL LETTERS.
- Remember to provide the date when you completed the questionnaire.

Please return the completed questionnaire in the stamped addressed envelope provided.

Date on which the questionnaire was completed ☐☐ Day ☐☐ Month ☐☐☐☐ Year (write the year with 4 numbers, e.g. 2000)

Menstruation

1. How old were you when you had your first menstrual period?

☐☐ Years

2.How many days are there usually between the first day in your menstrual period and the first day in your next menstrual period?

☐☐ Days

3. Are you usually depressed or irritable before your period?

☐ No
☐ Yes, but just slightly
☐ Yes, noticeably
☐ Yes, very much

4. If yes, does this feeling disappear after you get your period?

☐ No
☐ Yes

5. Were your periods regular the year before you became pregnant?

☐ No
☐ Yes

6. During the last year before you became pregnant, did you lose your period for more than three months?

☐ No
☐ Yes, due to an earlier pregnancy
☐ Yes, for other reasons

7. Date of first day of last menstrual period.

☐☐ Day ☐☐ Month ☐☐☐☐ Year

8. Did your last menstrual period come at the expected time?

☐ No
☐ Yes

9. Are you certain about the date of first day of last menstrual period?

☐ Certain
☐ Uncertain

10. Describe the duration, amount of bleeding and menstrual pains of your last period ?

	As usual	More than usual	Less than usual
Duration	☐	☐	☐
Amount of bleeding	☐	☐	☐
Menstrual pains	☐	☐	☐

Contraception and pregnancy

11. Have you/your partner at any time during the last year used the following methods to avoid becoming pregnant? (Fill in all that apply.)

- ☐ Condom
- ☐ Diaphragm
- ☐ IUD
- ☐ Hormone IUD
- ☐ Hormone injection
- ☐ Mini pill
- ☐ Pill
- ☐ Spermicides (foam, suppositories, cream)
- ☐ Safe period
- ☐ Withdrawal
- ☐ No such methods
- ☐ Other_____

12. If you have used the pill/mini-pill, how long altogether have you used them?

	Pill	Mini-pill
Less than one year	☐	☐
1-3 years	☐	☐
4-6 years	☐	☐
7-9 years	☐	☐
10 years or more	☐	☐

13. If you have used the pill/mini-pill, how old were you when you first used it?

☐☐ Years old

14. Were you taking the pill/mini-pill during the last 4 months before this pregnancy?

- ☐ No
- ☐ Yes

15. If yes, how long before your last menstrual period did you stop taking the pill/mini-pill?

☐☐ Weeks

16. Was this pregnancy planned?

- ☐ No
- ☐ Yes

17. If yes, how many months did you have regular intercourse without contraception before you became pregnant?

- ☐ Less than I month
- ☐ 1-2 months
- ☐ 3 months or more

☐☐ Number of months if more than 3

18. Did you become pregnant even though you or your partner used contraceptives?

- ☐ No (proceed to question 21)
- ☐ Yes

19. If yes, which type? (Fill in all that apply.)

- ☐ Condom
- ☐ Diaphragm
- ☐ IUD
- ☐ Hormone IUD
- ☐ Hormone injection
- ☐ Mini pill
- ☐ Pill
- ☐ Spermicides (foam, suppositories, cream)
- ☐ Safe period
- ☐ Withdrawal
- ☐ Other_____

20. If you became pregnant while using an IUD, has it now been removed?

- ☐ No
- ☐ Yes

21. How long have you and the baby's father had a sexual relationship?

☐☐ months or ☐☐ years

22. How often did you have sexual intercourse during the four weeks before you became pregnant and during the last four weeks?

	Before	Now
Every day	☐	☐
5-6 times a week	☐	☐
3-4 times a week	☐	☐
1-2 times a week	☐	☐
1-2 times every two weeks	☐	☐
Less than 1-2 times every 2 weeks	☐	☐
Never	☐	☐

23. Have you ever been treated for infertility?

- ☐ No
- ☐ Yes

24. If yes, was it in connection with this pregnancy or an earlier pregnancy and what type of treatment did you have? (Fill in all that apply.)

	Earlier Pregnancy	This Pregnancy
Fallopian tube surgery	☐	☐
Other surgery	☐	☐
Medication for endometriosis	☐	☐
Hormone treatment	☐	☐
Insemination (injection of sperm)	☐	☐
IVF (test tube) method	☐	☐
Other	☐	☐

25. Have you been given information about having an amniocentesis performed?

- ☐ No
- ☐ Yes

26. What was your blood pressure at your first antenatal visit? (Check your medical card.)

☐☐☐/☐☐☐ E.g. 150/95

27. What did you weigh at the time you became pregnant and what do you weigh now (in kilograms)?

When I became pregnant : ☐☐ kg Now: ☐☐ kg

28. How tall are you?

☐☐ cm

29. How tall is the baby's father?

☐☐ cm

30. How much does the baby's father weigh (in kilograms)?

☐☐ kg

Previous pregnancies

31. Have you been pregnant before? (Include all pregnancies that ended in abortion, miscarriage or stillbirth as well)

☐ No (proceed to question 36)
☐ Yes

32. If yes, fill in for all earlier pregnancies. Include all pregnancies that ended in abortion, miscarriage or stillbirth as well as ectopic pregnancies. State the year the pregnancy began, how many kilos you gained during the pregnancy and the number of months you breast-fed each baby. State whether or not you smoked during earlier pregnancies.

Pregnancy Number	Year pregnancy started	Live infant born	Spontaneous abortion/ stillbirth	Termination of pregnancy	Ectopic pregnancy	Week of pregnancy for abortion/ still birth	Number of months breast feeding	Weight gain during pregnancy (in kg)	Smoked during pregnancy
1		☐	☐	☐	☐				☐
2		☐	☐	☐	☐				☐
3		☐	☐	☐	☐				☐
4		☐	☐	☐	☐				☐
5		☐	☐	☐	☐				☐
6		☐	☐	☐	☐				☐
7		☐	☐	☐	☐				☐
8		☐	☐	☐	☐				☐
9		☐	☐	☐	☐				☐
10		☐	☐	☐	☐				☐

33. Have you had any of the following problems during previous pregnancies? (Fill in all that apply.)

	No	Yes
1. Pelvic girdle pain requiring medical leave	☐	☐
2. Pelvic girdle pain requiring bed rest	☐	☐
3. Serious nausea and vomiting	☐	☐
4. Pre-eclampsia during pregnancy	☐	☐
5. Pregnancy diabetes	☐	☐
6. Sugar in urine	☐	☐
7. Problems with incontinence	☐	☐

34. If you had pelvic girdle pain in a previous pregnancy that led to bed rest or medical leave, when did the pain start?

☐☐ months after start of pregnancy

35. When did the pain stop?

☐☐ months after pregnancy
☐ still have pain

Illnesses and health problems during this pregnancy

36. Have you had bleeding from the vagina once or more during this pregnancy?

☐ No
☐ Yes

37. If yes, describe the first and last bleeding. Give the date the bleeding started, how many days the bleeding lasted and how much you bled.

	Date when bleeding started			No. of days variation	(Enter a cross in a box indicating the amount of blood (trace blood means a few drops) Amount		
	Day	Month	Year				
First bleeding	☐☐	☐☐	☐☐☐☐	☐☐	☐ Trace of blood	☐ More than just a trace	☐ Clots
Last bleeding	☐☐	☐☐	☐☐☐☐	☐☐	☐ Trace of blood	☐ More than just a trace	☐ Clots

If more than two episodes of bleeding write in the number of times ☐☐

38. Have you experienced any of the following illnesses or problems during this pregnancy? If you have used medication in connection with these problems give the name of the medicine, the weeks you took the medicines and how many days you took them. (Include all types of medication, both prescription and over the counter medicines in addition to alternative and herbal remedies. Do not include vitamins and dietary supplements as these are discussed elsewhere.)

Illness/health problem during this pregnancy					Use of medication during this pregnancy					
	Week of pregnancy					Week of pregnancy				Number of days taken
Illness/health problem	0-4	5-8	9-12	13+	Name of medicine taken	0-4	5-8	9-12	13+	
1 Pelvic girdle pain	☐	☐	☐	☐		☐	☐	☐	☐	
2 Abdominal pain	☐	☐	☐	☐		☐	☐	☐	☐	
3 Back pain	☐	☐	☐	☐		☐	☐	☐	☐	
4 Neck and shoulder pain	☐	☐	☐	☐		☐	☐	☐	☐	
5 Nausea	☐	☐	☐	☐		☐	☐	☐	☐	
6 Nausea with vomiting	☐	☐	☐	☐		☐	☐	☐	☐	
7 Vaginal thrush	☐	☐	☐	☐		☐	☐	☐	☐	
8 Vaginal catarrh/unusual discharge	☐	☐	☐	☐		☐	☐	☐	☐	
9 Pregnancy itch	☐	☐	☐	☐		☐	☐	☐	☐	
10 Constipation	☐	☐	☐	☐		☐	☐	☐	☐	
11 Diarrhoea/gastric flu	☐	☐	☐	☐		☐	☐	☐	☐	
12 Unusual tiredness/sleepiness	☐	☐	☐	☐		☐	☐	☐	☐	
13 Sleeping problems	☐	☐	☐	☐		☐	☐	☐	☐	
14 Heartburn/reflux	☐	☐	☐	☐		☐	☐	☐	☐	
15 Oedema	☐	☐	☐	☐		☐	☐	☐	☐	
16 Fever with rash	☐	☐	☐	☐		☐	☐	☐	☐	
17 Fever over 38.5 C	☐	☐	☐	☐		☐	☐	☐	☐	
18 Common cold	☐	☐	☐	☐		☐	☐	☐	☐	
19 Throat infection	☐	☐	☐	☐		☐	☐	☐	☐	
20 Sinusitis/ear infection	☐	☐	☐	☐		☐	☐	☐	☐	
21 Influenza	☐	☐	☐	☐		☐	☐	☐	☐	
22 Pneumonia/bronchitis	☐	☐	☐	☐		☐	☐	☐	☐	
23 Sugar in urine	☐	☐	☐	☐		☐	☐	☐	☐	
24 Protein in urine	☐	☐	☐	☐		☐	☐	☐	☐	

Previous and current illnesses and health problems

39. Do you have or have you had any of the following illnesses or health problems? If you have taken medication (tablets, mixtures, suppositories, inhalers, creams, etc.) in conjunction with the illness or health problem give the name(s) of the medication(s) and when you took them.

Illness/health problem during this pregnancy		Use of medication					
Illness/health problem	Before Pregnancy	During Pregnancy	Name of medicines	Last 6 months before pregnancy	Pregnancy week 0-4	5-8	9-12	13+	Number of days used
Asthma/Allergy/Skin disorders									
1 Asthma	☐	☐	_____	☐	☐	☐	☐	☐	
2 Hay fever, pollen allergy	☐	☐	_____	☐	☐	☐	☐	☐	
3 Animal hair allergy	☐	☐	_____	☐	☐	☐	☐	☐	
4 Other allergy	☐	☐	_____	☐	☐	☐	☐	☐	
5 Atopic dermatitis (childhood eczema)	☐	☐	_____	☐	☐	☐	☐	☐	
6 Urticaria (hives)	☐	☐	_____	☐	☐	☐	☐	☐	
7 Psoriasis	☐	☐	_____	☐	☐	☐	☐	☐	
8 Other eczema	☐	☐	_____	☐	☐	☐	☐	☐	
9 Cold sores (herpes)	☐	☐	_____	☐	☐	☐	☐	☐	
10 Acne/pimples (serious)	☐	☐	_____	☐	☐	☐	☐	☐	
Diabetes									
11 Diabetes treated with insulin	☐	☐	_____	☐	☐	☐	☐	☐	
12 Diabetes not treated with insulin	☐	☐	_____	☐	☐	☐	☐	☐	
Heart/Blood/Metabolism/Blood vessels									
13 Congenital heart defect	☐	☐	_____	☐	☐	☐	☐	☐	
14 Other heart disease	☐	☐	_____	☐	☐	☐	☐	☐	
15 High cholesterol	☐	☐	_____	☐	☐	☐	☐	☐	
16 High blood pressure	☐	☐	_____	☐	☐	☐	☐	☐	
17 Hypothyroidism or hyperthyroidism	☐	☐	_____	☐	☐	☐	☐	☐	
18 Anaemia/low haemoglobin	☐	☐	_____	☐	☐	☐	☐	☐	
19 B-12/folic acid insufficiency	☐	☐	_____	☐	☐	☐	☐	☐	
Gastrointestinal									
20 Hepatitis/jaundice	☐	☐	_____	☐	☐	☐	☐	☐	
21 Gall stones	☐	☐	_____	☐	☐	☐	☐	☐	
22 Duodenal/stomach ulcer	☐	☐	_____	☐	☐	☐	☐	☐	
23 Crohn's disease/ulcerative colitis	☐	☐	_____	☐	☐	☐	☐	☐	
24 Celiac sprue (gluten sensitivity)	☐	☐	_____	☐	☐	☐	☐	☐	
25 Other gastro-intestinal problems	☐	☐	_____	☐	☐	☐	☐	☐	
Muscle/Skeleton/Connective tissue									
26 Arthritis (rheumatoid arthritis)/ Bechterev's reflex	☐	☐	_____	☐	☐	☐	☐	☐	

Illness/health problem during this pregnancy			Use of medication					
Illness/health problem	Before Pregnancy	During Pregnancy	Name of medicines	Last 6 months before pregnancy	Pregnancy week 0-4	5-8	9-12	13+	Number of days used
27 Lupus (SLE)	☐	☐		☐	☐	☐	☐	☐	
28 Sciatica	☐	☐		☐	☐	☐	☐	☐	
29 Fibromyalgia	☐	☐		☐	☐	☐	☐	☐	
Genital and urinary tract									
30 Ovary/fallopian tube infection	☐	☐		☐	☐	☐	☐	☐	
31 Endometriosis	☐	☐		☐	☐	☐	☐	☐	
32 Uterus prolaps	☐	☐		☐	☐	☐	☐	☐	
33 Ovarian cyst	☐	☐		☐	☐	☐	☐	☐	
34 Myoma	☐	☐		☐	☐	☐	☐	☐	
35 Cervical cell changes	☐	☐		☐	☐	☐	☐	☐	
36 Herpes	☐	☐		☐	☐	☐	☐	☐	
37 Venereal warts/condyloma	☐	☐		☐	☐	☐	☐	☐	
38 Gonorrhea	☐	☐		☐	☐	☐	☐	☐	
39 Chlamydia	☐	☐		☐	☐	☐	☐	☐	
40 Kidney stones	☐	☐		☐	☐	☐	☐	☐	
41 Kidney infection/pyelonephritis	☐	☐		☐	☐	☐	☐	☐	
42 Urinary tract infections/cystitis	☐	☐		☐	☐	☐	☐	☐	
43 Incontinence	☐	☐		☐	☐	☐	☐	☐	
Other illnesses/health problems									
44 Anorexia/bulimia/other eating disorders	☐	☐		☐	☐	☐	☐	☐	
45 Migraine	☐	☐		☐	☐	☐	☐	☐	
46 Other headache	☐	☐		☐	☐	☐	☐	☐	
47 Epilepsy	☐	☐		☐	☐	☐	☐	☐	
48 Multiple sclerosis	☐	☐		☐	☐	☐	☐	☐	
49 Cerebral palsy	☐	☐		☐	☐	☐	☐	☐	
50 Cancer	☐	☐		☐	☐	☐	☐	☐	
51 Depression	☐	☐		☐	☐	☐	☐	☐	
52 Anxiety	☐	☐		☐	☐	☐	☐	☐	
53 Other long illness or health problems	☐	☐		☐	☐	☐	☐	☐	

Which .....

40. Do you have a congenital malformation/birth defect?

☐ No
☐ Yes

41. If yes, which? _____

42. Do your gums bleed when you brush your teeth at present?

☐ No, rarely or never
☐ Yes, sometimes
☐ Yes, often
☐ Yes, almost always

43. If you had diabetes before you became pregnant, what was your last long-term blood sugar level (HbA1c) before you became pregnant?

☐ Less than 7.5
☐ 7.5 - 12
☐ More than 12
☐ Don't Know

Other medicines

44. Have you used other medication not previously mentioned? If yes, which and when did you take them?

Name of medication (e.g. Valium, Rohypnol, Paracetamol)	Use of medication during pregnancy weeks: Last 6 months before pregnancy	0-4	5-8	9-12	13+	Number of days used
_____	☐	☐	☐	☐	☐	
_____	☐	☐	☐	☐	☐	
_____	☐	☐	☐	☐	☐	
_____	☐	☐	☐	☐	☐	
_____	☐	☐	☐	☐	☐	

Vitamins, minerals and dietary supplements

45. Do you take vitamins, minerals or other dietary supplements?

☐ No (proceed to question 49)
☐ Yes

46. If yes, fill in the table below for the vitamins and minerals found in the contents list on the vitamin package/bottle. (For instance, if you have taken cod liver oil for the last six months before becoming pregnant, enter a cross for each period under "When" (i.e. 7 crosses) and enter a cross in "Daily" under "How often").

	When did you take the supplements? Last 6 months before pregnancy: 26-9 weeks	8-5 weeks	4-0 weeks	During pregnancy: 0-4 weeks	5-8 weeks	9-12 weeks	13+ weeks	In this period how often did you take this? Daily	4-6 times a week	1-3 times a week
1 Folate/folic acid	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2 Vitamin B1 (Thiamine)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3 Vitamin B2 (Riboflavin)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4 Vitamin B6 (Pyridoxine)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5 Vitamin B12	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6 Niacin	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7 Pantothenic acid	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8 Biotin	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9 Vitamin C	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10 Vitamin A	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
11 Vitamin D	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
12 Vitamin E	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
13 Iron	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
14 Calcium	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
15 Iodine	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
16 Zinc	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
17 Selenium	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
18 Copper	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
19 Chromium	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
20 Magnesium	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
21 Cod liver oil	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
22 Omega-3 fatty acid	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

47. Give the complete name(s) of all vitamins and dietary supplements you take. Include alternative/herbal remedies and diet products. (Write clearly in CAPITAL LETTERS.)

E.g. VITAPLEX WITH IRON

1

2

3

4

5

6

48. If you use multivitamins (with or without minerals) do these contain folic acid?

☐ Yes
☐ No
☐ Don't Know

Civil status and education

49. What is your civil status?

☐ Married
☐ Cohabitant
☐ Single
☐ Divorced/separated
☐ Widow
☐ Other

50. What education do you and the baby's father have? (Enter a cross indicating the highest level of education you both have completed and current studies if you are still studying.)

	You		Baby's Father	
	Completed	On-going	Completed	On-going
1 9-year secondary school	☐	☐	☐	☐
2 1-2 year high school	☐	☐	☐	☐
3 Technical high school	☐	☐	☐	☐
4 3-year high school general studies, junior college	☐	☐	☐	☐
5 Regional technical college, 4-year university degree (Bachelor's degree, nurse, teacher, engineer)	☐	☐	☐	☐
6 University, technical college, more than 4 years (Master's degree, medical doctor, PhD)	☐	☐	☐	☐
7 Other education	☐	☐	☐	☐

Work and leisure

51. What was your and the baby's father's work situation when you became pregnant? (Fill in one or several boxes for each.)

	You	Baby's Father
1 Student	☐	☐
2 At home	☐	☐
3 Intern/apprentice	☐	☐
4 Military service	☐	☐
5 Unemployed/laid off	☐	☐
6 Rehabilitation/disabled	☐	☐
7 Employed in public sector	☐	☐
8 Employed in private sector	☐	☐
9 Self-employed	☐	☐
10 Family member without steady income in family company (e.g. Farming, business)	☐	☐
11 Other	☐	☐

52. Did you have an extra job (with or without salary) when you became pregnant? (For example, accountant, hair dresser, singer in a dance band, club leader)

☐ No

☐ Yes, describe_____

53. Have you been absent from your usual work more than two weeks altogether during this pregnancy?

☐ No

☐ Yes

54 Are you absent from your work at the present time?

☐ No

☐ Yes

55. If yes, what is the reason for your absence? (Fill in one or several boxes.)

☐ Medical leave

☐ Leave of absence

☐ Sick child

☐ Other _____

56. The usual number of paid working hours a week before you became pregnant and at present.

Before the pregnancy: ☐☐,☐ Hours

During the pregnancy : ☐☐,☐ Hours

(Questions about current work situation to be answered by anyone in paid employment, even if they are temporarily absent due to illness, being on leave or for similar reasons.)

57. Describe the type of work carried out at your and the baby's father's place of work as accurately as possible.
(Write for example, hospital department for children with cancer, body shop at a garage for diesel vehicles, farming with grain and swine, work in the home.)

58. Occupation/title at this workplace?
(Write for example, staff nurse, mechanic, foreman, lecturer, student, cleaning assistant, housewife/at home.)

You	Baby's Father

59. Indicate the appropriate answer for each of the following questions concerning your present work situation. (Fill in only one box in each line.)

	Yes every day more than half of the working day	Yes every day less than half of the working day	Yes, periodically but not daily	Seldom or never
Do you sometimes have so much to do that your work situation becomes taxing?	☐	☐	☐	☐
Do you have to turn or bend many times in the course of an hour?	☐	☐	☐	☐
Do you work with your hands up at shoulder level or higher?	☐	☐	☐	☐
Do you work standing or walking?	☐	☐	☐	☐
Can you choose to work a little faster some days and a little slower on other days?	☐	☐	☐	☐
Are you subjected to a lot of uncomfortable background noise?	☐	☐	☐	☐
Are you subjected to a lot of background noise that makes you have to raise your voice when talking to others, even at a distance of one metre?	☐	☐	☐	☐

60. How do the following statements describe your work situation? (Fill in only one box in each line.)

	Agree	Agree mostly	Disagree mostly	Disagree completely
I have physically heavy work.	☐	☐	☐	☐
My work is very stressful	☐	☐	☐	☐
I learn a lot at work	☐	☐	☐	☐
My work is very monotonous	☐	☐	☐	☐
My work demands a lot of me.	☐	☐	☐	☐
I am able to decide how my work is to be carried out.	☐	☐	☐	☐
There is a good team spirit at my place of work.	☐	☐	☐	☐
I enjoy my work	☐	☐	☐	☐

61. When are your working hours? (Fill in one or several boxes.)

☐ Permanent day work

☐ Permanent afternoon or evening work

☐ Permanent night work

☐ Shift work or shift rotations

☐ No set times (extra help, extra shifts, temporary employment, etc.)

☐ Other

62. During your pregnancy do you lift anything that weighs more than 10 kg (10 kilos is the equivalent of a full bucket of water.)

	At Home	At Work
Seldom or never	☐	☐
Yes, less than 20 times a week	☐	☐
Yes, more than 20 times a week	☐	☐
Yes, 10-20 times a day	☐	☐
Yes, more than 20 times a day	☐	☐

63. How often have you worked with radio transmitters or radar after becoming pregnant?

- ☐ Seldom/Never
- ☐ A few times a week
- ☐ Daily
- ☐ On average more than an hour daily

64. How often do you talk on a cell phone?

- ☐ Seldom/Never
- ☐ A few times a week
- ☐ Daily
- ☐ On average more than an hour daily

65. Do your cell phone calls last more than 15 minutes?

- ☐ Never
- ☐ Seldom
- ☐ Often

66. How often have you worked with a computer monitor, laser printer or copying machine (at a distance of less than two metres) after you became pregnant?

	Computer monitor	Laser printer	Copying machine
Seldom/Never	☐	☐	☐
A few times per week	☐	☐	☐
Daily	☐	☐	☐
On average more than an hour daily	☐	☐	☐

67. How often have you worked with X-ray equipment (at a distance of less than two metres) after you became pregnant?
(This does not include treatment as a patient)

- ☐ Seldom/Never
- ☐ A few times a week
- ☐ Daily
- ☐ On average more than an hour daily

68. Have you been in contact with any of the following substances either at work or in your leisure time during the last six months? (Fill in each line.)

	No	Yes	If Yes, number of days the last 6 months (daily = 180 days)	Fill in if you have used a hood for gases or breathing protection	Fill in if you have used protective gloves
1 Lead vapours, lead dust, lead particles or lead alloys	☐	☐		☐	☐
2 Chrome, arsenic, cadmium or combinations of these	☐	☐		☐	☐
3 Gasoline or exhaust (does not apply to filling gasoline in your own car)	☐	☐		☐	☐
4 Mercury vapours, mercury or work with amalgam fillings (does not apply to your own dental treatment)	☐	☐		☐	☐
5 Disinfectants, vermin poisons	☐	☐		☐	☐
6 Weed killers, insecticides, fungicides	☐	☐		☐	☐
7 Oil-based paint	☐	☐		☐	☐
8 Water-based or latex paint	☐	☐		☐	☐
9 Paint thinner, paint-lacquer-glue remover or other solvents (e.g. lynol, turpentine, toluene, carbon tetrachloride)	☐	☐		☐	☐
10 Industrial dyes or ink	☐	☐		☐	☐
11 Motor oil, lubrication oil or other types of oil	☐	☐		☐	☐
12 Photographic chemicals (fixatives or developers)	☐	☐		☐	☐
13 Substances used in welding	☐	☐		☐	☐
14 Substances used in soldering	☐	☐		☐	☐
15 Formalin/formaldehyde	☐	☐		☐	☐
16 Chemotherapeutic substances/chemotherapy treatment (does not apply to your own medical treatment)	☐	☐		☐	☐
17 Laughing gas or other anaesthetic gases (does not apply to your own treatment as a patient)	☐	☐		☐	☐
18 Other substances and conditions, describe_____	☐	☐		☐	☐

69. How often have you been to a discotheque since you became pregnant?

- ☐ 1-2 times a week
- ☐ Less often
- ☐ Never

70. Are you in contact with animals either at work or in your leisure time?

- ☐ No
- ☐ Yes

71. If yes, what sort of animals and how often are you in contact with them on a weekly basis?

	Daily	3-6 times a week	1-2 times a week	Less than 1 time a week
1 Dog	☐	☐	☐	☐
2 Cat	☐	☐	☐	☐
3 Guinea pig	☐	☐	☐	☐
4 Hamster	☐	☐	☐	☐
5 Rabbit	☐	☐	☐	☐
6 Canary or other bird	☐	☐	☐	☐
7 Aquarium fish	☐	☐	☐	☐
8 Cow	☐	☐	☐	☐
9 Pig	☐	☐	☐	☐
10 Sheep, goat	☐	☐	☐	☐
11 Horse	☐	☐	☐	☐
12 Poultry	☐	☐	☐	☐
13 Other	☐	☐	☐	☐

Housing and household

72. With whom do you live? (Fill in one or several boxes.)

- ☐ Spouse/partner
- ☐ Parents
- ☐ Parents-in-law
- ☐ Children
- ☐ No one
- ☐ Other describe_____

73. How many people including you live in your home?

Number of people over 18 years . . . . . ☐☐

Number of people between 12 - 18 years . . . . . ☐☐

Number of people between 6 - 11 years . . . . . ☐☐

Number of people under 6 years . . . . . ☐☐

74. How many children are at nursery school/day care?

☐ children

75. Do you or the baby's father have a mother tongue other than Norwegian?

- ☐ No
- ☐ Yes

76. If yes, which language?

	You	Baby's Father
Sámi	☐	☐
Urdu	☐	☐
English	☐	☐
Other	☐	☐

If other, which?_____

77. Do your parents or the baby's father's parents have a mother tongue other than Norwegian?

- ☐ No
- ☐ Yes

78. If yes, which language?

	Your Mother	Your Father	Mother of the child's father	Father of the child's father
Sámi	☐	☐	☐	☐
Urdu	☐	☐	☐	☐
English	☐	☐	☐	☐
Other	☐	☐	☐	☐

If other, which? _____

79. What is your and the baby's father's yearly gross income? (Include child support, unemployment benefits and other allowances.)

Your gross income	Child's father's gross income
☐ No income	☐ No income
☐ Under 150.000 NOK	☐ Under 150.000 NOK
☐ 150-199.999 NOK	☐ 150-199.999 NOK
☐ 200-299.999 NOK	☐ 200-299.999 NOK
☐ 300-399.999 NOK	☐ 300-399.999 NOK
☐ 400-499.999 NOK	☐ 400-499.999 NOK
☐ over 500.000 NOK	☐ over 500.000 NOK
	☐ Don't know

80. Is it possible for your household to manage financially without your income?

- ☐ No
- ☐ Yes, but with difficulty
- ☐ Yes, without difficulty

81. What type of house do you live in?

- ☐ Detached house
- ☐ Farm
- ☐ Semi detached
- ☐ Four-flat house
- ☐ Maisonette
- ☐ Terraced flat
- ☐ Basement flat
- ☐ Apartment building
- ☐ Townhouse/tenement
- ☐ Which floor? ☐☐
- ☐ Other_____

82. Has there been damp damage, visible signs of fungus/mildew or a smell of mildew in your home in the past 3 months? (Fill in one or several boxes.)

- ☐ No
- ☐ Yes, damp damage
- ☐ Yes, signs of fungus and mould
- ☐ Yes, a smell of mildew

83. Where does your drinking water come from?

- ☐ Public or private water company
- ☐ Water from a local source (e.g. own well)

84. How many times have you moved in the last 3 years?

☐☐ times

85. Has anyone in your home had influenza, a prolonged cough, childhood disease or an illness with fever and a rash after you became pregnant?

- ☐ No
- ☐ Yes

86. If yes, which illness? (fill in one or several boxes)

- ☐ German measles
- ☐ Chicken pox
- ☐ Measles
- ☐ Roseola infantum
- ☐ Other fever with rash
- ☐ Influenza
- ☐ Prolonged cough
- ☐ Tuberculosis
- ☐ Hand, foot and mouth disease
- ☐ Other

Living habits

87. Did your mother smoke when she was pregnant with you?
☐ No
☐ Yes
☐ Don't Know

88. Are you exposed to passive smoking at home?
☐ No
☐ Yes

89. If yes, how many hours a day are you exposed to passive smoking?
☐☐ hours per day

90. Are you exposed to passive smoking at work?
☐ No
☐ Yes

91. If yes, how many hours a day are you exposed to passive smoking?
☐☐ hours per day

92. Did the baby's father smoke before you became pregnant?
☐ No
☐ Yes

93. Does he smoke now?
☐ No
☐ Yes

94. Have you ever smoked?
☐ No (proceed to question 104)
☐ Yes

95. Do you smoke now (after you became pregnant)?
☐ No
☐ Sometimes ☐☐ cigarettes per week
☐ Daily ☐☐ cigarettes per day

96. Did you smoke during the last 3 months before you became pregnant this time?
☐ No
☐ Sometimes ☐☐ cigarettes per week
☐ Daily ☐☐ cigarettes per day

97. How old were you when you started to smoke on a daily basis?
☐☐ Years

98. Have you stopped smoking completely?
☐ No
☐ Yes

99. If yes, how old were you when you stopped smoking?
☐☐ Years

100. If you stopped smoking after you became pregnant, in which week of pregnancy did you stop?
☐☐ week of pregnancy

101. How long after you get up in the morning until you light your first cigarette?
☐ 5 minutes
☐ 6-29 minutes
☐ 30-60 minutes
☐ More than one hour

102. Do you smoke when you are ill?
☐ No
☐ Yes

103. Do you smoke more often during the first few hours after you wake up than you do during the rest of the day?
☐ No
☐ Yes

104. If you have used other kinds of nicotine indicate which and when you used them.

	Before pregnancy	During pregnancy
Chewing tobacco/snuff	☐	☐
Nicotine chewing gum	☐	☐
Nicotine adhesive patch	☐	☐
Nicotine inhaler	☐	☐

105. What was your fluid consumption (number of cups/glasses) per day before and during pregnancy? (1 mug = 2 cups, 1 small plastic bottle (0.5 litre) = 4 cups, 1 large plastic bottle (1.5 litres) = 12 cups)

	Number of cups/glasses: Before pregnancy	Number of cups/glasses: Now	Decaffeinated (Enter a cross)
1 Filter coffee	☐☐	☐☐	☐
2 Instant coffee	☐☐	☐☐	☐
3 Boiled coffee	☐☐	☐☐	☐
4 Tea	☐☐	☐☐	☐
5 Herbal tea	☐☐	☐☐	☐
6 Coca Cola/Pepsi etc.	☐☐	☐☐	☐
7 Other fizzy drinks	☐☐	☐☐	☐
8 Diet Coca Cola/Pepsi	☐☐	☐☐	☐
9 Other diet fizzy drinks	☐☐	☐☐	☐
10 Tap water	☐☐	☐☐	☐
11 Bottled water	☐☐	☐☐	☐

	Before pregnancy	Now	Ecological (Enter a cross)
12 Juice/squash	☐☐	☐☐	☐
13 Diet juice/squash	☐☐	☐☐	☐
14 Milk (skim, low fat, whole)	☐☐	☐☐	☐
15 Yogurt, all types	☐☐	☐☐	☐
16 Yogurt/active Lactobacillus	☐☐	☐☐	☐
17 Other type of cultured milk - Kefir	☐☐	☐☐	☐
18 Other	☐☐	☐☐	☐

106. Have you used any of the following substances?

	Never	Previously	Last month before pregnancy	During pregnancy
1 Hash	☐	☐	☐	☐
2 Amphetamine	☐	☐	☐	☐
3 Ecstasy	☐	☐	☐	☐
4 Cocaine	☐	☐	☐	☐
5 Heroin	☐	☐	☐	☐

107. Have you ever consumed alcohol?

☐ No (proceed to question 117)
☐ Yes

Alcohol units are used to compare the different types of alcoholic beverages. 1 alcohol unit (= 1.5 cl. pure alcohol) is equivalent to:

1 bottle/can energy drink or cider
1 glass (1/3 litre) of beer
1 wine glass red or white wine
1 sherry glass sherry or fortified wine
1 snaps glass spirits or liqueur

108. How often did you consume alcohol in the 3 months before you became pregnant and how often do you consume alcohol during the pregnancy?

	Last 3 months before pregnancy	During pregnancy
1 Approximately 6-7 times a week	☐	☐
2 Approximately 4-5 times a week	☐	☐
3 Approximately 2-3 times a week	☐	☐
4 Approximately once a week	☐	☐
5 Approximately 1-3 times a month	☐	☐
6 Less than once a month	☐	☐
7 Never	☐	☐

109. What type of alcohol do you usually drink? (Fill in one or several boxes.)

1 Light beer	☐
2 Beer	☐
3 Red wine	☐
4 White wine	☐
5 Low alcohol sodas	☐
6 Fortified wines (sherry, port, Madeira)	☐
7 Spirits (vodka, gin, snaps, cognac, whisky, liqueur)	☐

110. Did you drink 5 units or more at least once during the last 3 months before pregnancy or during pregnancy?

	Last 3 months before pregnancy	During pregnancy
1 Several times per week	☐	☐
2 Once a week	☐	☐
3 1-3 times a month	☐	☐
4 Less than once a month	☐	☐
5 Never	☐	☐

111. How many units of alcohol do you usually drink when you consume alcohol?

	Last 3 months before pregnancy	During pregnancy
10 or more	☐	☐
7-9	☐	☐
5-6	☐	☐
3-4	☐	☐
1-2	☐	☐
Less than 1	☐	☐

112. How many units of alcohol do you have to drink before you feel any effect?

☐☐ units

113. Have other people irritated you or hurt your feelings by criticising how much you drink?

☐ No
☐ Yes

114. Have you ever felt that you ought to drink less alcohol?

☐ No
☐ Yes

115. Have you ever drunk alcohol in the morning to calm your nerves or to get rid of a hangover?

☐ No
☐ Yes

116. Have you ever experienced any of the following problems during the last year in relation to your alcohol consumption?

	Never	Once	Several times
Argued with or had negative feelings for a family member	☐	☐	☐
Suddenly found yourself somewhere without knowing how you got there	☐	☐	☐
Been absent from work or school	☐	☐	☐
Fainted or passed out suddenly	☐	☐	☐
Had a sad period	☐	☐	☐

Weight and weight control

117. Do you think you were overweight just before this pregnancy?

☐ Yes, a lot
☐ Yes, a little
☐ No

118. Are you worried about putting on more weight than necessary during this pregnancy?

☐ Yes, very worried
☐ Somewhat worried
☐ No, not especially worried

119. Has anyone said that you were too thin while you felt that you were overweight during the last 2 years?

☐ Yes, often
☐ Yes, occasionally
☐ No

120. Have you ever felt that you lost control while eating and were not able to stop before you have eaten far too much?

	Last 6 months before this pregnancy	Now
No	☐	☐
Infrequently	☐	☐
Yes, at least once a week	☐	☐

121. Have you ever used any of the following methods to control your weight?

	Last 6 months before this pregnancy		Now	
	At least once a week	Seldom/ Never	At least once a week	Seldom/ Never
Vomiting	☐	☐	☐	☐
Laxatives	☐	☐	☐	☐
Fasting	☐	☐	☐	☐
Hard physical exercise	☐	☐	☐	☐

122. Is it important for your self-image that you maintain a certain weight?

☐ Yes, very important
☐ Yes, quite important
☐ No, not especially important

Physical activity

123. How often do you exercise? (Fill in each line for both before and during this pregnancy.)

	Last 3 months before this pregnancy					During this pregnancy				
	Never	1-3 times a month	1 time a week	2 times a week	3 or more times a week	Never	1-3 times a month	1 time a week	2 times a week	3 or more times a week
1 Walking	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2 Brisk walking	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3 Running/jogging/orienteering	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4 Bicycling	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5 Training studio/weight training	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6 Special gymnastics/aerobics for pregnant women	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7 Aerobics/gymnastics/dance without running and jumping	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8 Aerobics/gymnastics/dance with running and jumping	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9 Dancing (swing/rock/folk)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10 Skiing	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
11 Ball sports	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
12 Swimming	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
13 Riding	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
14 Other	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

124. How often do you do exercises for the following muscle groups? (Fill in each line for both before and during this pregnancy.)

	Last 3 months before pregnancy					During pregnancy				
	Never	1-3 times a month	1 time a week	2 times a week	3 or more times a week	Never	1-3 times a month	1 time a week	2 times a week	3 or more times a week
Abdominal muscles	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Back muscles	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pelvic floor muscles (muscles around the vagina, urethra, anus)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

125. How often are you so physically active in your leisure and/or at work that you get out of breath or sweat?

	Last 3 months before this pregnancy		During this pregnancy	
	Leisure	At work	Leisure	At work
Never	☐	☐	☐	☐
Less than once a week	☐	☐	☐	☐
Once a week	☐	☐	☐	☐
2 times a week	☐	☐	☐	☐
3-4 times a week	☐	☐	☐	☐
5 times a week or more	☐	☐	☐	☐

A little more about yourself and how you are keeping now

126. Do you agree or disagree with the following statements? (Fill in only one box in each line.)

	Disagree completely	Disagree	Disagree somewhat	Don't agree or disagree	Agree somewhat	Agree	Agree completely
My life is largely what I wanted it to be	☐	☐	☐	☐	☐	☐	☐
My life is very good	☐	☐	☐	☐	☐	☐	☐
I am satisfied with my life	☐	☐	☐	☐	☐	☐	☐
To date, I have achieved what is important for me in my life	☐	☐	☐	☐	☐	☐	☐
If I could start all over, there is very little I would do differently	☐	☐	☐	☐	☐	☐	☐

127. How do these statements describe your relationship? (Only answer if you have a partner.) (Fill in only one box in each line.)

	Agree Completely	Agree	Agree somewhat	Disagree somewhat	Disagree	Disagree completely
My husband/partner and I have a close relationship	☐	☐	☐	☐	☐	☐
My partner and I have problems in our relationship	☐	☐	☐	☐	☐	☐
I am very happy in my relationship	☐	☐	☐	☐	☐	☐
My partner is usually understanding	☐	☐	☐	☐	☐	☐
I often think about ending our relationship	☐	☐	☐	☐	☐	☐
I am satisfied with my relationship with my partner	☐	☐	☐	☐	☐	☐
We often disagree about important decisions	☐	☐	☐	☐	☐	☐
I have been lucky in my choice of a partner	☐	☐	☐	☐	☐	☐
We agree about how children should be raised	☐	☐	☐	☐	☐	☐
I think my partner is satisfied with our relationship	☐	☐	☐	☐	☐	☐

128. Do you have anyone other than your husband/partner you can ask for advice in a difficult situation?

- ☐ No
- ☐ Yes 1-2 people
- ☐ Yes more than 2 people

129. How often do you meet or talk on the telephone with your family (other than those you live with) or close friends?

- ☐ Once a month or less
- ☐ 2-8 times a month
- ☐ More than twice a week

130. Do you often feel lonely?

- ☐ Almost never
- ☐ Seldom
- ☐ Sometimes
- ☐ Usually
- ☐ Almost always

131. Have you been bothered by any of the following during the last two weeks? (Enter a cross for each line.)

	Not bothered	A little bothered	Quite bothered	Very bothered
Feeling fearful	☐	☐	☐	☐
Nervousness or shakeiness inside	☐	☐	☐	☐
Feeling hopeless about the future	☐	☐	☐	☐
Feeling blue	☐	☐	☐	☐
Worrying too much about things	☐	☐	☐	☐

132. Have you ever in your adult life been slapped, hit, kicked or bothered in any way physically? (fill in one or several boxes)

	During this pregnancy	Last 6 months before pregnancy	Earlier
No	☐	☐	☐
Yes	☐	☐	☐
Don't remember	☐	☐	☐

133. Have you ever been pressured or forced to have sexual intercourse? (Fill in one or several boxes.)

	During this pregnancy	Last 6 months before pregnancy	Earlier
No, never	☐	☐	☐
Yes, pressured	☐	☐	☐
Yes, forced with violence	☐	☐	☐
Yes, raped	☐	☐	☐

134. How do you feel about yourself? (Enter a cross for each line.)

	Agree completely	Agree	Disagree	Disagree completely
I have a positive attitude toward myself	☐	☐	☐	☐
I feel completely useless at times	☐	☐	☐	☐
I feel that I do not have much to be proud about	☐	☐	☐	☐
I feel that I am a valuable person, as good as anyone else	☐	☐	☐	☐

135. Have you ever experienced the following for a continuous period of 2 weeks or more? (Fill in each line.)

	No	Yes
Felt depressed, sad	☐	☐
Had problems with appetite or eaten too much	☐	☐
Been bothered by feeling weaker or a lack of energy	☐	☐
Really blamed yourself and felt worthless	☐	☐
Had problems with concentration or had problems making decisions	☐	☐
Had at least 3 of the problems named above simultaneously	☐	☐

136. If you have had 3 or more of these problems at the same time, how many weeks did the longest period last?

☐☐ weeks

137. Was there a particular reason for this?

- ☐ No, no particular reason
- ☐ Yes (e.g. death, divorce, miscarriage, accident)

We would be grateful if you would write anything else you would like to tell us about this pregnancy or previous births/pregnancies that are not addressed in this questionnaire on the next page.

Comments

Have you remembered to fill in the date on which you completed the questionnaire on page 1?

Thank you very much for your help!

Please return the completed questionnaire in the stamped addressed envelope provided.

Avd. for medisinsk fødselsregister
Kalfarveien 31
5018 Bergen

Bording

den norske Mor & barn undersøkelsen

Questionnaire 3C

This questionnaire applies mainly to the period after week 12 of your pregnancy. We will ask you some questions which you may recognise from the first questionnaire. We do this because we want to continue following your and your child's progress. It would be useful for you to consult your pregnancy health card before you start answering the questions so that you can use the information contained in it when completing this questionnaire. If you feel uncomfortable with a question or it is difficult to answer, you can skip this question and go on to the next one.

This questionnaire will be processed by a computer. It is therefore important that you follow these instructions:

- Use a blue or black ballpoint pen.
- Put a cross in the box that is most relevant like this: ☒
- If you put a cross in the wrong box, correct it by filling in the box completely like this: ■
- Write a number or capital letter in the large green boxes.

It is important that you only write in the white area of each box like this:

Number: 1 2 3 4 5 6 7 8 9 0 Letter: A B C D

- When entering a single-digit number in boxes containing two or more squares, use the square on the right.
  For example: 5 is written like this: 5
- A number of questions in this questionnaire concern the week of pregnancy. *For example: If you want to indicate something that happened 14 weeks after your last period, enter a cross in the box for week 13-16.*
- Specific information concerning, for example, medication or profession should be written in the boxes or on the lines provided. Please write clearly in CAPITAL LETTERS.
- Remember to enter the date when you completed the questionnaire.

Please return the completed questionnaire in the stamped addressed envelope provided.

Date when the questionnaire was completed Day Month Year (write the year in full, e.g. 2001)

Antenatal care and health

1. Where have you been to antenatal check- ups? (Fill in one or more boxes.) Specify how many times.

- ☐ Public health centre ___ times
- ☐ Doctor's surgery ___ times
- ☐ Hospital (outpatients) clinic ___ times

2. Who has examined you each time? (Fill in one or more boxes.) Specify how many times.

- ☐ Midwife ___ times
- ☐ General practitioner ___ times
- ☐ Gynaecologist ___ times
- ☐ Public health nurse ___ times

3. Is your doctor male or female? How many times have you gone to him/her?

General practitioner	☐ female	___ times
	☐ male	___ times
Gynaecologist	☐ female	___ times
	☐ male	___ times

4. If you visit or have visited a gynaecologist or hospital clinic for your antenatal check-ups, what is or was the reason?

- ☐ Referred due to complications during this pregnancy
- ☐ Referred due to previous illness or complications in previous pregnancies
- ☐ On your own initiative without a referral
- ☐ Referred for another reason

Questionnaire 3c M&B 20,000 1101

5. Do you agree with the following statements concerning your antenatal check-ups?

	Agree completely	Agree	Agree somewhat	Disagree somewhat	Disagree	Disagree completely
I have been given sufficient advice and information	☐	☐	☐	☐	☐	☐
I have been well taken care of	☐	☐	☐	☐	☐	☐
There was not enough time during the consultations	☐	☐	☐	☐	☐	☐
I felt secure during these check-ups	☐	☐	☐	☐	☐	☐
I have been able to discuss everything I needed to during the check-ups	☐	☐	☐	☐	☐	☐
On the whole, I am satisfied with the way I have been followed up by the health service	☐	☐	☐	☐	☐	☐

6. Have you contacted a midwife or doctor in addition to your normal check-ups?

	No	Yes
Midwife	☐	☐
Doctor	☐	☐

7.If yes, was it difficult to get an appointment?

	Midwife	Doctor
Not difficult	☐	☐
Somewhat difficult	☐	☐
Very difficult	☐	☐

8. Have you had a gynaecological examination during your pregnancy (internal examination)? If so, how many times?

☐ No
☐ Yes ☐☐ Times

9. How many ultrasound examinations have you had during your pregnancy?

External ultrasound examination ☐☐ Times
Internal ultrasound examination ☐☐ Times

10. How many children are you expecting? ☐

11. Have you been offered an amniocentesis or placenta biopsy?

☐ No (go to question 16)
☐ Yes

12. If yes, were any tests performed and what were the results?

	Was the test performed? Yes	Was the test performed? No	Were the results normal? Yes	Were the results normal? No
Amniocentesis	☐	☐	☐	☐
Placenta biopsy	☐	☐	☐	☐

If the tests were abnormal, describe the findings:

_____

13. If an amniocentesis or placenta biopsy was performed, what was the reason?

☐ Due to my age (normally 38 or older at the time of delivery)
☐ Previous child with a chromosome disorder
☐ Previous child with neural tube defect (spina bifida)
☐ Epilepsy (medication for epilepsy)
☐ Ultrasound findings
☐ Other

14. Were there complications during the first 2 weeks following the amniocentesis?

☐ No
☐ Yes

15. If yes, what kind of complications?

☐ Vaginal bleeding
☐ Leakage of amniotic fluid
☐ Abdominal pain (similar to or stronger than menstrual pains)
☐ Other _____

16. Have you had an X-ray during pregnancy?

☐ No
☐ Yes

17. If yes, what part of your body was X-rayed? How many X-rays were taken and in which week of pregnancy? (Fill in one or more boxes.)

	Week of pregnancy 0-12	13-16	17-20	21-24	25-28	29+	No. of times
Teeth	☐	☐	☐	☐	☐	☐	
Lungs.	☐	☐	☐	☐	☐	☐	
Arms or legs	☐	☐	☐	☐	☐	☐	
Pelvis/abdomen/ back	☐	☐	☐	☐	☐	☐	
Other	☐	☐	☐	☐	☐	☐	

18. Have you received treatment to prevent a premature birth during this pregnancy? (Fill in one or more boxes.)

☐ No
☐ Yes, relax or bed-rest
☐ Yes, medication
Which medicines?_____

19. Have you been vaccinated during this pregnancy?

☐ No
☐ Yes
Which vaccine?_____

20. Has the midwife or doctor told you that you have or have had high blood pressure during this pregnancy?

☐ No
☐ Yes

21. If yes, what was the highest reading during this pregnancy? (High blood pressure is over 140/90) (Refer to your health card.)

☐☐☐ / ☐☐☐ *E.g.* 150 / 95

☐ Don't know

22. Have you had high blood pressure without being pregnant?

☐ No
☐ Yes
☐ Don't know

23. If yes, what was the highest reading before this pregnancy?

☐☐☐ / ☐☐☐ *E.g.* 150 / 95

☐ Don't know

24. What was your blood percentage/haemoglobin (Hb) value during this pregnancy? (Refer to your health card and note the most recent, in addition to the highest and lowest values.)

	Haemoglobin (Hb)	Week of preg
Value at last antenatal check-up during pregnancy	,	
Highest value during pregnancy	,	
Lowest value during pregnancy	,	

☐ Don't know

25. How much did you weigh at your last antenatal check-up and when was it? (Refer to your health card.)

Weight , kg

Date of antenatal check -up Day Month Year

26. Have you been admitted to the hospital since you became pregnant?

☐ No

☐ Yes, which hospital(s) _____

27. If yes, why and when were you hospitalised? (Fill in one or more boxes.)

	In which week of pregnancy were you admitted? 0–4	5–8	9–12	13–16	17–20	21–24	25–28	29+
☐ Prolonged nausea and vomiting	☐	☐	☐	☐	☐	☐	☐	☐
☐ Bleeding	☐	☐	☐	☐	☐	☐	☐	☐
☐ Leakage of amniotic fluid	☐	☐	☐	☐	☐	☐	☐	☐
☐ Threatening preterm labour	☐	☐	☐	☐	☐	☐	☐	☐
☐ High blood pressure	☐	☐	☐	☐	☐	☐	☐	☐
☐ (Pre-)Eclampsia	☐	☐	☐	☐	☐	☐	☐	☐
☐ Other _____	☐	☐	☐	☐	☐	☐	☐	☐

28. Do you have or have you ever had any of the following?

		If yes, how often have you had problems?				How much at a time?	
Before this pregnancy:	No / Yes	1–4 times a month	1–6 times a week	Once a day	More than once a day	Drops	Large amounts
Incontinence when coughing, sneezing or laughing	☐ ☐	☐	☐	☐	☐	☐	☐
Incontinence during physical activity (running / jumping)	☐ ☐	☐	☐	☐	☐	☐	☐
Incontinence with a strong need to urinate	☐ ☐	☐	☐	☐	☐	☐	☐
Problems retaining faeces	☐ ☐	☐	☐	☐	☐	☐	☐
Problems with flatulence	☐ ☐	☐	☐	☐	☐	☐	☐
In this pregnancy:							
Incontinence when coughing, sneezing or laughing.							
Incontinence during physical activity (running / jumping)	☐ ☐	☐	☐	☐	☐	☐	☐
Incontinence with a strong need to urinate.	☐ ☐	☐	☐	☐	☐	☐	☐
Problems retaining faeces	☐ ☐	☐	☐	☐	☐	☐	☐
Problems with flatulence	☐ ☐	☐	☐	☐	☐	☐	☐

29. Do you have or have you had pain in any of the following parts of your body? Where and when? (Fill in one or more boxes.)

		During this pregnancy		During earlier pregnancies		Between pregnancies		Prior to first pregnancy	
	No	Mild Pain	Severe Pain	Mild Pain	Severe Pain	Mild Pain	Severe Pain	Mild Pain	Severe Pain
Small of the back	☐	☐	☐	☐	☐	☐	☐	☐	☐
One of the pelvic/sacroiliac joints at the back	☐	☐	☐	☐	☐	☐	☐	☐	☐
Both pelvic/sacroiliac joints at the back	☐	☐	☐	☐	☐	☐	☐	☐	☐
Over the coccygeal bone	☐	☐	☐	☐	☐	☐	☐	☐	☐
In the buttocks	☐	☐	☐	☐	☐	☐	☐	☐	☐
Over the pubic bone	☐	☐	☐	☐	☐	☐	☐	☐	☐
Groin	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other back pains	☐	☐	☐	☐	☐	☐	☐	☐	☐

30. Do you wake up at night due to pelvic pain?

- ☐ Yes, frequently
- ☐ Yes, sometimes
- ☐ No, never

31. Do you have to use a stick or crutches in order to walk due to pelvic pain?

- ☐ No, never
- ☐ Yes, but not every day, the pain varies from day to day
- ☐ Yes, I have to use a stick or crutches every day

32. Have you received an anaesthetic in connection with surgery or dental treatment during this pregnancy?

- ☐ No
- ☐ Yes

33. If yes, what type of anaesthetic have you had? (Fill in one or more boxes.)

- ☐ General (full) anaesthetic
- ☐ Spinal anaesthetic (epidural)
- ☐ Local anaesthetic
- ☐ Don't know

34. Have you been to the dentist during this pregnancy?

- ☐ No
- ☐ Yes

35. If yes, did the dentist perform any of the following treatments? (Fill in one or more boxes.)

	Yes	No
Put in new amalgam fillings (silver fillings)	☐	☐
Removed or replaced amalgam fillings	☐	☐
Put in new white fillings	☐	☐

36. How many teeth do you have and how many have fillings? (Look in the mirror and count.)

Total number of teeth ☐☐

Number of teeth with amalgam fillings ☐☐

Number of teeth with other types of fillings ☐☐

37. At present, do your gums bleed when you brush your teeth?

- ☐ No, seldom or never
- ☐ Yes, sometimes
- ☐ Yes, frequently
- ☐ Yes, nearly always

38. Have you had a tattoo or body piercing, including extra holes in the ears? (Do not include pierced ears if you have one hole in each ear.)

- ☐ No
- ☐ Yes

39. If yes, where and when was it done? (Fill in one or more boxes.)

	Tattoo	Body piercing
Before this pregnancy:		
In Norway	☐	☐
Abroad	☐	☐
During this pregnancy:		
In Norway	☐	☐
Abroad	☐	☐

40. Have you ever had a blood transfusion? If yes, give the number of transfusions.

- ☐ No
- ☐ Yes, during this pregnancy ☐☐ Times
- ☐ Yes, before this pregnancy ☐☐ Times

41. If yes, in which country and which year? (Give the last 2 transfusions.) **YEAR**

Country: _____ ☐☐☐☐

Country: _____ ☐☐☐☐

42. Have you ever had breast surgery?

- ☐ No
- ☐ Yes

43. If yes, was it:

- ☐ Breast enlargement
- ☐ Breast reduction
- ☐ Cancer/biopsy
- ☐ Other, describe: _____

44. Have you ever had cervical dysplasia?

- ☐ No
- ☐ Yes

☐☐☐☐ Year the dysplasia was detected the first time

45. Have you had an operation on your cervix?

- ☐ No
- ☐ Yes

☐☐☐☐ Year of operation

46. Have you ever had a gamma globulin injection? (used to prevent infection of hepatitis A, primarily when travelling abroad.)

- ☐ No
- ☐ Yes

If yes, which year? ☐☐☐☐

How have you been recently?

Some questions about the time that has elapsed since the 13th week of pregnancy.

47. Have you had one or more episodes of vaginal bleeding after the 13th week of pregnancy?

☐ No
☐ Yes

48. If yes, how much did you bleed, in which week(s) of pregnancy and how many days did the bleeding last? (If you have had more than 2 episodes of bleeding, describe the last 2 only.)

	The amount of blood (spotting means a few drops)			In which week of pregnancy did the bleeding occur? 13–16	17–20	21–24	25–28	29+	No. of days bleeding lasted
1.	☐ Spotting	☐ More than spotting	☐ Large amounts	☐	☐	☐	☐	☐	☐☐
2.	☐ Spotting	☐ More than spotting	☐ Large amounts	☐	☐	☐	☐	☐	☐☐

☐ Number of episodes of bleeding if more than 2 ☐☐

49. Do you know why you bled?

☐ No
☐ Yes

50. If yes, what was the reason? (Fill in one or more boxes.)

☐ The placenta is too low/is in a difficult position/placenta previa
☐ Premature separation of the placenta/abruptio/ablatio placenta
☐ Threatening miscarriage/premature birth
☐ Cervical ulcer, bleeding of the mucous membrane in the vagina
☐ Following intercourse
☐ Other reason

51. Have you been bothered by uterine contractions?

☐ No
☐ Yes, a little
☐ Yes, a lot

52. Do you have or have you had any of the following illnesses or problems after the 13th week of pregnancy? If you have used tablets, mixtures, suppositories, inhalers, creams, etc. in connection with the illness or problem, give the name(s) of the medication(s), when and how long you took them. (Fill in one or more boxes.) (This applies to all types of medicines including alternative and herbal remedies, both regular and occasional use. Do not include vitamins and nutritional supplements as these are asked about elsewhere.)

		In which week of pregnancy did you have problems? 13-16	17-20	21-24	25-28	29+	The name of the medication taken	In which week of pregnancy did you take medication 13-16	17-20	21-24	25-28	29+	No. of days taken
1	Pelvic girdle pain . . .	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐☐☐
2	Back pains	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐☐☐
3	Other pains in muscles/joints	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐☐☐
4	Nausea	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐☐☐
5	Long-term nausea and vomiting	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐☐☐
6	Vaginal thrush	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐☐☐
7	Vaginal catarrh, unusual discharge . . .	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐☐☐
8	Pregnancy itch	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐☐☐
9	Constipation	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐☐☐
10	Diarrhoea/gastric flu. . . .	☐	☐	☐	☐	☐	_____	☐	☐	☐	☐	☐	☐☐☐

Continued...

	In which week of pregnancy did you have problems? 13-16	17-20	21-24	25-28	29+	The name of the medication taken	In which week of pregnancy did you take medication 13-16	17-20	21-24	25-28	29+	No. of days taken
11 Unusual fatigue /drowsiness	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
12 Heartburn	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
13 Swelling of the body (oedema)	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
14 Common cold	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
15 Throat infection	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
16 Sinusitis/ear infection	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
17 Influenza	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
18 Pneumonia /bronchitis	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
19 Other cough	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
20 Sugar in urine	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
21 Protein in urine	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
22 Bladder infection/ cystitis	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
23 Incontinence	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
24 High blood pressure	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
25 Leg cramps	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
26 Asthma	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
27 Hay fever/other allergy	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
28 Headache/migraine	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
29 Depression	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
30 Other psychological problems	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	
31 Other	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	

53. If you have had a fever once or more since the 13th week of pregnancy, indicate in which week of pregnancy, name of any medication taken to reduce the fever and the highest temperature measured. (If more than 3 times, indicate the last 3.)

	Which week of pregnancy did you have a fever? 13–16	17–20	21–24	25–28	29+	Name any medication taken to lower the fever	Highest recorded temperature *(e.g. 38.9° C)*	Temperature not taken
1st time	☐	☐	☐	☐	☐		, °C	☐
2nd time	☐	☐	☐	☐	☐		, °C	☐
3rd time	☐	☐	☐	☐	☐		, °C	☐

☐ Fever more than 3 times

54. Have you taken other medication after the 13th week of pregnancy not previously mentioned, for example, sleeping tablets or sedatives? Give the name, when and how many days altogether the medication was taken **for.** (This applies to all types of medicines including alternative and herbal remedies, both regular and occasional use. Do not include vitamins and nutritional supplements as these are discussed elsewhere.)

Name of medication (e.g. Valium, Rohypnol, Paracetamol)	Use of medication in week of pregnancy 13–16	17–20	21–24	25–28	29+	No. of days taken
_____	☐	☐	☐	☐	☐	
_____	☐	☐	☐	☐	☐	
_____	☐	☐	☐	☐	☐	
_____	☐	☐	☐	☐	☐	

55. During this pregnancy have you been involved in an accident or been injured *(e.g. traffic accident, fall, hit in the stomach)?*

☐ No
☐ Yes

56. If yes, in which week of pregnancy?

Vitamins, minerals and dietary supplements

57. Have you taken vitamins, minerals or other nutritional supplements after the 13th week of pregnancy?

☐ No (go to question 61)
☐ Yes

If you take supplements, please find the package/bottle.

58. Fill in the table below for the vitamins and minerals found on the vitamin package/bottle. Fill in when and approximately how often you have taken them.

	Week of pregnancy supplement taken? 13–16	17–20	21–24	25–28	29+	How often did you take this supplement? Daily	4-6 times a week	1-3 times a week
1 Folate/folic acid	☐	☐	☐	☐	☐	☐	☐	☐
2 Vitamin B1 (Thiamine)	☐	☐	☐	☐	☐	☐	☐	☐
3 Vitamin B2 (Riboflavin)	☐	☐	☐	☐	☐	☐	☐	☐
4 Vitamin B6 (Pyridoxine)	☐	☐	☐	☐	☐	☐	☐	☐
5 Vitamin B12	☐	☐	☐	☐	☐	☐	☐	☐
6 Niacin	☐	☐	☐	☐	☐	☐	☐	☐
7 Pantothenic acid	☐	☐	☐	☐	☐	☐	☐	☐
8 Biotin	☐	☐	☐	☐	☐	☐	☐	☐
9 Vitamin C	☐	☐	☐	☐	☐	☐	☐	☐
10 Vitamin A	☐	☐	☐	☐	☐	☐	☐	☐
11 Vitamin D	☐	☐	☐	☐	☐	☐	☐	☐
12 Vitamin E	☐	☐	☐	☐	☐	☐	☐	☐
13 Iron	☐	☐	☐	☐	☐	☐	☐	☐
14 Calcium	☐	☐	☐	☐	☐	☐	☐	☐
15 Iodine	☐	☐	☐	☐	☐	☐	☐	☐
16 Zinc	☐	☐	☐	☐	☐	☐	☐	☐
17 Selenium	☐	☐	☐	☐	☐	☐	☐	☐
18 Copper	☐	☐	☐	☐	☐	☐	☐	☐
19 Chromium	☐	☐	☐	☐	☐	☐	☐	☐
20 Magnesium	☐	☐	☐	☐	☐	☐	☐	☐
21 Cod liver oil	☐	☐	☐	☐	☐	☐	☐	☐
22 Omega-3 fatty acid	☐	☐	☐	☐	☐	☐	☐	☐

59. Give the complete name(s) of all the vitamins and nutritional supplements you take. Include also herbal remedies and diet products. (Write clearly using CAPITAL LETTERS since this will be read by a computer.)

1 e.g. V I T A P L E X M E D J E R N

2

3

4

5

6

60. If you take multivitamins (with or without minerals), do these contain folate/folic acid?

- ☐ No
- ☐ Yes
- ☐ Don't know

WORK

61. Have you been in paid employment during this pregnancy?

- ☐ No *(go to question 76)*
- ☐ Yes

62. Do you have the same job conditions now after the 13th week of pregnancy that you described in the first questionnaire?

- ☐ No
- ☐ Yes *(go to question 66)*

63. If no, in which week of your pregnancy did your work situation change?

Week of pregnancy ☐☐

64. How has your work situation changed?

- ☐ I have stopped working
- ☐ I have gone over to a part-time position
- ☐ Other

65. If you have stopped working, why did you stop?

- ☐ I handed in my notice
- ☐ The work was temporary (seasonal, short-term contract)
- ☐ I was fired
- ☐ Other

66. Have your working arrangements been changed during this pregnancy making your job more suitable for you now that you are pregnant?

- ☐ No
- ☐ Yes

67. If no, why have your working conditions not been changed to make them more suitable for you?

- ☐ Not necessary
- ☐ Impossible or nearly impossible
- ☐ I have asked for changes but no changes have been made
- ☐ It is difficult to ask
- ☐ None of the above (explain why)

68. What are your working hours? (Fill in one or more boxes.)

- ☐ Permanent day work
- ☐ Permanent afternoon or evening work
- ☐ Permanent night work
- ☐ Shift work or shift rotas
- ☐ No set times (extra work, extra shifts, temporary employment, etc.)
- ☐ Other

69. Answer each of the following questions for your present work. (Fill in each item.)

	Yes daily, more than half of working hours	Yes daily, less than half of working hours	Yes periodically, but not daily	Seldom or never
Do you ever have so much to do that your work situation becomes stressful and annoying?	☐	☐	☐	☐
Do you have to bend or turn many times a day?	☐	☐	☐	☐
Do you work with your hands at shoulder level or higher?	☐	☐	☐	☐
Do you work standing or walking about?	☐	☐	☐	☐
In some jobs it is possible to decide yourself how much and how quickly you work. You can, for example, work a little faster one day and take it a little easier the next. Do you have this opportunity?	☐	☐	☐	☐
Is there so much noise at your workplace that it is uncomfortable?	☐	☐	☐	☐
Is there so much noise that you have to raise your voice to speak with others even at a distance of one metre?	☐	☐	☐	☐

70. How often have you worked with a radio transmitter or radar after the 13th week of pregnancy?

- ☐ Seldom/never
- ☐ A few times a week
- ☐ Daily
- ☐ On average, more than 1 hour a day

71. How often have you worked with X-ray equipment (at a distance of less than 2 metres) after the 13th week of pregnancy? *(Do not include treatment as a patient.)*

- ☐ Seldom/never
- ☐ A few times a week
- ☐ Daily
- ☐ On average, more than 1 hour a day

72. Have you been absent from your normal job for more than two weeks after the 13th week of pregnancy?

- ☐ No
- ☐ Yes, part time
- ☐ Yes

73. Are you absent from regular work at the present time?

- ☐ No
- ☐ Yes, part time
- ☐ Yes

74. If yes, why are you currently absent from work?

(Fill in for only one item.)

- ☐ Sick leave (with sick compensation pay)
- ☐ Absent due to sick child
- ☐ Made redundant with compensation
- ☐ Absent with maternity allowance due to the working environment
- ☐ Started maternity leave (with allowance)
- ☐ Service leave
- ☐ Other (describe)

_____

_____

_____

75. Complete the table below if you were on sick leave (full or part time) after the 13th week of pregnancy. Fill in the reason (e.g. pelvic girdle pain, pneumonia), which weeks you were on sick leave, the number of days and the percentage of time each period of sick leave represents. (*Give one reason for sick leave per line.***)**

Reason for sick leave	Sick leave during week of pregnancy: 13-16	17-20	21-24	25-28	29+	Number of days	% sick leave
Example: Pelvic girdle pain	☐	☐	☐	☐	☐	14	50
	☐	☐	☐	☐	☐		
	☐	☐	☐	☐	☐		
	☐	☐	☐	☐	☐		
	☐	☐	☐	☐	☐		

76. Do you currently lift anything over 10 kilos while you are pregnant? *(10 kilos is equivalent to a full bucket of water)*

	Home	Work
Seldom or never	☐	☐
Yes, less than 20 times a week	☐	☐
Yes, more than 20 times a week	☐	☐
Yes, 10-20 times a day	☐	☐
Yes, more than 20 times a day	☐	☐

77. Have others helped you with housework or childcare more than they usually do to relieve you during this pregnancy?

- ☐ Yes, considerably
- ☐ Yes, to a fair extent
- ☐ No, no one has offered
- ☐ No, it has not been necessary

78. If you are on maternity leave for this pregnancy, when did it start?

Date: ☐☐ ☐☐ ☐☐☐☐

day month year

Habits

79. How often do you talk on a mobile phone?

- ☐ Seldom/never
- ☐ A few times a week
- ☐ Daily
- ☐ On average, more than 1 hour a day

80. Do you talk on your mobile phone for longer than 15 minutes at a time?

- ☐ Never
- ☐ Seldom
- ☐ Frequently

81. How frequently have you worked with a computer monitor, laser printer or photocopy machine (at a distance of less than 2 metres) after the 13th week of pregnancy?

	Computer monitor	Laser printer	Photocopy machine
Seldom/never	☐	☐	☐
A few times a week	☐	☐	☐
Daily	☐	☐	☐
On average, more than 1 hour a day	☐	☐	☐

82. Do you live close to high-voltage power lines?

- ☐ No
- ☐ Yes, closer than 50 metres
- ☐ Yes, between 50 - 100 metres
- ☐ Yes, more than 100 metres

83. How often have you been to a discotheque since you answered the previous questionnaire?

- ☐ Never
- ☐ At least 1-2 times a week
- ☐ Less often

84. How often do you exercise at present? *(Fill in for each item.)*

	Never	1-3 times a month	Once a week	Twice a week	3 times or more a week
1. Walking	☐	☐	☐	☐	☐
2. Brisk walking	☐	☐	☐	☐	☐
3. Running/jogging/orienteering	☐	☐	☐	☐	☐
4. Cycling	☐	☐	☐	☐	☐
5. Training studio/weight training	☐	☐	☐	☐	☐
6. Special gymnastics/aerobics for pregnant women	☐	☐	☐	☐	☐
7. Aerobics/gymnastics/dance without running and jumping	☐	☐	☐	☐	☐
8. Aerobics/gymnastics/dance with running and jumping	☐	☐	☐	☐	☐
9. Dancing (swing/rock/folk)	☐	☐	☐	☐	☐
10. Skiing	☐	☐	☐	☐	☐
11. Ball sports	☐	☐	☐	☐	☐
12. Swimming	☐	☐	☐	☐	☐
13. Riding	☐	☐	☐	☐	☐
14. Other	☐	☐	☐	☐	☐

85. How often do you do exercises at home or at a gym for the following groups of muscles? *(Fill in for each item.)*

	Never	1-3 times a month	Once a week	Twice a week	3 times a week or more
Abdominal muscles	☐	☐	☐	☐	☐
Back muscles	☐	☐	☐	☐	☐
Pelvic floor muscles *(Muscles around the vagina, urethra, anus)*	☐	☐	☐	☐	☐

86. How often at the moment are you so physically active in your spare time and/or at work that you get out of breath or sweat? *(Fill in for both spare time and work.)*

	Spare time	At work
Never	☐	☐
Less than once a week	☐	☐
Once a week	☐	☐
Twice a week	☐	☐
3-4 times a week	☐	☐
5 or more times a week	☐	☐

87. How often on average have you had sexual intercourse during the last month?

- ☐ Daily
- ☐ 5-6 times a week
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ Less frequently
- ☐ Never

88. Have you been abroad during the last year?

- ☐ No
- ☐ Yes

89. If yes, which countries did you visit and when?

Country	Month	Year
_____	☐☐	☐☐☐☐
_____	☐☐	☐☐☐☐
_____	☐☐	☐☐☐☐

90. Have you come into contact with animals either at work or in your free time?

- ☐ No
- ☐ Yes

91. If yes, which animals have you come into contact with and how often?

	Daily	3–6 times a week	1-2 times a week	Less often
Dog	☐	☐	☐	☐
Cat	☐	☐	☐	☐
Guinea pig/hamster/rabbit/rat, etc.	☐	☐	☐	☐
Canary or other caged birds	☐	☐	☐	☐
Hens and other poultry	☐	☐	☐	☐
Cow/sheep/goat	☐	☐	☐	☐
Horse	☐	☐	☐	☐
Pig	☐	☐	☐	☐
Other	☐	☐	☐	☐

92. How many hours a day do you usually sleep now when you are pregnant?

☐ Over 10 hours
☐ 8–9 hours
☐ 6-7 hours
☐ 4-5 hours
☐ Less than 4 hours

93. Do you currently sleep on a waterbed or use an electric blanket?

	Yes	No
Waterbed	☐	☐
Electric blanket	☐	☐

94. Can you rest during the day (both at home and at work)?

☐ No
☐ Yes

95. Have you been in a sauna while you have been pregnant?

☐ No
☐ 1–5 times
☐ 6-10 times
☐ More than 10 times

96. Have you been in a solarium while you have been pregnant?

☐ No
☐ 1-5 times
☐ 6-10 times
☐ More than 10 times

97. Are you exposed to passive smoking either at home or at work? If yes, how many hours a day?

	No	Yes	No. of hrs
Home	☐	☐	☐☐
Work	☐	☐	☐☐

98. Do you smoke at present? If yes, how many cigarettes?

☐ No
☐ Sometimes ☐☐ Cigarettes per week
☐ Daily ☐☐ Cigarettes per day

99. Does the baby's father smoke at present? If yes, how many cigarettes?

☐ No
☐ Sometimes ☐☐ Cigarettes per week
☐ Daily ☐☐ Cigarettes per day

100. If one or both of you have stopped smoking during the pregnancy, in which week of pregnancy did you stop?

☐ You ☐☐ Week of pregnancy
☐ Baby's father ☐☐ Week of pregnancy

101. If you or the baby's father have smoked during the pregnancy, were there periods during which you or the baby's father did not smoke? *(Fill in the weeks during pregnancy when you did not smoke.)*

	Weeks of pregnancy without smoking							
	0–4	5–8	9–12	13–16	17–20	21–24	25–28	29+
You	☐	☐	☐	☐	☐	☐	☐	☐
Baby's father	☐	☐	☐	☐	☐	☐	☐	☐

102. Have you used other forms of nicotine after the 13th week of pregnancy?

	No	Yes
Nicotine chewing gum	☐	☐
Nicotine patches	☐	☐
Nicotine inhaler	☐	☐
Chewing tobacco/snuff	☐	☐

103. Have you used any of the following substances after the 13th week of pregnancy?

	No	Yes
Hash	☐	☐
Amphetamine	☐	☐
Ecstasy	☐	☐
Cocaine	☐	☐
Heroin	☐	☐

104. Have you ever used any of the following substances? (Fill in for each item.)

	No	Previously	Last 6 months before pregnancy	During this pregnancy
Anabolic steroids	☐	☐	☐	☐
Testosterone products	☐	☐	☐	☐
Growth hormones *(e.g. genotropin/somatropin)*	☐	☐	☐	☐

Food and drink

105. How often do you eat the following foods? *(Fill in for each item.)*

		Before the pregnancy				During the pregnancy		
		Never	A few times a year	1–3 times a Month	Once a week or more	Never	1–3 times a month	Once a week or more
1	Crab	☐	☐	☐	☐	☐	☐	☐
2	Shrimps	☐	☐	☐	☐	☐	☐	☐
3	Shellfish (e.g. mussels, oysters)	☐	☐	☐	☐	☐	☐	☐
4	Fish liver	☐	☐	☐	☐	☐	☐	☐
5	Tuna fish or halibut	☐	☐	☐	☐	☐	☐	☐
6	Flounder/other flat fish	☐	☐	☐	☐	☐	☐	☐
7	Pike or perch	☐	☐	☐	☐	☐	☐	☐
8	Other fresh water fish	☐	☐	☐	☐	☐	☐	☐
9	Reindeer meat	☐	☐	☐	☐	☐	☐	☐
10	Mutton	☐	☐	☐	☐	☐	☐	☐
11	Liver or kidney from game	☐	☐	☐	☐	☐	☐	☐
12	Wild mushrooms	☐	☐	☐	☐	☐	☐	☐

106. How often do you eat the following types of food? *(Fill in for each item.)*

	Never	A few times a year	1-3 times a month	Once a week or more
Food from restaurant/street vendors/canteen or the like	☐	☐	☐	☐
Meat (not including tinned) bought in other countries	☐	☐	☐	☐
Meat (including poultry) that is raw or undercooked (pink near the bone)	☐	☐	☐	☐
Raw minced meat/meat mixtures (even to taste)	☐	☐	☐	☐
Smoked or cured salmon or trout (uncooked)	☐	☐	☐	☐
Soft cheeses (e.g. cream cheese, camembert, blue cheese, etc.)	☐	☐	☐	☐
Unwashed raw vegetables, unwashed fruit	☐	☐	☐	☐

107. Do you avoid eating the following foods during this pregnancy?

	No	Yes
Fish	☐	☐
Eggs	☐	☐
Nuts	☐	☐
Oranges, lemons	☐	☐
Strawberries	☐	☐

Other, specify _____

108. What type of drinking water do you have where you live?

- ☐ Own water source (e.g. well)
- ☐ Water company (public or private)
- ☐ Other source

Name of water company _____

- ☐ Don't know the name of the water company

109. Is your water treated (chlorinated or UV-radiated)?

- ☐ No
- ☐ Yes, UV radiation
- ☐ Yes, chlorinated
- ☐ Don't know

110. What was your fluid consumption (number of cups/glasses) per day after the 13th week of pregnancy? *(1 mug = 2 cups, 1 small plastic bottle (0.5 litre) = 4 cups, 1 large plastic bottle (1.5 litres) = 12 cups)*

	Number of cups / glasses	Decaffeinated (fill in)
1. Filter coffee		☐
2. Instant coffee		☐
3. Boiled coffee		☐
4. Other coffee		☐
5. Tea		☐
6. Coca Cola/Pepsi, etc.		☐
7. Other fizzy drinks		☐
8. Diet Coca Cola, diet Pepsi		☐
9. Other diet fizzy drinks		☐
10. Tap water		
11. Bottled water		

	Number of cups/glass	Organic (fill in)
12. Juice/squash		☐
13. Diet juice/squash		☐
14. Milk (skimmed, low fat, whole)		☐
15. Yogurt, all types		☐
16. Yogurt with active Lactobacillus all types		☐
17. Other type of cultured milk (kefir)		☐
18. Other		☐

111. How often did you consume alcohol before and how often do you consume it now?

	Last 3 months before last period	In this pregnancy week of pregnancy 0–12	13–24	25+
Roughly 6-7 times a week	☐	☐	☐	☐
Roughly 4–5 times a week	☐	☐	☐	☐
Roughly 2-3 times a week	☐	☐	☐	☐
Roughly 1 time a week	☐	☐	☐	☐
Roughly 1–3 times a month	☐	☐	☐	☐
Less then once a month	☐	☐	☐	☐
Never	☐	☐	☐	☐

Alcohol units
Alcohol units are used to compare the different types of alcoholic beverages. 1 alcohol unit = 1.5 cl. pure alcohol.

1 glass of beer	= 1 alcohol unit
1 wine glass of red or white wine	= 1 alcohol unit
1 sherry glass of sherry or other fortified wine	= 1 alcohol unit
1 spirit glass of spirits or liqueur	= 1 alcohol unit
1 bottle/can breezer or cider	= 1 alcohol unit

112. In the period just before you became pregnant and during this pregnancy, how many times have you consumed 5 units or more of alcohol? *(See the explanation for units.)*

	Last 3 mths before last period	In this pregnancy week of pregnancy 0–12	13–24	25+
Several times a week	☐	☐	☐	☐
Once a week	☐	☐	☐	☐
1-3 times a month	☐	☐	☐	☐
Less than once a month	☐	☐	☐	☐
Never	☐	☐	☐	☐

113. How many units do you usually drink when you consume alcohol? *(See the above explanation.)*

	Last 3 mths before last period	In this pregnancy week of pregnancy 0–12	13–24	25+
10 or more	☐	☐	☐	☐
7–9	☐	☐	☐	☐
5–6	☐	☐	☐	☐
3–4	☐	☐	☐	☐
1–2	☐	☐	☐	☐
Less than 1	☐	☐	☐	☐

114. If you have changed your drinking habits before this pregnancy, when did the change occur? *(Fill in one or more boxes.)*

	Reduced intake	Increased intake
Last 3 months before last period	☐	☐
During pregnancy weeks 0-6	☐	☐
During pregnancy weeks 7-12	☐	☐
During pregnancy weeks 13-24	☐	☐
After pregnancy week 25	☐	☐

115. If you have modified your consumption of alcohol, how important were the following factors? *(Fill in one or more boxes.)*

	Not relevant	Not very important	Quite important	Important	Very important
Nausea, discomfort	☐	☐	☐	☐	☐
Altered taste	☐	☐	☐	☐	☐
For the baby's sake	☐	☐	☐	☐	☐
Depression/problems	☐	☐	☐	☐	☐
Other reasons	☐	☐	☐	☐	☐

You and your life now

116. What is your current civil status?
- ☐ Married
- ☐ Cohabiting
- ☐ Single
- ☐ Divorced/separated
- ☐ Widowed
- ☐ Other

117. Do you have anyone other than your husband/partner you can ask for advice in a difficult situation?
- ☐ No.
- ☐ Yes, 1 or 2 people
- ☐ Yes, more than 2 people

118. How frequently do you meet or talk on the telephone with your family (other than your husband/partner and children) or close friends?
- ☐ Once a month or less
- ☐ 2-8 times a month
- ☐ More than twice a week

119. Do you often feel lonely?
- ☐ Almost never
- ☐ Seldom
- ☐ Sometimes
- ☐ Usually
- ☐ Almost always

120. If you have given birth before, in general, how was the experience of giving birth?
- ☐ Very good
- ☐ Good
- ☐ Alright
- ☐ Bad
- ☐ Very bad

121. Do you agree or disagree with the following statements relating to the forthcoming birth of your baby?
(Fill in for each statement.)

	Agree completely	Agree	Agree somewhat	Disagree somewhat	Disagree	Disagree completely
I want to give birth as naturally as possible without painkillers or intervention	☐	☐	☐	☐	☐	☐
I am really dreading giving birth	☐	☐	☐	☐	☐	☐
I want to have enough medication so that the birth will be painless	☐	☐	☐	☐	☐	☐
I want to have an epidural regardless	☐	☐	☐	☐	☐	☐
I want to have an epidural if the midwife agrees	☐	☐	☐	☐	☐	☐
If I could choose I would have a caesarean	☐	☐	☐	☐	☐	☐
I think the woman herself should decide whether or not to have a caesarean	☐	☐	☐	☐	☐	☐
I worry all the time that the baby will not be healthy or normal	☐	☐	☐	☐	☐	☐
I am really looking forward to the baby coming	☐	☐	☐	☐	☐	☐

122. How do these statements describe your relationship? (Only answer if you have a partner.)
(Fill in for each statement.)

	Agree completely	Agree	Agree somewhat	Disagree somewhat	Disagree	Completely disagree
My husband/partner and I have a close relationship	☐	☐	☐	☐	☐	☐
My partner and I have problems in our relationship	☐	☐	☐	☐	☐	☐
I am very happy in my relationship	☐	☐	☐	☐	☐	☐
My partner is usually understanding	☐	☐	☐	☐	☐	☐
I often think about ending our relationship	☐	☐	☐	☐	☐	☐
I am satisfied with my relationship with my partner	☐	☐	☐	☐	☐	☐
We often disagree about important decisions	☐	☐	☐	☐	☐	☐
I have been lucky in my choice of a partner	☐	☐	☐	☐	☐	☐
We agree on how children should be raised	☐	☐	☐	☐	☐	☐
I think my partner is satisfied with our relationship	☐	☐	☐	☐	☐	☐

123. Have you been bothered during the last 2 weeks by any of the following? *(Enter a cross in a box for each item.)*

	Not bothered	Slightly bothered	Fairly much bothered	Very much bothered
1. Feeling fearful	☐	☐	☐	☐
2. Nervousness or shakiness inside	☐	☐	☐	☐
3. Feeling hopeless about the future	☐	☐	☐	☐
4. Feeling blue	☐	☐	☐	☐
5. Worrying too much about things	☐	☐	☐	☐
6. Feeling everything is an effort	☐	☐	☐	☐
7. Feeling tense or keyed up	☐	☐	☐	☐
8. Suddenly scared for no reason	☐	☐	☐	☐

124. How often do you experience the following in your everyday life? *(Fill in for each statement.)*

	Seldom/ never	Fairly seldom	Sometimes	Often	Very often
Feel pleased about something	☐	☐	☐	☐	☐
Feel happy	☐	☐	☐	☐	☐
Feel joyful, as though everything is going your way	☐	☐	☐	☐	☐
Feel that you will scream at someone or hit something	☐	☐	☐	☐	☐
Feel angry, irritated or annoyed	☐	☐	☐	☐	☐
Feel mad at someone	☐	☐	☐	☐	☐

125. How well do these statements describe you? *(Fill in for each statement.)*

	Incorrect	Partly correct	Almost correct	Completely correct
I always manage to solve difficult problems if I try hard enough	☐	☐	☐	☐
If anyone opposes me, I find a way to get what I want	☐	☐	☐	☐
I am sure that I can cope with unexpected events	☐	☐	☐	☐
I am calm when I encounter difficulties because I trust my ability to cope	☐	☐	☐	☐
When I am in a difficult situation, I usually find a solution	☐	☐	☐	☐

126. Do you agree or disagree with the following statements? *(Fill in for each statement.)*

	Disagree completely	Disagree	Disagree somewhat	Don't agree or disagree	Agree somewhat	Agree	Agree completely
My life is largely what I wanted it to be	☐	☐	☐	☐	☐	☐	☐
My life is very good	☐	☐	☐	☐	☐	☐	☐
I am satisfied with my life	☐	☐	☐	☐	☐	☐	☐
I have achieved so far what is important for me in my life	☐	☐	☐	☐	☐	☐	☐
If I could start all over, there is very little I would do differently	☐	☐	☐	☐	☐	☐	☐

127. How do you feel about yourself? *(Fill in for each statement.)*

	Agree completely	Agree	Disagree	Disagree completely
I have a positive attitude toward myself	☐	☐	☐	☐
I feel completely useless at times	☐	☐	☐	☐
I feel that I do not have much to be proud about	☐	☐	☐	☐
I feel that I am a valuable person, as good as anyone else	☐	☐	☐	☐

128. Have you experienced any of the following during the last 12 months? If yes, how painful or difficult was it for you? *(Fill in for each statement.)*

			IF YES		
	No	Yes	Not too bad	Painful/ difficult	Very painful/ difficult
Have you had problems at work or where you study?	☐	☐	☐	☐	☐
Have you had financial problems?	☐	☐	☐	☐	☐
Have you been divorced, separated or ended your relationship with your partner?	☐	☐	☐	☐	☐
Have you had problems or conflicts with your family, friends or neighbours?	☐	☐	☐	☐	☐
Have you been seriously ill or injured?	☐	☐	☐	☐	☐
Has anyone close to you been seriously ill or injured?	☐	☐	☐	☐	☐
Have you been involved in a serious accident, fire or robbery?	☐	☐	☐	☐	☐
Have you lost someone close to you?	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐

129. Have you ever experienced any of the following? *(Fill in for each statement.)*

				Who was responsible for this?			Has this occurred during the last year?	
	No, never	Yes, as a child *(under 18)*	Yes, as an adult *(over 18)*	A stranger	Family or relative	Another known person	No	Yes
Someone has over a long period of time systematically tried to subdue, degrade or humiliate you	☐	☐	☐	☐	☐	☐	☐	☐
Someone has threatened to hurt you or someone close to you	☐	☐	☐	☐	☐	☐	☐	☐
You have been subjected to physical abuse	☐	☐	☐	☐	☐	☐	☐	☐
You have been forced to have sexual intercourse	☐	☐	☐	☐	☐	☐	☐	☐

Miscellaneous

130. Has anyone living with you had any of the following illnesses during this pregnancy? *(Enter a cross and specify the period)*

	In which week of pregnancy? 0–9	10–19	20–29	30+
☐ Influenza	☐	☐	☐	☐
☐ Childhood diseases (fever and rash)	☐	☐	☐	☐
☐ Prolonged cough	☐	☐	☐	☐
☐ Other infectious disease	☐	☐	☐	☐

131. Have there been any instances of cot death in your family or your partner's family?

- ☐ No
- ☐ Don't know
- ☐ Yes, in my family (see question 132)
- ☐ Yes, in the baby's father's family (see question 133)

132. The child that died of cot death in my family was:

- ☐ My sister
- ☐ My brother
- ☐ My sister's child ☐ Boy ☐ Girl
- ☐ My brother's child ☐ Boy ☐ Girl
- ☐ My mother's sibling ☐ Boy ☐ Girl ☐ Sex unknown
- ☐ My father's sibling ☐ Boy ☐ Girl ☐ Sex unknown
- ☐ Other

133. The child that died of cot death in the baby's father's family was:

- ☐ Baby's father's sister
- ☐ Baby's father's brother
- ☐ Baby's father's sister's child ☐ Boy ☐ Girl
- ☐ Baby's father's brother's child ☐ Boy ☐ Girl
- ☐ Baby's paternal grandmother's sibling ☐ Boy ☐ Girl ☐ Sex unknown
- ☐ Baby's paternal grandfather's sibling ☐ Boy ☐ Girl ☐ Sex unknown
- ☐ Other

134. Have you ever lost a child?

- ☐ No *(if no, you are finished with the questionnaire)*
- ☐ Yes

135. If yes, what was the cause of death and when did the death occur?

- ☐ Stillbirth (Birth after the 16th week of pregnancy.)
- ☐ Cot death
- ☐ Accident
- ☐ Illness/birth defect
  Which illness/birth defect: _____
- ☐ Other

	Year	Child's age	
		Years	Months
Child 1			
Child 2			

136. Did you receive counselling from healthcare staff or other persons after the death? How many sessions did you have with healthcare staff, and/or parent support group, family and friends? How many weeks did you receive support?

	Healthcare staff	Parent support group, family, friends
Number of meetings (approximately):		
Number of sessions via telephone (approximately):		
Weeks of support (approximately):		

137. Do you feel that the follow -up you received after your child's death was adequate?

- ☐ No follow-up was provided
- ☐ Very good
- ☐ Good enough
- ☐ Should have been better
- ☐ Bad

138. Has the death made you more anxious during this pregnancy?

- ☐ No, not at all
- ☐ No, not very much
- ☐ Yes, to a fair extent
- ☐ Yes, very much

139. Do you feel that the health care staff at the antenatal clinics took into consideration this painful experience in their contact with you?

- ☐ Yes, very much
- ☐ Yes, to a fair extent
- ☐ No, not at all

Have you remembered to fill in the date on which you completed the questionnaire on page 1?

Thank you very much for your help!

Please return the completed questionnaire in the stamped addressed envelope provided.

den norske **Mor & barn undersøkelsen**

Questionnaire 4 - When your child is around 6 months old

This questionnaire comes in two parts. The first part is about your child, while the other part is about yourself. It will help if you have your child's health card to hand before you start answering the questions so that you can use the information contained in it when completing this questionnaire. If you find a question difficult to answer, you can skip it and go onto the next question.

If you have had twins or triplets, complete one questionnaire for each child.

The questionnaire will be processed by a computer. *It is therefore important that you follow these instructions when completing it:*

- Use a blue or black ballpoint pen.
- In the small check boxes, enter *a cross* to indicate what you think is the most appropriate answer like this: ☒
  If you make a mistake you can delete the cross by filling in the box completely like this: ■
- Write numbers in the large green boxes.
  It is important that you only write in the white area of each box like this:
  Number: 0 1 2 3 4 5 6 7 8 9
- In the case of numbered boxes with more than one square, enter a one-digit number in the right box. *Example: 5 is entered as follows* 5
- Date boxes are split into 3 sections, with the first one for the day of the month, the second one for the month and the last one for the year.
  So, enter the date as follows: 6 (Day) 5 (Month) 2005 (Year)
- Specific information concerning, *for example, medication* should be written on the lines provided. *Please write clearly!*

As soon as you have completed the questionnaire, return it to us in the enclosed stamped addressed envelope.

Specify the day, month and year when the questionnaire was completed ☐☐ Day ☐☐ Month ☐☐☐☐ Year *(write the year in full, e.g. 2005)*

About your child's birth

1. Is your child a boy or girl?

☐ Boy

☐ Girl

2. How big was your child when he/she was born?

Birth weight: ☐☐☐☐ g

Length: ☐☐,☐ cm

3. In which week of your pregnancy did you give birth?

☐☐ week

4. How long was your child in hospital after the birth?

Number of days ☐☐ or weeks ☐☐

5. Was your child transferred to another department or hospital after the birth?

☐ No

☐ Yes

If yes, specify _____

6. Was your child delivered by caesarean section?

☐ No

☐ Yes

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7. If yes, was the caesarean section planned?

- ☐ No
- ☐ Yes

If yes, why?

- ☐ Breech presentation
- ☐ Previous caesarean
- ☐ Pregnancy complication or mother taken ill
- ☐ Poor growth or other factor relating to the foetus
- ☐ Own preference
- ☐ Other

8. Were there any complications during the birth?

- ☐ No
- ☐ Yes

If so, describe:_____

9. Were you admitted or transferred to another department or other hospital due to complications in connection with the birth? *(Applies both before and after the birth.)*

- ☐ No
- ☐ Yes

10. If yes, where?

Department:
_____

Hospital: _____

11. How many days were you in hospital in connection with the birth?

Before the birth ☐☐ Number of days

After the birth ☐☐ Number of days

12. Did the birth go as you had expected?

- ☐ Yes, as expected
- ☐ No, it went better
- ☐ Neither/nor
- ☐ No, it was worse
- ☐ Don't know

13. How true do you think the following descriptions are of the birth? *(Enter a cross in a box for each item.)*

	Fairly true	Partially true	Not true
I felt safe and in good hands	☐	☐	☐
I was in a lot of pain	☐	☐	☐
I received too few pain-killing drugs	☐	☐	☐

14. Was anyone from your close family present at the birth?

- ☐ Yes, child's father
- ☐ Yes, someone else
- ☐ No

About your child

Nutrition

15. What did you give your child to drink during the first week of life?
(You can enter a cross in more than one box.)

- ☐ Breast milk
- ☐ Water
- ☐ Sugar water
- ☐ Formula
- ☐ Other, specify: _____
- ☐ Don't know/don't remember

16. What has your child been given to drink during the first 6 months of his/her life?
(Enter a cross for each month you gave your child the relevant drink.)

	Child's age in months						
	0	1	2	3	4	5	6
Breast milk	☐	☐	☐	☐	☐	☐	☐
Standard Collett formula	☐	☐	☐	☐	☐	☐	☐
Collett formula with Omega 3	☐	☐	☐	☐	☐	☐	☐
Standard NAN formula	☐	☐	☐	☐	☐	☐	☐
Nan HA1 formula	☐	☐	☐	☐	☐	☐	☐
Other milk, specify: _____	☐	☐	☐	☐	☐	☐	☐
Water	☐	☐	☐	☐	☐	☐	☐
Squash/Juice	☐	☐	☐	☐	☐	☐	☐

17. How often do you give your child the following to drink at the moment? *(Enter a cross in a box for each item.)*

	Never/ seldom	1-3 times a week	4-6 times a week	At least once a day
1. Breast milk	☐	☐	☐	☐
2. Breast milk supplement	☐	☐	☐	☐
3. Normal sweet milk, any type	☐	☐	☐	☐
4. sour milk (yogurt, buttermilk, etc.)	☐	☐	☐	☐
5. Organic milk products (milk, yogurt)	☐	☐	☐	☐
6. Boiled water	☐	☐	☐	☐

Cont.

	Never/ seldom	1-3 times a week	4-6 times a week	At least once a day
7. Tap water	☐	☐	☐	☐
8. Bottled water	☐	☐	☐	☐
9. Bottled baby cordial	☐	☐	☐	☐
10. Other type of cordial, sweetened	☐	☐	☐	☐
11. Cordial, artificially sweetened	☐	☐	☐	☐
12. Juice	☐	☐	☐	☐
13. Other, specify: _____	☐	☐	☐	☐

18. How often does your child eat the following food at the moment, and how old was your child when you started giving him/her this food?

	How often do you give this to your child? Never/ seldom	1-3 times a week	4-6 times a week	At least once a day	How old was your child when you gave him/her this foodfor the first time?
Instant porridge					
1. Rice porridge, maize porridge	☐	☐	☐	☐	☐ months
2. Oatmeal porridge, different types	☐	☐	☐	☐	☐ months
3. Wheat porridge, all types, rusk porridge	☐	☐	☐	☐	☐ months
Home-made porridge using:					
4. Wheat flour (rough/fine), rusk, semolina, oats	☐	☐	☐	☐	☐ months
5. Iron-enriched wheat flour	☐	☐	☐	☐	☐ months
6. Helios baby flour	☐	☐	☐	☐	☐ months
7. Millet	☐	☐	☐	☐	☐ months
Processed dinner in a jar:					
8. Vegetables	☐	☐	☐	☐	☐ months
9. Vegetables and meat	☐	☐	☐	☐	☐ months
Home-made dinner:					
10. Potato/vegetable puree	☐	☐	☐	☐	☐ months
11. Meat and vegetables/potatoes	☐	☐	☐	☐	☐ months
12. Fish and vegetables/potatoes	☐	☐	☐	☐	☐ months
13. Other type of home-made dinner	☐	☐	☐	☐	☐ months
Snack/dessert:					
14. Home-made fruit puree	☐	☐	☐	☐	☐ months
15. Fruit/berry puree in a jar	☐	☐	☐	☐	☐ months
16. Rusks/biscuits/bread	☐	☐	☐	☐	☐ months
17. Other, specify: _____	☐	☐	☐	☐	☐ months

19. Do you think or do you know that your child has a reaction to milk/dairy products?

☐ No
☐ Yes

20. If yes, which products?

☐ Whole milk
☐ Low-fat milk/skimmed milk
☐ Cream/whipped cream/ice cream
☐ Yogurt/sour milk
☐ Breast milk when mother is drinking milk
☐ Other

21. Do you give your child cod liver oil, vitamins, iron or any other dietary supplement?

☐ No ☐ Yes

22. If you give your child cod liver oil, vitamins, iron or another dietary supplement, specify how much you give your child each time and how often. How old was your child in months and weeks when you gave him/her the product for the first time?

Name of product	How many teaspoons each time?	How often do you give your child this?	How old was your child when you started giving the product?
1. Cod liver oil	☐ teaspoons	☐ daily ☐ sometimes	☐ months and ☐ weeks
2. Biovit	☐ teaspoons	☐ daily ☐ sometimes	☐ months and ☐ weeks
3. Sanasol	☐ teaspoons	☐ daily ☐ sometimes	☐ months and ☐ weeks
4. Nycoplus Multi-Vitamin mixture for children	☐ teaspoons	☐ daily ☐ sometimes	☐ months and ☐ weeks
5. Fluoride		☐ daily ☐ sometimes	☐ months and ☐ weeks
6. Iron supplement, specify: _____		☐ daily ☐ sometimes	☐ months and ☐ weeks
7. Other dietary supplement, specify: _____		☐ daily ☐ sometimes	☐ months and ☐ weeks

Growth, health and use of medication

You will find the information to help you answer the following questions on your child's health card.

23. How many times have you been to the mother and child health centre with your child?

☐ Never
☐ 1-2 times
☐ 3-5 times
☐ 6-10 times
☐ more than 10 times

24. Has your child been given the vaccinations recommended by the health centre?

☐ Yes
☐ No, don't want vaccination
☐ No, your child has been often ill
☐ No, vaccinations postponed for practical reasons
☐ Don't know

25. Referring to your child's health card, enter a cross for the vaccinations which your child has received and whether the vaccinations had any side-effect. *(Enter a cross in a box for each item.)*

Vaccinations	Has your child received the vaccination?		Was there any side-effect after the vaccination?		Was there any side-effect resulting in contact with a doctor?		Was there any side-effect resulting in hospital admission?	
	No	Yes	No	Yes	No	Yes	No	Yes
1. DTP (Infanrix)	☐	☐	☐	☐	☐	☐	☐	☐
2. DT (diphtheria/tetanus)	☐	☐	☐	☐	☐	☐	☐	☐
3. Polio – Hib (Act-Hib polio)	☐	☐	☐	☐	☐	☐	☐	☐
4. Hepatitis B (Engerix-B)	☐	☐	☐	☐	☐	☐	☐	☐
5. BCG (tuberculosis)	☐	☐	☐	☐	☐	☐	☐	☐
6. Pneumococcus (Prevenar)	☐	☐	☐	☐	☐	☐	☐	☐
7. Other vaccination:_____	☐	☐	☐	☐	☐	☐	☐	☐

26. Referring to your child's health card, enter below your child's weight, length and head circumference when he/she was around 6 weeks, 3 months and 6 months.

+	Date of examination Day	Month	Year	Length	Head circumference	Weight
Approx. 6 weeks				, cm	, cm	g
Approx. 3 months				, cm	, cm	g
5-6 months				, cm	, cm	g

The following questions concern any illnesses or health problems your child has had. We will first ask you about more longterm problems, then about illnesses and problems of a more acute nature.

27. Does your child have or has he/she had any of the following health problems? If yes, has the mother and child health centre or someone else referred your child for further specialist investigation? *(Enter a cross in a box for each item.)*

+	Has(had) your child problems? No	Yes	Has your child been referred for a specialist investigation? No	Yes, referred from health centre	Yes, referred by someone else
1. Hip disorder/dislocated hip	☐	☐	☐	☐	☐
2. Impaired hearing	☐	☐	☐	☐	☐
3. Impaired vision	☐	☐	☐	☐	☐
4. Delayed motor development (movement development)	☐	☐	☐	☐	☐
5. Too little weight gain	☐	☐	☐	☐	☐
6. Too much weight gain	☐	☐	☐	☐	☐
7. Abnormal head circumference	☐	☐	☐	☐	☐
8. Heart defect	☐	☐	☐	☐	☐
9. Testicles not descended into scrotum	☐	☐	☐	☐	☐
10. Asthma	☐	☐	☐	☐	☐ +
11. Atopic eczema (childhood eczema)	☐	☐	☐	☐	☐
12. Hives	☐	☐	☐	☐	☐
13. Food allergy/intolerance	☐	☐	☐	☐	☐
14. Delayed psychomotor development (several functions)	☐	☐	☐	☐	☐
15. (Other) malformations: _____	☐	☐	☐	☐	☐
16. Other:_____	☐	☐	☐	☐	☐

28. If your child was referred for a specialist investigation, what did this investigation show?

☐ Everything was fine +
☐ Still some doubts/further investigations needed
☐ Don't know
☐ Given the following diagnosis: _____

_____

_____

29. Is you child suspected of having a syndrome or chromosomal defect?

☐ No
☐ Yes, a syndrome
☐ Yes, a chromosomal defect
☐ If yes, specify the name or describe the problem:_____

_____

_____

30. Has your child been treated for a hip problem (hip dysplasia)?

☐ No
☐ Yes, treated with a cushion
☐ Yes, treated with a plaster cast
☐ Yes, treated with braces +

If yes, how long did the treatment go on for? ☐ months

31. Has your child had the following illness/health problem? If yes, did you go to a doctor or hospital about it? *(Enter a cross in a box for each item.)*

	Has your child had health problems?		Number of times doctor/clinic	Did you go to a doctor/clinic for this?		Has your child been admitted to hospital for this?	
	No	Yes		No	Yes	No	Yes
1. Common cold	☐	☐		☐	☐	☐	☐
2. Throat infection	☐	☐		☐	☐	☐	☐
3. Ear infection	☐	☐		☐	☐	☐	☐
4. Pseudocroup	☐	☐		☐	☐	☐	☐
5. Bronchitis/RS virus/pneumonia	☐	☐		☐	☐	☐	☐
6. Gastric flu/diarrhoea	☐	☐		☐	☐	☐	☐
7. Urinary tract infection	☐	☐		☐	☐	☐	☐
8. Conjunctivitis	☐	☐		☐	☐	☐	☐
9. Febrile convulsions	☐	☐		☐	☐	☐	☐
10. Other convulsions (without any fever)	☐	☐		☐	☐	☐	☐
11. Colic	☐	☐		☐	☐	☐	☐
12. Nappy rash	☐	☐		☐	☐	☐	☐
13. Other, describe _____	☐	☐		☐	☐	☐	☐

32. Have your child ever been given any medication?

☐ No
☐ Yes

33. If yes, give the name of the medicines and when they were given. *(Include all types of medication, as well as natural medicines, taken both on a regular and occasional basis.)*

Name of medicine *(e.g. Apocilin, Paracetamol)*	How old was your child when you gave the medicine? <1 Month	1-2 months	3-4 months	5-6 months	Number of days given in total
_____	☐	☐	☐	☐	
_____	☐	☐	☐	☐	
_____	☐	☐	☐	☐	
_____	☐	☐	☐	☐	

34. Has your child been examined at or admitted to hospital (since returning home from hospital after birth)?

☐ No

☐ Yes, specify: _____

35. Has your child been operated on or does he/she have a condition requiring an operation?

☐ No

☐ Yes, specify:

_____

Development, childcare and life style

36. The following questions concern your child's development. If you haven't actually observed your child, spend a little time looking at what he/she can actually do. *(Enter a cross in a box for each question.)*

	Yes often	Yes, but seldom	No, not yet	Don't know
1. When your child is lying on his/her back, does he/she play by grabbing hold of his/her feet?	☐	☐	☐	☐
2. When your child is lying on his/her tummy, does he/she raise his/her upper body off the ground with straight arms?	☐	☐	☐	☐
3. Does your child roll over from his/her back onto his/her tummy?	☐	☐	☐	☐
4. When you "chat" to your child, does he/she try to "chat" back to you?	☐	☐	☐	☐
5. Does your child babble and make sounds when he/she is lying on his/her own?	☐	☐	☐	☐
6. Can you tell how your child is just by listening to the sounds he/she is making *(e.g. contented, hungry, angry,in pain)?*	☐	☐	☐	☐
7. Do you get a smile from your child when you just smile at him/her *(without touching or tickling him/her and without holding up a toy)?*	☐	☐	☐	☐
8. When you call your child, does he/she turn towards you one of the first times you say his/her name?	☐	☐	☐	☐
9. Does your child grab hold of a toy you give him/her and then put it in his/her mouth or hold it?	☐	☐	☐	☐
10. When your child is sitting on your lap, does he/she stretch out for a toy or something else on the table in front of you?	☐	☐	☐	☐
11. Does your child hold onto a toy with both hands when he/she is examining it?	☐	☐	☐	☐

37. Where is your child cared for during the day?

☐ At home with mother/father/other family member
☐ At home with an unqualified childminder
☐ At a childminder's/family creche
☐ In an outdoor nursery
☐ In a nursery

38. How many other children are there usually along with your child during the day?

☐☐ children

39. Does your child go to baby swimming?

☐ No
☐ Yes

If yes, indicate the number of times during the last 2 months ☐☐

40. How often is your child outside? *(Enter just one cross.)*

☐ Seldom
☐ Often, but less than 1 hour a day
☐ 1-3 hours a day
☐ More than 3 hours a day

41. Does your child use a dummy/pacifier?

☐ Seldom or never
☐ Only when he/she goes to sleep
☐ Often
☐ Most of the time

42. How many hours in total does your child sleep per 24 hours?

☐ Less than 8 hours
☐ 8 - 10 hours
☐ 11 - 13 hours
☐ 13 - 14 hours
☐ More than 14 hours

43. How do you put your child down when he/she is going to sleep? *(Enter a cross in a box for each item.)*

	On back	On side	On tummy
After the birth	☐	☐	☐
At 2 months	☐	☐	☐
At 4 months	☐	☐	☐
At 6 months	☐	☐	☐

44. Does your child share a bed with his/her mother/father (at least half the night)? *(Enter a cross in a box for each item.)*

	No	sometimes	Often
After the birth	☐	☐	☐
At 2 months	☐	☐	☐
At 4 months	☐	☐	☐
At 6 months	☐	☐	☐

45. Enter a cross to indicate whether you agree or disagree with the following statements about your child's mood and temperament. Think about how he/she usually is. *(Enter a cross in a box for each item.)*

	Totally disagree	Disagree	Slightly disagree	Neither agree or disagree	Slightly agree	Agree	Totally agree
1. Your child whimpers and cries a lot	☐	☐	☐	☐	☐	☐	☐
2. Your child is usually easy to pacify when he/she is crying	☐	☐	☐	☐	☐	☐	☐
3. It doesn't take much for your child to become upset and start crying	☐	☐	☐	☐	☐	☐	☐
4. When your child is crying, he/she usually screams angrily and loudly	☐	☐	☐	☐	☐	☐	☐
5. Your child is very easy to deal with	☐	☐	☐	☐	☐	☐	☐
6. Your child demands an awful lot of attention	☐	☐	☐	☐	☐	☐	☐
7. When your child is left alone, he/she usually plays contentedly on his/her own	☐	☐	☐	☐	☐	☐	☐
8. Your child is so demanding that he/she would pose a major problem for most parents	☐	☐	☐	☐	☐	☐	☐
9. Your child smiles and laughs often	☐	☐	☐	☐	☐	☐	☐
10. Your child is easy to put down and goes to sleep quickly	☐	☐	☐	☐	☐	☐	☐

46. Currently how often does your child usually wake up during the night? *(Enter just one cross.)*

- ☐ 3 or more times every night
- ☐ Once or twice every night
- ☐ A few times a week
- ☐ Seldom or never

Comments

About yourself

The last time you completed a questionnaire was around week 30 of your pregnancy. The questions we are asking you now are mainly about the period after this up until your child was 6 months old.

Health and use of medication

47. Did you go to your doctor/midwife/health visitor for your own health problems during the first month after the birth?

☐ No
☐ Yes ☐☐ times

48. If yes, what was the reason for this?

☐ Perninealwound/stitches
☐ Caesarean section wound
☐ Mastitis
☐ Sore nipples
☐ Breastfeeding problems
☐ Other, specify: _____

49. When you think back to the time just after the birth, did you feel depressed during that period?

☐ No
☐ Yes, specify how long: ☐☐ weeks

50. Apart from being in hospital for the birth, have you been admitted to hospital since you completed the previous questionnaire?

☐ No
☐ Yes, specify hospital: _____

51. Do you have a chronic/long-term illness which has started since you completed the previous questionnaire?

☐ No
☐ Yes, specify: _____

52. Overall, how would you describe your physical health at the moment?

☐ Very good
☐ Good
☐ Poor
☐ Very poor

53. Have you had any of the following problems/illnesses since you completed the previous questionnaire? If yes, are you taking or have you taken medication for these problems? *(This includes every type of medication, including natural medicines, taken on both a regular and occasional basis.) (Enter a cross in a box for each item.)*

Have you suffered from?				If you have taken medication				
Illness / problem	No	Yes, last part of during pregnancy	Yes, after the birth	Name of medication taken	Last part of this pregnancy	After the birth 0-3 mth	After the birth 4-6 mth	Number of days taken in total
1. Sugar in urine	☐	☐	☐	_____	☐	☐	☐	☐☐☐
2. Protein in urine	☐	☐	☐	_____	☐	☐	☐	☐☐☐
3. High blood pressure . .	☐	☐	☐	_____	☐	☐	☐	☐☐☐
4. Swelling (oedema)	☐	☐	☐	_____	☐	☐	☐	☐☐☐
5. Cystitis	☐	☐	☐	_____	☐	☐	☐	☐☐☐
6. Sluggish bowels/constipation	☐	☐	☐	_____	☐	☐	☐	☐☐☐
7. Diarrhoea/vomiting	☐	☐	☐	_____	☐	☐	☐	☐☐☐
8. Heartburn/acidity	☐	☐	☐	_____	☐	☐	☐	☐☐☐
9. Common cold/influenza	☐	☐	☐	_____	☐	☐	☐	☐☐☐
10. Sore throat/sinusitis/earinfection	☐	☐	☐	_____	☐	☐	☐	☐☐☐

cont. next page

Have you suffered from?				If you have taken medication				
Illness / problem	No	Yes, last part of during pregnancy	Yes, after the birth	Name of medication taken	Last part of this pregnancy	After the birth 0-3 mth	After the birth 4-6 mth	Number of days taken in total
11. Pneumonia/bronchitis . .	☐	☐	☐	_____	☐	☐	☐	
12. Asthma	☐	☐	☐	_____	☐	☐	☐	
13. Hay fever/other allergy.	☐	☐	☐	_____	☐	☐	☐	
14. Headache/other pains .	☐	☐	☐	_____	☐	☐	☐	
15. Vaginitis	☐	☐	☐	_____	☐	☐	☐	
16. Mental health problems	☐	☐	☐	_____	☐	☐	☐	
17. Mastitis.	☐	☐	☐	_____	☐	☐	☐	
18. Fever	☐	☐	☐	_____	☐	☐	☐	
19. Other, specify: _____	☐	☐	☐	_____	☐	☐	☐	

54. Have you taken medicines other than those mentioned in Question 52? *(For instance, sleeping tablets, sedatives or analgesics.)*

☐ No ☐ Yes

55. If yes, give the name of the medicines and when you took them. *(Include all types of medication, as well as natural medicines, taken both on a regular and occasional basis.)*

Name of medicine (e.g. Valium, Rohypnol, Paracetamol)	Last part of pregnancy: Taken medication	Last part of pregnancy: Number of days	0-3 months after the birth: Taken medication	0-3 months after the birth: Number of days	4-6 months after the birth: Taken medication	4-6 months after the birth: Number of days
_____	☐		☐		☐	
_____	☐		☐		☐	
_____	☐		☐		☐	

56. Do you take or have you taken cod liver oil, vitamins or other dietary supplements since the previous questionnaire?

☐ No ☐ Yes

57. If yes, which product, when did you take it and how often? *(One line for each product.)*

Name of product	When did you take the product? Last part of pregnancy	0-3 months after the birth	4-6 months after the birth	How often? Taken daily	Taken sometimes
_____	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐

58. Have you experienced any pain in your back or pelvis since you completed the previous questionnaire?

☐ No
☐ Yes

59. If yes, enter a cross to indicate where you have experienced pain, when and how much.

Where was the pain?	Last part of pregnancy: Some pain	Last part of pregnancy: Major pain	0-3 months after the birth: Some pain	0-3 months after the birth: Major pain	4-6 months after the birth: Some pain	4-6 months after the birth: Major pain
Small of the back	☐	☐	☐	☐	☐	☐
One of the pelvic/sacroiliac joints at the back	☐	☐	☐	☐	☐	☐
Both pelvic/sacroiliac joints at the back	☐	☐	☐	☐	☐	☐
Over the coccygeal bone	☐	☐	☐	☐	☐	☐
In the buttocks	☐	☐	☐	☐	☐	☐
Over the pubic bone	☐	☐	☐	☐	☐	☐
Groin	☐	☐	☐	☐	☐	☐
Other back pains	☐	☐	☐	☐	☐	☐

60. Currently, do you wake up at night because of pelvic pain?

☐ No, never
☐ Yes, but only sometimes
☐ Yes, often

61. Do you have such problems walking at the moment due to pelvic pain that you have to use a stick or crutches?

☐ No, never
☐ Yes, but not every day
☐ Yes, every day

62. Have you *ever* received treatment for pelvic pain?

☐ No
☐ Yes

63. If yes, enter a cross to indicate the type of treatment and when it was.

	Before this pregnancy	During this pregnancy	After this birth
Physiotherapy	☐	☐	☐
Chiropractic	☐	☐	☐
Medication	☐	☐	☐
Other, specify: _____	☐	☐	☐

64, How long was it before you resumed sexual intercourse after the birth?

☐☐ weeks

☐ Have not had sexual intercourse

65. Do you have any of the following problems at the moment; if so, how often and to what extent? *(Enter a cross in a box for each item.)*

Problem	How often do you have these problems? Never	1-4 times a month	1-6 times a week	Once a day	More than Once a day	How much at a time? Drops	Large amounts
Incontinence when coughing, sneezing or laughing	☐	☐	☐	☐	☐	☐	☐
Incontinence during physical activity (running/jumping)	☐	☐	☐	☐	☐	☐	☐
Incontinence with a strong need to urinate	☐	☐	☐	☐	☐	☐	☐
Problems retaining faeces	☐	☐	☐	☐	☐	☐	☐
Problems with flatulence	☐	☐	☐	☐	☐	☐	☐

66. How many times did you go for an ultrasound scan during your pregnancy?

☐☐ times

67. Was everything OK with the ultrasound scan(s)?

☐ Yes
☐ No

68. If no, what was the problem?

☐ The baby was not growing enough.
☐ Suspected malformation,describe:

_____

☐ Other, specify: _____

69. How much did you weigh at the end of your pregnancy and how much do you weigh now?

At end of pregnancy ☐☐☐,☐ kg

Now ☐☐☐,☐ kg

+

70. Were you completely or partly on sick leave after week 30 of your pregnancy? *(Don't include maternity leave)*

- ☐ No
- ☐ Yes,partly on sick leave
- ☐ Yes,completely on sick leave

+

71. If you were on sick leave after week 30 of your pregnancy, complete the table below with a line for each time you were on sick leave. Give the reason and enter a cross indicating which weeks of your pregnancy you were on sick leave. Specify how many days and what percentage of the period you were on sick leave each time.

Reason for sick leave:	Was on sick leave during pregnancy weeks 30-33	34-37	38+	Number of days	% sick leave
Example: pelvic girdle pains	☐	☒	☐	10	50
	☐	☐	☐		
	☐	☐	☐		
	☐	☐	☐		

Finances – lifestyle

72. Would your current financial situation allow you to cope with an unexpected bill of NOK 10,000 for a dental visit or a repair, for a instance?

- ☐ No
- ☐ Yes
- ☐ Don't know

73. Have you found it difficult sometimes during the last six month to cope with running expemces for food, transport, rent etc.?

- ☐ No, never
- ☐ Yes, but infrequently
- ☐ Yes, sometimes
- ☐ Yes, often

74. Are there pets in the child's home?

- ☐ No
- ☐ Yes

+

75. If yes, which type(s)? *(You can enter a cross in more than one box.)*

- ☐ Dog
- ☐ Cat
- ☐ Guinea pig, rabbit, mouse, rat, etc.
- ☐ Budgie, other type of bird
- ☐ Other type of animal:

_____

76. Do you have heating based on electrical heating cables under the floor in rooms where you child is? (Do <u>not</u> include waterborne heating)

- ☐ No
- ☐ Yes

77. If yes, in which rooms? *(You can enter a cross in more than one box.)*

- ☐ Living room
- ☐ Kitchen
- ☐ Child's room
- ☐ Bedroom
- ☐ Hall
- ☐ Bathroom
- ☐ Other rooms

78. How often do you exercise these muscle groups at home or at the gym at present? *(Enter a cross in a box for each item.)*

	Never	1-3 times times a month	Once a week	Twice a week	Three times or more a week
Stomach muscles	☐	☐	☐	☐	☐
Back muscles	☐	☐	☐	☐	☐
Pelvic floor muscles (muscles around the vagina, urethra, rectum)	☐	☐	☐	☐	☐

79. How often are you physically active at present? *(Enter a cross in a box for each item.)*

	Never	1-3 times a month	Once a week	Twice a week	Three times or more a week
1 Didn't smoke	☐	☐	☐	☐	☐
2 Brisk walking	☐	☐	☐	☐	☐
3 Running/jogging/orienteering	☐	☐	☐	☐	☐
4 Cycling	☐	☐	☐	☐	☐
5 Training studio/weight training	☐	☐	☐	☐	☐
6 Special gymnastics/aerobics for pregnant women	☐	☐	☐	☐	☐
7 Aerobics/gymnastics/dancing without running and jumping	☐	☐	☐	☐	☐
8 Aerobics/gymnastics/dancing with running and jumping	☐	☐	☐	☐	☐
9 Dancing (swing, rock, folk)	☐	☐	☐	☐	☐
10 Skiing	☐	☐	☐	☐	☐
11 Ball sport	☐	☐	☐	☐	☐
12 Swimming	☐	☐	☐	☐	☐
13 Riding	☐	☐	☐	☐	☐
14 Other	☐	☐	☐	☐	☐

80. Currently how often are you physically active (during your spare time or at work) that you get out of breath or sweat?

	Spare time	At work
Never	☐	☐
Less than once a week	☐	☐
Once a week	☐	☐
Twice a week	☐	☐
3-4 times a week	☐	☐
5 times or more a week	☐	☐

81. What were your and your partner/husband's smoking habits during the last 3 months of your pregnancy and in the period after the birth? *(Enter a cross in a box for each period.)*

	Yourself			Your partner/husband		
	Last 3 mths during pregnancy	0-3 mths after birth	4-6 mths after birth	Last 3 mths during pregnancy	0-3 mths after birth	4-6 mths after birth
Didn't smoke	☐	☐	☐	☐	☐	☐
Smoked sometimes	☐	☐	☐	☐	☐	☐
Smoked every day	☐	☐	☐	☐	☐	☐
If every day, number of cigarettes per day	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
If sometimes, number of cigarettes per week	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐

82. Is your child ever present in a room where someone smokes?

- ☐ No
- ☐ Yes, sometimes
- ☐ Yes, several times a week
- ☐ Yes, every day

If every day, number of hours ☐☐

83. Did you take any of the following substances during the last 3 months of your pregnancy and after the birth? *(Enter a cross in a box for each item.)*

	No	Yes, last 3 month of pregnancy	Yes after birth
Hanish	☐	☐	☐
Amphetamines	☐	☐	☐
Ecstasy	☐	☐	☐
Cocaine	☐	☐	☐
Heroin	☐	☐	☐
Other, specify: _____	☐	☐	☐

84. Have you taken any of the following substances during the last 3 months of your pregnancy and after the birth? *(Enter a cross in a box for each item.)*

	No	Yes, last 3 months of pregnancy	Yes, after birth
Anabolic steroids	☐	☐	☐
Testosterone preparations	☐	☐	☐
Growth hormone (e.g. genotropin/somatropin)	☐	☐	☐

85. How often did you drink alcohol during the last 3 months of your pregnancy and how often do you drink now? *(Enter a cross in a box for each period.)*

	Last 3 months of pregnancy	After the birth	
		0-3 months	4-6 months
Roughly 6-7 times a week	☐	☐	☐
Roughly 4-5 times a week	☐	☐	☐
Roughly 2-3 times a week	☐	☐	☐
Roughly once a week	☐	☐	☐
Roughly 1-3 times a month	☐	☐	☐
Less often than once a month	☐	☐	☐
Never	☐	☐	☐

Alcohol units
In order compare different types of alcohol, we ask for the number of alcohol units (= 1.5 cl of pure alcohol). In practice, this means the following:

1 glass (1/3 litre) of beer	= 1 alcohol unit
1 wine glass of red or white wine	= 1 alcohol unit
1 sherryglass of sherry	= 1 alcohol unit
1 brandy glass of spirits or liquer	= 1 alcohol unit
1 bottle of alcopop/cider	= 1 alcohol unit

86. How many units of alcohol do you usually drink when you consume alcohol (complete both for the last 3 months of your pregnancy and afterwords)? *(See explanation about alcohol units.) (Enter a cross in a box for each period.)*

Number of alcohol units	Last 3 months of pregnancy	After the birth	
		0-3 months	4-6 months
10 or more	☐	☐	☐
7-9	☐	☐	☐
5-6	☐	☐	☐
3-4	☐	☐	☐
1-2	☐	☐	☐
Less than 1	☐	☐	☐

A little more about yourself and how you are keeping now

87. Do you have a boyfriend/ husband/partner?

☐ Yes
☐ No

88. If yes, to what extent do you agree with the following descriptions? *(Enter just one cross in a box for each item.)*

	Totally agree	Agree	Slightly agree	Slightly disagree	Disagree	Totally disagree
My husband/partner and I have a close relationship	☐	☐	☐	☐	☐	☐
My partner and I have problems in our relationship	☐	☐	☐	☐	☐	☐
I am very happy in my relationship	☐	☐	☐	☐	☐	☐
My partner is usually understanding	☐	☐	☐	☐	☐	☐
I often think about ending our relationship	☐	☐	☐	☐	☐	☐
I am satisfied with my relationship with my partner	☐	☐	☐	☐	☐	☐
We often disagree about important decisions	☐	☐	☐	☐	☐	☐
I have been lucky in my choice of partner	☐	☐	☐	☐	☐	☐
We agree on how children should be raised	☐	☐	☐	☐	☐	☐
I think my partner is satisfied with our relationship	☐	☐	☐	☐	☐	☐

89. In your daily life, how often do you *(Enter just one cross in a box for each item.)*

	Seldom never	Fairly seldom	A few times	Often	Very often
Feel pleased about something	☐	☐	☐	☐	☐
Feel happy	☐	☐	☐	☐	☐
Feel joyful, as though everything is going your way	☐	☐	☐	☐	☐
Feel that you will scream at someone or hit something	☐	☐	☐	☐	☐
Feel angry, irritated or annoyed	☐	☐	☐	☐	☐
Feel mad at somebody	☐	☐	☐	☐	☐

90. Indicate with a cross whether you agree or disagree with the following statements.
(Enter just one cross in a box for each item.)

	Totally disagree	Disagree	Slightly disagree	Neither agree or disagree	Slightly agree	Agree	Totally agree
My life is largely what I wanted it to be	☐	☐	☐	☐	☐	☐	☐
My life is very good	☐	☐	☐	☐	☐	☐	☐
I am satisfied with my life	☐	☐	☐	☐	☐	☐	☐
I have achieved so far what is important for me in my life	☐	☐	☐	☐	☐	☐	☐
If I could start all over, there is very little I would do differently	☐	☐	☐	☐	☐	☐	☐

91. Have you experienced any of the following situations since the previous questionnaire? If yes, how painful or difficult was this for you? *(Enter a cross in a box for each item.)*

			If yes		
	No	Yes	Not so bad	Painful/ difficult	Very painful/ difficult
Have you had problems at work or where you study?	☐	☐	☐	☐	☐
Have you had financial problems?	☐	☐	☐	☐	☐
Have you been divorced, separated or ended your relationship with your partner?	☐	☐	☐	☐	☐
Have you had problems or conflicts with family, friends or neighbours?	☐	☐	☐	☐	☐
Have you been seriously worried that there is something wrong with your child?	☐	☐	☐	☐	☐
Have you been seriously ill or injured?	☐	☐	☐	☐	☐
Has anyone close to you been seriously ill or injured?	☐	☐	☐	☐	☐
Have you been involved in a serious accident, fire or robbery?	☐	☐	☐	☐	☐
Have you lost someone close to you?	☐	☐	☐	☐	☐
Have you been pressurized into having sexual intercourse?	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐

92. Have you experienced any of the following feelings during the last week? *(Enter just one cross in a box for each item.)*

	Yes, almost all the time	Yes, now and then	Not very often	No, never
Really reproached yourself when something went wrong	☐	☐	☐	☐
Have been anxious or worried for no reason	☐	☐	☐	☐
Have been afraid or panicked for no reason	☐	☐	☐	☐
Have been so unhappy that you've had problems sleeping	☐	☐	☐	☐
Felt down or unhappy	☐	☐	☐	☐
Have been so unhappy that you've cried	☐	☐	☐	☐

93. How do you feel about yourself? *(Enter just one cross in a box for each item.)*

	Totally agree	Agree	Disagree	Totally disagree
I have a positive attitude towards myself	☐	☐	☐	☐
I feel completely useless at times	☐	☐	☐	☐
I feel that I do not have much to be proud about	☐	☐	☐	☐
I feel that I am a valuable person, as good as anyone else	☐	☐	☐	☐

94. Have you been bothered by any of the following feelings during the past 2 weeks? *(Enter just one cross in a box for each item.)*

	Not bothered	A little bothered	Quite bothered	Very bothered
Feeling fearful	☐	☐	☐	☐
Nervousness or shakiness inside	☐	☐	☐	☐
Feeling hopeless about the future	☐	☐	☐	☐
Feeling blue	☐	☐	☐	☐
Worrying too much about things	☐	☐	☐	☐
Feeling everything is an effort	☐	☐	☐	☐
Feeling tense or keyed up	☐	☐	☐	☐
Suddenly scared for no reason	☐	☐	☐	☐

Thank you very much for your help!

Insert the completed questionnaire in the stamped addressed envelope.

APPENDIX 2:

MBRN standardized form

REPORT ON COMPLETED PREGNANCY AFTER 12 WEEKS
BIRTHS, STILLBIRTHS, MISCARRIAGES

A – Civil information

Institution no: A01 Institution name A02		**Birth outside institution** A03 ☐ At home, planned A04 ☐ At home, not planned A05 ☐ During transportation A06 ☐ Elsewhere	Mother's full name and address A09 Maiden name (Surname) A10
Mother's marital status	A11 ☐ Married A13 ☐ Unmarried/single A15 ☐ Others A12 ☐ Cohabitant A14 ☐ Divorced/separated/widow		
Are parents related	☐ No ☐ Yes A16 If yes, how? A18	**Mother's municipality** A21	A22
Father's date of birth A19	Father's full name A20	**Mother's National ID no. (11 digits)** A07 A08	

Autorisert

Dato: 23/8-2007

Signatur:

B –About the pregnancy and mother's health

Last menstrual period:

1st day of bleeding B01

B02 ☐ Certain ☐ Uncertain

Mother's previous pregnancies/births

Live births	Stillborn (24 wks or more)	Miscarriages / stillborn (12-23 wks)	Miscarriages (under 12 wks)
B04	B05	B06	B07

Ultrasound performed? B08 ☐ No ☐ Yes

Ultra-sound due date B10

Other prenatal diagnostics? B11 ☐ No ☐ Yes, specify: B13

Pathological findings at prenatal diagnostics? B14 ☐ No ☐ Yes, if confirmed – specify

Special conditions before pregnancy:

B16 **None**

B17 Asthma
B18 Allergy
B19 Previous caesarean
B20 Recurring urinary tract infection
B21 Chronic renal disease
B22 Chronic hypertension
B23 Rheumatoid arthritis
B24 Heart disease
B25 Epilepsy
B26 Diabetes type 1
B27 Diabetes type 2
B49 other, specify in "B"

Regular dietary supplement:

B70 ☐ No

	Before pregn.	During pregn.
Multi vitamins	B28	B29
Folic acid	B30	B31

Specification of conditions before or during pregnancy

B

B66

Special conditions during pregnancy:

B32 **None**

B33 Bleeding< 13 wk
B34 Bleeding 13-28 wk
B35 Bleeding> 28 wk
B36 Glycosuria
B37 Gestational diabetes
B38 Hypertension only
B39 Preeclampsia light
B40 Preeclampsia severe
B41 Preeclampsia<34wks
B42 HELLP syndrome
B43 Eclampsia
B44 Hb< 9.0 g/dl
B45 Hb > 13.5 g/dl
B46 Thrombosis, treated
B48 Infections, specify in "B"
B47 Other, specify in "B"

Medication during pregnancy

☐ No
B50 ☐ Yes – specify in "B"

Smoking and Occupation
Conditioned on mother's consent – see instructions on reverse.

B52 ☐ Written info given to mother
B53 ☐ Does not consent to smoking info

Did mother smoke at start of pregnancy? B54 No B55 Sometimes B56 Daily **No. of** cigs. daily: B57

- **at the end of of pregnancy?** B58 No B59 Sometimes B60 Daily **No. of** cigs. daily: B61

Mother's occupation B62 **Does not consent to employment info**

B63 Not emplyed
B64 Employed fulltime
B65 Employed part time

Mother's occupation:

Business, trade, line etc.:

B67

C – about birth

Presentation

C01 **Normal cephalic**

C02 Breech

C03 Transverse

C04 Cephalic, abnormal

C05 Other, specify in "C"

Inception of labour

C06 **Spontaneous**

C07 Induced

C08 Caesarean

Induction method

C09 Prostaglandin

C10 Oxytocin

C11 Amniotomy

C12 Others, specify in "C"

Indication for intervention and/or induction

C13 Complications, as described below

C14 Birth defects

C15 Postterm

C16 Other, specify in "C"

Intervention

C17 **None**

C18 Low forceps, cephalic

C19 Other forceps, cephalic

C20 Vacuum extractor

C21 Episiotomy

Assistance at breech delivery:

C22 Usual procedure

C23 Extraction

C24 Forceps on head

Caesarean section

Was the section planned prior to delivery?

C27 No C27 Yes

C25 Performed elective section

C25 Performed emergency section

Specification of conditions during delivery / other complications

C C84

Complications

C29 **None**

C30 Rupture of membrane 12-24 hours

C31 Rupture of membrane >24 hours

C32 Mechanical obstruction

C33 Complicated shoulder delivery

C34 Placenta previa

C35 Abruptio placentae

C36 Perineal rupture (degree 1-2)

C37 Sphincter ruptur (degree 3-4)

C38 Haemorrhage >1500 ml, transf

C39 Haemorrhage 500-1500 ml

C40 Eclampsia during delivery

C41 Prolaps of cord

C42 Threatening intrauterine asphyxia

C43 Reduced contractions - stimulated

C44 Slow progress

C45 Uterine atony

C86 Other:

Anaesthetics / analgesic

C46 **None**

C47 Nitrous oxide

C48 Pethidine

C49 Epidural

C50 Spinal

C51 Pudendal

C52 Infiltration

C53 Paracervical block

C54 General anaesthetics

C87 Other:

Placenta

C55 **Normal**

C56 Membranal residue

C57 Incomplete

C58 Infarction

C59 Blood clots

C60 Curettage

C61 Manual extraction

Weight of Placenta: C62

Umbilical cord

C63 **Normal**

C64 Velamentous attachment

C65 Peripheral attachment

C66 Vessel anomalies

C67 Coiled round neck

C68 Other form of coiling

C69 Genuine knot

Length of umbilical cord: C85

Amniotic fluid

C70 **Normal**

C71 Polyhydramnion

C72 Oligohydramnion

C73 Discoloured

C74 Malodorous, infected

C75 Bloodstained

After-delivery complications - mother

C76 **None**

C77 Fever >38.5 C

C78 Thrombosis

C79 Eclampsia postpartum

C80 Mother transferred

C81 Mother intensive care

C82 Sepsis

C83 Other, specify

D – About the child

Date of Birth: D01

Time: D02

Plurality

D03 **Single delivery**

D04 Multiple birth

For multiple birth:

No.: D05

Of total: D06

Sex

D07 Male D08 Female

If uncertain, specify in "D"

For stillborn: D09 Uncertain sex

Child's weight: D10

Total length: D12

Head circumference: D11

Buttocks-vertex length: D13

Apgar score:

1 min: D14

5 min: D15

The child was:

D16 **Live born** D17 Stillborn/miscarriage

Specify cause of death in "D"

For stillborn: D18 Died before labour

D19 Died during labour

D20 Time of death unknown

For stillborn, note also:

D21 Dead before arrival

D22 Dead after arrival

Live birth, died within 24 hours

Life lasted:

Hours: D23 Mins.: D24

Died later:

Date: D25

Time: D26

Transferred to neonatal unit:

☐ **No** D27 ☐ Yes

Date: D29

Transferred to (name of unit): D30

Indication for transfer:

D31 Respiratory problems

D32 Pre-mature

D33 Birth defects

D34 Perinatal infections

D35 Other, specify

Neonatal diagnoses: (To be completed by physician / pediatrician)

D36 **None**

D37 Hypoglyco. (<2 mmol/l)

D38 Cong.anaemia (Hb<13.5 g/dl)

D39 Hip joint dysplasia treated with pillow

D40 Transit. tachypnea

D41 Resp. distress syndrome

D42 Aspiration syndrome

D43 Intracranial hemorrhage

D44 Cerebral irritation

D45 Cerebral depression

D46 Abstinence

D47 Neonatal fits

D48 Conjunctivitis treated

D49 Navel/dermal infection treated

D50 Perinatal infections, bacterial

D51 Perinatal infections, other

D52 Fract. claviculae

D53 Other fracture

D54 Facial paresis

D55 Plexus injury

Treatment codes:

D56 Systematic antibiotics

D57 Respiratory treatment

D58 CPAP treatment

Icterus, treated:

D59 Light treatment

D60 Transfusion

Icterus, cause:

D61 ABO incompatible

D62 RH immunization

D63 Physiological

D64 Other cause

Signs of birth defects:

D65 ☐ No ☐ Yes

Specification of injuries, neonatal diagnoses and birth defects – to be completed by physician:

D D67

Record no: D68 / D69

Physician:

Maternity ward / Pediatric ward:

Discharged date:

Mother: D70

Child: D71

APPENDIX 3:

Directed Acyclic Graphs (paper II)

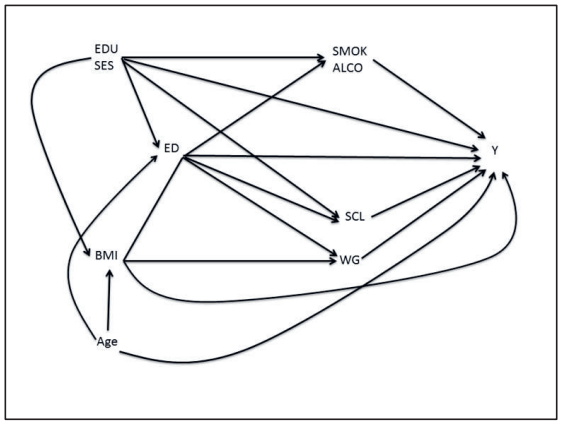

Figure a: Directed Acyclic Graph (DAG) where ED is eating disorder before and/or during pregnancy, EDU/SES is education and socioeconomic status at conception, BMI is body mass index at conception, age is maternal age at delivery, SMOK/ALCO is smoking during pregnancy until gestational week 30 and alcohol use during pregnancy, WG is weight gain during entire pregnancy, SCL is maternal underlying depressive and anxiety symptoms throughout the pregnancy, Y is the outcome: psychotropic medication use in pregnancy. EDU/SES and SMOK/ALCO were combined in the same node for readability purposes. They were two separate nodes in DAGitty (http://www.dagitty.net/).

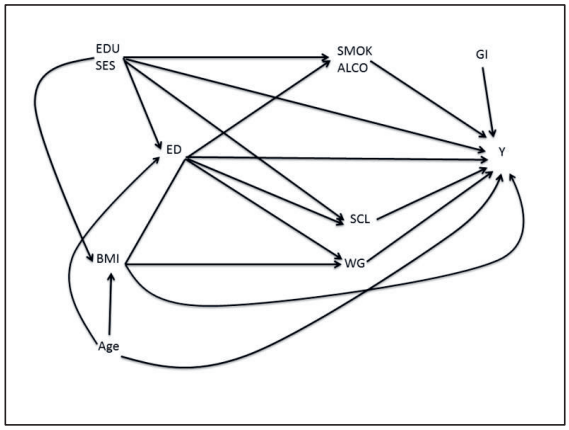

Figure b: Directed Acyclic Graph (DAG) where ED is eating disorder before and/or during pregnancy, EDU/SES is education and socioeconomic status, BMI is body mass index at conception, age is maternal age at delivery, SMOK/ALCO is smoking during pregnancy until gestational week 30 and alcohol use during pregnancy, WG is weight gain during entire pregnancy, SCL is maternal underlying depressive and anxiety symptoms throughout the pregnancy, GI is gastrointestinal disorders and includes heartburn/reflux, duodenal/stomach ulcers, Crohn disease/ulcerative colitis and other gastrointestinal problems during pregnancy, Y is the outcome: gastrointestinal medication use in pregnancy. EDU/SES and SMOK/ALCO were combined in the same node for readability purposes. They were two separate nodes in DAGitty (http://www.dagitty.net/).

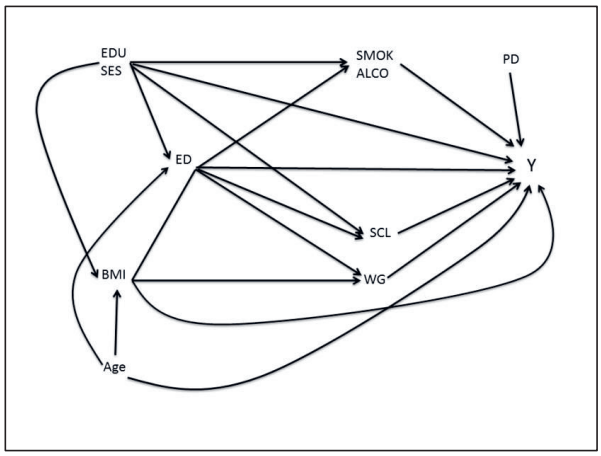

Figure c: Directed Acyclic Graph (DAG) where ED is eating disorder before and/or during pregnancy, EDU/SES is education and socioeconomic status, BMI is body mass index at conception, age is maternal age at delivery, SMOK/ALCO is smoking during pregnancy until gestational week 30 and alcohol use during pregnancy, WG is weight gain during entire pregnancy, SCL is maternal underlying depressive and anxiety symptoms throughout the pregnancy, PD is pain disorders and includes pelvic girdle, back and other pains, headache/migraine during pregnancy, Y is the outcome: analgesic medication use in pregnancy. EDU/SES and SMOK/ALCO were combined in the same node for readability purposes. They were two separate nodes in DAGitty (http://www.dagitty.net/).

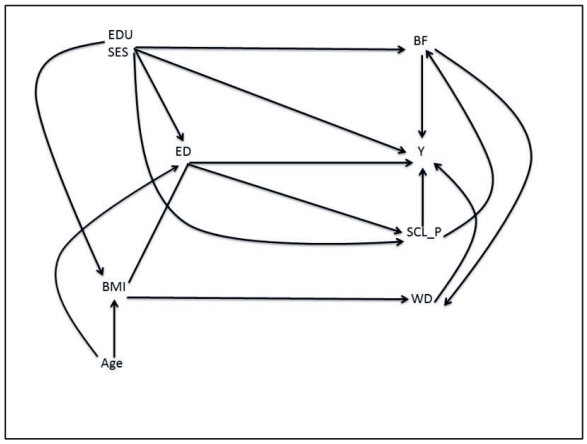

Figure d: Directed Acyclic Graph (DAG) where ED is eating disorder before and/or during pregnancy, EDU/SES is education and socioeconomic status, BMI is body mass index at conception, age is maternal age at delivery, WD is weight decrease at six months postpartum, SCL-P is maternal underlying depressive and anxiety symptoms at six months postpartum, BF is breastfeeding in the 0-6 months period postpartum, Y is the outcome: psychotropic medication use in in the 0-6 months period postpartum. EDU/SES was combined in the same node for readability purposes. They were two separate nodes in DAGitty (http://www.dagitty.net/).

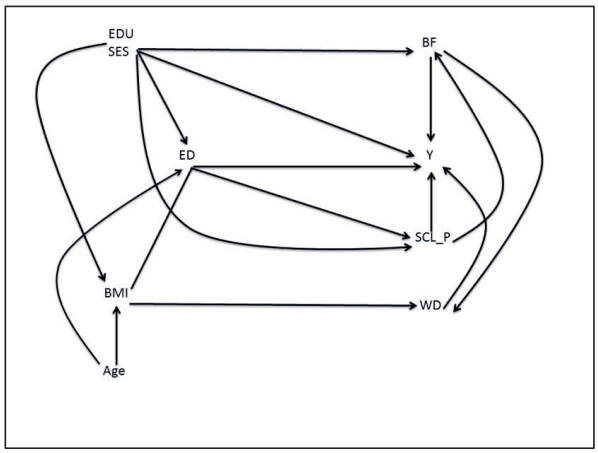

Figure e: Directed Acyclic Graph (DAG) where ED is eating disorder before and/or during pregnancy, EDU/SES is education and socioeconomic status, BMI is body mass index at conception, age is maternal age at delivery, WD is weight decrease at six months postpartum, SCL-P is maternal underlying depressive and anxiety symptoms at six months postpartum, BF is breastfeeding in the 0-6 months period postpartum, Y is the outcome: gastrointestinal medication use in in the 0-6 months period postpartum. EDU/SES was combined in the same node for readability purposes. They were two separate nodes in DAGitty (http://www.dagitty.net/).

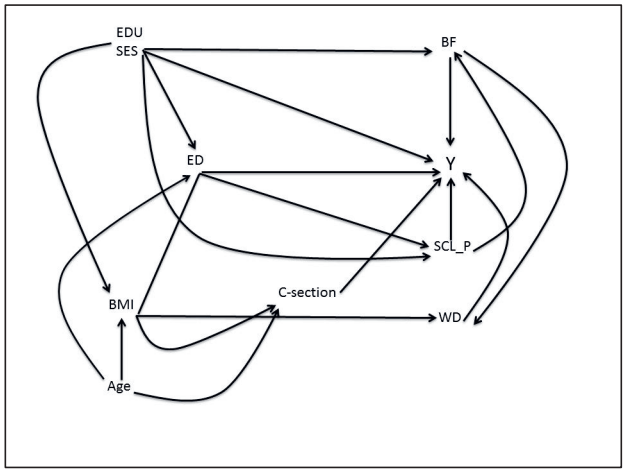

Figure f: Directed Acyclic Graph (DAG) where ED is eating disorder before and/or during pregnancy, EDU/SES is education and socioeconomic status, BMI is body mass index at conception, age is maternal age at delivery, WD is weight decrease at six months postpartum, SCL-P is maternal underlying depressive and anxiety symptoms at six months postpartum, BF is breastfeeding in the 0-6 months period postpartum, C-section is cesarean section, Y is the outcome: analgesic medication use in in the 0-6 months period postpartum. EDU/SES was combined in the same node for readability purposes. They were two separate nodes in DAGitty (http://www.dagitty.net/).

APPENDICES 4a-4b:

Additional analyses (paper III)

Appendix 4a: Prevalence of self-reported depression and anxiety and most common medications used at any time during pregnancy for these indications across the six regions (n=9,459)[*†]

	REGION						
Prevalence of depression and anxiety in pregnancy and related medication use, overall and by drug groups	**Western European n=3,201** *n (%)*	**Northern European n=2,820** *n (%)*	**Eastern European n=2,342** *n (%)*	**North American n=533** *n (%)*	**South American n=346** *n (%)*	**Australian n=217** *n (%)*	**Total n=9,459** *n (%)*
Prevalence of self-reported depression	95 (3.0)	144 (5.1)	29 (1.2)	52 (9.8)	4 (1.2)	25 (11.5)	349 (3.7)
Medication use for depression, total	**61 (1.9)**	**100 (3.5)**	**11 (0.5)**	**29 (5.4)**	**1 (0.3)**	**23 (10.6)**	**225 (2.4)**
By drug group							
SSRI antidepressants (N06AB)	44 (1.4)	82 (2.9)	6 (0.3)	14 (2.6)	-	14 (6.5)	160 (1.7)
SNRIs/mianserin/trazodone/mirtazapine/bupropion	9 (0.3)	11 (0.4)	1 (0.0)	15 (2.8)	-	7 (3.2)	43 (0.5)
Anxiolytics, benzodiazepine (N05BA)	6 (0.2)	2 (0.1)	5 (0.2)	-	-	1 (0.5)	14 (0.1)
Antipsychotics quetiapine/olanzapine (N05AH)	2 (0.1)	4 (0.1)	-	3 (0.6)	-	3 (1.4)	12 (0.1)
Tricyclic antidepressants (N06AA)	4 (0.1)	-	-	-	-	1 (0.5)	5 (0.1)
Prevalence of self-reported anxiety	87 (2.7)	111 (3.9)	49 (2.1)	42 (7.9)	5 (1.4)	17 (7.8)	311 (3.3)
Medication use for anxiety, total	**48 (1.5)**	**54 (1.9)**	**12 (0.5)**	**23 (4.3)**	**2 (0.6)**	**11 (5.1)**	**150 (1.6)**
By drug group							
SSRI antidepressants (N06AB)	20 (0.6)	33 (1.2)	3 (0.1)	9 (1.7)	2 (0.6)	5 (2.3)	72 (0.8)
Anxiolytics, benzodiazepine (N05BA)	18 (0.6)	11 (0.4)	6 (0.3)	9 (1.7)	-	2 (0.9)	46 (0.5)
SNRI antidepressants/trazodone (N06AX)	4 (0.1)	-	-	4 (0.8)	-	3 (1.4)	11 (0.1)
Zopiclone (N05CF)	-	2 (0.1)	-	-	-	-	2 (0.0)
Total prevalence of depression and/or anxiety	**131 (4.1)**	**177 (6.3)**	**60 (2.3)**	**62 (11.6)**	**8 (2.3)**	**26 (12.0)**	**464 (4.9)**
Total medication use for depression and/or anxiety	**82 (2.6)**	**119 (4.2)**	**18 (0.8)**	**36 (6.8)**	**3 (0.9)**	**23 (8.2)**	**281 (3.0)**

Abbreviations: SSRIs=Selective serotonin re-uptake inhibitors; SNRIs= Serotonin–norepinephrine reuptake inhibitors.

Countries are grouped as follows: Western Europe (United Kingdom, Italy, Switzerland, France, The Netherlands, and Austria); Northern Europe (Norway, Sweden, Finland, Iceland); Eastern Europe (Russia, Poland, Croatia, Serbia, Slovenia); North America (USA, Canada); South America (Uruguay, Paraguay, Argentina, Peru, Bolivia, Venezuela, Colombia, Chile, Ecuador, Brazil); Australia.

Statistically significant results are in bold.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Appendix 4b: Factors associated with use of psychotropic medication for treatment of depression and/or anxiety in pregnancy (n=9,459)[†]

	Psychotropic medication use	
	Analysis 1	***Analysis 2***
	aOR (95% CI)	***aOR (95% CI)***
Region of residence[*]		
Western Europe	Reference	NA
Northern Europe	**2.05 (1.54-2.79)**	
Eastern Europe	**0.38 (0.23-0.65)**	
North America	**3.03 (1.98-4.65)**	
South America	**0.25 (0.08-0.82)**	
Australia	**4.35 (2.61-7.25)**	
Maternal age (years)		
<=20	**0.20 (0.07-0.56)**	**0.22 (0.09-0.52)**
21-30	Reference	Reference
31-40	**1.80 (1.37-2.37)**	**1.91 (1.42-2.57)**
>=41	**2.75 (1.47-5.12)**	**2.84 (1.36-5.92)**
Previous children		
No	Reference	Reference
Yes	0.92 (0.71-1.21)	0.96(0.83-1.12)
Marital status		
Married/cohabiting	Reference	Reference
Single/divorced/others	**1.73 (1.13-2.63)**	**1.82 (1.09-3.04)**
Working status		
Employed, but not as HCP	Reference	Reference
HCP	1.10 (0.75-1.64)	**1.32 (1.02-1.69)**
Student	**1.69 (1.06-2.68)**	**1.86 (1.31-2.65)**
Housewife	**2.20 (1.51-3.21)**	**2.31 (1.73-3.07)**
Job seeker	1.53 (0.89-2.63)	**1.66 (1.08-2.56)**
Other than above	**2.19 (1.39-3.45)**	**2.26 (1.57-3.28)**
Educational level		
High school	Reference	Reference
< High school	**2.99 (1.93-4.63)**	**2.67 (1.31-5.42)**
> High school	0.92 (0.68-1.26)	0.90 (0.66-1.24)
Others, unspecified	0.99 (0.64-1.54)	0.91 (0.65-1.47)
Alcohol use after awareness of pregnancy		
No	Reference	Reference
Yes	**1.66 (1.22-2.25)**	**1.48 (1.19-1.85)**
Smoking during pregnancy		
No	Reference	Reference
Smoking < than before pregnancy	**1.69 (1.16-2.45)**	**1.65 (1.37-1.99)**
Smoking ≥ than before pregnancy	**2.10 (1.03-4.30)**	**2.16 (0.98-4.78)**
Planned pregnancy		
Yes	Reference	Reference
No	**1.55 (1.08-2.21)**	**1.60 (1.18-2.16)**
First language different from the official main language in the country of residency		
No	Reference	Reference
Yes	0.72 (0.40-1.27)	0.78 (0.46-1.32)

Abbreviation: HCP=health care provider. NA=Not applicable.
In analysis 1, we compared users of psychotropics for treatment of depression and/or anxiety during pregnancy (n=281) versus non-users (n=9,178). In analysis 2, we performed an equivalent analysis by using GEE with binomial distribution, accounting for clustering on region of residency.
Statistically significant results are in bold.

*Countries are grouped as follows: Western Europe (United Kingdom, Italy, Switzerland, France, The Netherlands, and Austria); Northern Europe (Norway, Sweden, Finland, Iceland); Eastern Europe (Russia, Poland, Croatia, Serbia, Slovenia); North America (USA, Canada); South America (Uruguay, Paraguay, Argentina, Peru, Bolivia, Venezuela, Colombia, Chile, Ecuador, Brazil); Australia.
†Numbers may not add up due to missing values. Missing values are less than 5% of the total.
Mineral supplements, vitamins, iron, herbal or alternative medicine products are not included in the medication use estimates.

APPENDICES 5a-5b:

Results of sensitivity analyses restricted to women with a single participation in the MoBa study (paper IV)

Appendix 5a: Association (adjusted OR, 95% CI) between the exposure groups and vaginal bleeding in early and midpregnancy (n=46,704) among women with single participation in the MoBa study*

Vaginal bleeding in early pregnancy		**Any type of bleeding No. (%) 9,350 (20.0)**		**Trace of blood No. (%) 5,603 (12.0)**		**Medium blood loss or clots No. (%) 3,377 (7.2)**		**>1 episode No. (%) 3,798 (8.1)**	
	n	**n (%)**	**aOR† (95% CI)**	**n (%)**	**aOR‡ (95% CI)**	**n (%)**	**aOR§ (95% CI)**	**n (%)**	**aOR¶ (95% CI)**
Non-exposed in pregnancy	45,068	8,993 (20.0)	Reference	5,403 (12.0)	Reference	3,237 (7.2)	Reference	3,648 (8.1)	Reference
Disease comparison	1,137	252 (22.2)	**1.16 (1.00;1.34)**	131 (11.5)	1.02 (0.84;1.22)	108 (9.5)	**1.35 (1.10;1.66)**	111 (9.8)	**1.29 (1.05;1.58)**
Non-exposed (1st trimester)	45,172	9,016 (20.0)	Reference	5,422 (12.0)	Reference	3,241 (7.2)	Reference	3,656 (8.1)	Reference
SSRIs/SNRIs (1st trimester)	364	77 (21.2)	0.92 (0.71;1.20)	47 (12.9)	0.99 (0.72;1.36)	26 (7.1)	0.79 (0.53;1.21)	29 (9.8)	0.79 (0.53;1.17)
TCAs/OADs (1st trimester)	31	5 (16.1)	0.71 (0.27;1.88)	3 (9.7)	0.78 (0.24;2.60)	2 (6.5)	-	2 (6.5)	-
Vaginal bleeding in mid pregnancy		**Any type of bleeding No. (%) 4,480 (9.6)**		**Trace of blood No. (%) 2,923 (6.3)**		**Medium or large blood loss No. (%) 1,469 (3.1)**		**>1 episode No. (%) 1,301 (2.8)**	
	n	**n (%)**	**aOR†† (95% CI)**	**n (%)**	**aOR‡‡ (95% CI)**	**(%)**	**aOR§§ (95% CI)**	**n (%)**	**aOR¶¶ (95% CI)**
Non-exposed in pregnancy	45,068	4,291 (9.5)	Reference	2,801 (6.2)	Reference	1,407 (3.1)	Reference	1,245 (2.8)	Reference
Disease comparison	1,137	142 (12.5)	**1.31 (1.08;1.60)**	88 (7.7)	1.24 (0.98;1.57)	50 (4.4)	**1.35 (1.00;1.83)**	43 (3.8)	1.34 (0.96;1.86)
Non-exposed (2nd trimester)	45,369	4,321 (9.5)	Reference	2,823 (6.2)	Reference	1,414 (3.1)	Reference	1,252 (2.8)	Reference
SSRIs/SNRIs (2nd trimester)	176	16 (9.1)	0.78 (0.45;1.36)	11 (6.3)	0.92 (0.49;1.73)	5 (2.8)	0.64 (0.26;1.57)	6 (3.4)	1.00 (0.43;2.36)
TCAs/OADs (2nd trimester)	22	1 (4.5)	-	1 (4.5)	-	-	-	-	-

Abbreviations: aOR=adjusted odds ratio; CI=confidence interval; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin–norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants; OADs=other antidepressants.

Statistically significant results are in bold.

*Analyses restricted to women participating with only one pregnancy in the MoBa study (women with more than one participation in the MoBa study: 18.5% of the population). The non-exposed group is the reference group in all models. The disease comparison group includes women using no antidepressants during pregnancy but with symptoms of depression at both gestational weeks 17 and 30.

In all models the disease comparison group is adjusted for all confounders as SSRI/SNRI and TCA/OAD groups, except for maternal depressive symptoms ("SCL-5" at gestational week 17).

†Adjusted for: Maternal age, parity, BMI, educational level, NSAIDs and antithrombotic use, smoking, previous abortions and/or miscarriages and depressive symptoms.

‡Adjusted for: Maternal age, parity, BMI, educational level, NSAIDs use, smoking, previous abortions/miscarriages and depressive symptoms.

[§]Adjusted for: Maternal age, marital status, BMI, NSAIDs and antithrombotic use, smoking, previous abortions/miscarriages and depressive symptoms.
[¶]Adjusted for: Parity, BMI, smoking, previous abortions/miscarriages, educational level and depressive symptoms.
[††]Adjusted for: Maternal age, marital status, BMI, smoking, placenta previa, bleeding episode in first trimester, depressive symptoms.
[‡‡]Adjusted for: Maternal age, marital status, BMI, smoking, bleeding episode in first trimester, depressive symptoms.
[§§]Adjusted for: Maternal age, educational level, BMI, placenta previa, bleeding episode in first trimester, depressive symptoms.
[¶¶]Adjusted for: Maternal age, BMI, placenta previa, bleeding episode in 1st trimester, history of previous abortion/miscarriage, depressive symptoms.

Appendix 5b: Association (adjusted OR, 95% CI) between the exposure groups and postpartum hemorrhage among women with a single participation in the MoBa study* (n=46,704)

Postpartum hemorrhage (>500 ml blood loss at delivery)		**Any type of delivery No. (%) 6,649 (14.2)**		**Stratum 1: Cesarean section No. (%) 2,159 (4.6)**		**Stratum 2: Vaginal delivery No. (%) 4,490 (9.6)**	
	n	**n (%)**	**aOR† (95% CI)**	**n (%)**	**aOR† (95% CI)**	**n (%)**	**aOR† (95% CI)**
Non-exposed in pregnancy	45,068	6,570 (14.6)	Reference	2,128 (4.7)	Reference	4,442 (9.9)	Reference
Disease comparison	1,137	192 (16.9)	**1.18 (1.00;1.39)**	78 (6.9)	1.25 (0.92;1.70)	114 (10.0)	1.06 (0.86;1.31)
Non-exposed (week 30-childbirth)	45,461	6,634 (14.6)	Reference	2,153 (4.7)	Reference	4,481 (9.9)	Reference
SSRIs/SNRIs (week 30-childbirth)	95	11 (11.6)	0.64 (0.32;1.29)	4 (4.2)	1.29 (0.37;4.51)	7 (7.3)	0.53 (0.21;1.33)
TCAs/OADs (week 30-childbirth)	11	4 (36.4)	**4.18 (1.17;14.98)**	2 (18.2)	-	2 (18.2)	-

Abbreviations: aOR=adjusted odds ratio; CI=confidence interval; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin–norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants; OADs=other antidepressants.

Statistically significant results are in bold.

*Analyses restricted to women participating with only one pregnancy in the MoBa study (women with more than one participation in the MoBa study: 18.5% of the population). The non-exposed group is the reference group in all models. The disease comparison group includes women using no antidepressants during pregnancy but with symptoms of depression at both gestational weeks 17 and 30.

In all models the disease comparison group is adjusted for all confounders as SSRI/SNRI and TCA/OAD groups, except for maternal depressive symptoms ("SCL-8" at gestational week 30).

†Adjusted for: Maternal age, parity, BMI, educational level, smoking, coagulation defects, history of previous abortion/miscarriage, abruption placentae, placenta previa and maternal depressive symptoms.

APPENDICES 6a-6b:

Results of sensitivity analyses restricted to women with a single participation in the MoBa study or participating with only the first pregnancy in case of multiple participations (paper IV)

Appendix 6a: Association (adjusted OR, 95% CI) between the exposure groups and vaginal bleeding in early and midpregnancy among women with a single participation in the MoBa study or participating with the first pregnancy* (n=51,925)

Vaginal bleeding in early pregnancy		**Any type of bleeding No. (%) 10,342 (20.1)**		**Trace of blood No. (%) 6,232 (12.1)**		**Medium blood loss or clots No. (%) 3,700 (7.2)**		**>1 episode No. (%) 4,224 (8.2)**	
	n	**n (%)**	**aOR† (95% CI)**	**n (%)**	**aOR‡ (95% CI)**	**n (%)**	**aOR§ (95% CI)**	**n (%)**	**aOR¶ (95% CI)**
Non-exposed in pregnancy	50,172	10,071 (20.1)	Reference	6,087 (12.1)	Reference	3,588 (7.2)	Reference	4,107 (8.2)	Reference
Disease comparison	1,210	271 (22.4)	**1.17 (1.01;1.34)**	145 (12.0)	1.04 (0.87;1.25)	112 (9.3)	**1.31 (1.07;1.61)**	117 (9.7)	**1.26 (1.03;1.53)**
Non-exposed (1st trimester)	50,286	10,098 (20.1)	Reference	6,109 (12.1)	Reference	3,593 (7.1)	Reference	4,117 (8.2)	Reference
SSRIs/SNRIs (1st trimester)	395	83 (21.0)	0.90 (0.70;1.16)	50 (12.7)	0.95 (0.70;1.29)	29 (7.3)	0.83 (0.56;1.23)	32 (8.1)	0.80 (0.55;1.16)
TCAs/OADs (1st trimester)	34	7 (20.6)	0.93 (0.40;2.18)	3 (8.8)	0.67 (0.20;2.23)	4 (11.8)	1.44 (0.50;4.17)	4 (11.8)	1.29 (0.45;3.73)
Vaginal bleeding in mid pregnancy		**Any type of bleeding No. (%) 4,884 (9.5)**		**Trace of blood No. (%) 3,181 (6.2)**		**Medium or large blood loss No. (%) 1,610 (3.1)**		**>1 episode No. (%) 1,416 (2.8)**	
	n	**n (%)**	**aOR†† (95% CI)**	**n (%)**	**aOR‡‡ (95% CI)**	**(%)**	**aOR§§ (95% CI)**	**n (%)**	**aOR¶¶ (95% CI)**
Non-exposed in pregnancy	50,172	4,735 (9.4)	Reference	3,087 (6.2)	Reference	1,559 (3.1)	Reference	1,371 (2.7)	Reference
Disease comparison	1,210	149 (12.3)	**1.30 (1.07;1.57)**	94 (7.8)	**1.26 (1.00;1.57)**	51 (4.2)	1.30 (0.96;1.75)	45 (3.7)	1.32 (0.96;1.82)
Non-exposed (2nd trimester)	50,492	4,767 (9.4)	Reference	3,110 (6.2)	Reference	1,567 (3.1)	Reference	1,379 (2.7)	Reference
SSRIs/SNRIs (2nd trimester)	199	20 (10.1)	0.82 (0.49;1.36)	13 (6.5)	0.87 (0.47;1.59)	7 (3.5)	0.81 (0.37;1.75)	8 (4.0)	1.20 (0.57;2.55)
TCAs/OADs (2nd trimester)	24	3 (12.5)	0.97 (0.26;3.59)	3 (12.5)	1.80 (0.50;6.46)	-	-	-	-

Abbreviations: aOR=adjusted odds ratio; CI=confidence interval; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin–norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants; OADs=other antidepressants.

Statistically significant results are in bold.

*The sample comprises women who participated only once in the MoBa study, and for women with multiple participations in the study, only the first pregnancy was included. The non-exposed group is the reference group in all models. The disease comparison group includes women using no antidepressants during pregnancy but with symptoms of depression at both gestational weeks 17 and 30.

In all models the disease comparison group is adjusted for all confounders as SSRI/SNRI and TCA/OAD groups, except for maternal depressive symptoms ("SCL-5" at gestational week 17).

†Adjusted for: Maternal age, parity, BMI, educational level, NSAIDs and antithrombotic use, smoking, previous abortions and/or miscarriages and depressive symptoms.

‡Adjusted for: Maternal age, parity, BMI, educational level, NSAIDs use, smoking, previous abortions/miscarriages and depressive symptoms.

§Adjusted for: Maternal age, marital status, BMI, NSAIDs and antithrombotic use, smoking, previous abortions/miscarriages and depressive symptoms.
¶Adjusted for: Parity, BMI, smoking, previous abortions/miscarriages, educational level and depressive symptoms.
††Adjusted for: Maternal age, marital status, BMI, smoking, placenta previa, bleeding episode in first trimester, depressive symptoms.
‡‡Adjusted for: Maternal age, marital status, BMI, smoking, bleeding episode in first trimester, depressive symptoms.
§§Adjusted for: Maternal age, educational level, BMI, placenta previa, bleeding episode in first trimester, depressive symptoms.
¶¶Adjusted for: Maternal age, BMI, placenta previa, bleeding episode in 1st trimester, history of previous abortion/miscarriage, depressive symptoms.

Appendix 6b: Association (adjusted OR, 95% CI) between exposure groups and postpartum hemorrhage among women with a single participation in the MoBa study or participating with the first pregnancy (n=51,925)*

Postpartum hemorrhage (>500 ml blood loss at delivery)		**Any type of delivery No. (%) 7,632(14.7)**		**Stratum 1: Cesarean section No. (%) 2,447 (4.7)**		**Stratum 2: Vaginal delivery No. (%) 5,185 (10.0)**	
	n	**n (%)**	**aOR† (95% CI)**	**n (%)**	**aOR† (95% CI)**	**n (%)**	**aOR† (95% CI)**
Non-exposed in pregnancy	50,172	7,346 (14.6)	Reference	2,334 (4.7)	Reference	5,012 (10.0)	Reference
Disease comparison	1,210	200 (16.5)	1.16 (0.98;1.36)	81 (6.7)	1.20 (0.89;1.62)	119 (9.8)	1.04 (0.84;1.27)
Non-exposed (week 30-childbirth)	50,598	7,414 (14.7)	Reference	2,360 (4.66)	Reference	5,054 (9.99)	Reference
SSRIs/SNRIs (week 30-childbirth)	106	14 (13.2)	0.79 (0.43;1.45)	4 (3.77)	0.98 (0.30;3.25)	10 (9.43)	0.80 (0.38;1.67)
TCAs/OADs (week 30-childbirth)	11	4 (36.4)	**4.21 (1.18;15.07)**	2 (18.18)	-	2 (18.18)	-

Abbreviations: aOR=adjusted odds ratio; CI=confidence interval; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin–norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants; OADs=other antidepressants.

Statistically significant results are in bold.

*The sample comprises women who participated only once in the MoBa study, and for women with multiple participations in the study, only the first pregnancy was included. The non-exposed group is the reference group in all models. The disease comparison group includes women using no antidepressants during pregnancy but with symptoms of depression at both gestational weeks 17 and 30.

In all models the disease comparison group is adjusted for all confounders as SSRI/SNRI and TCA/OAD groups, except for maternal depressive symptoms ("SCL-8" at gestational week 30).

†Adjusted for: Maternal age, parity, BMI, educational level, smoking, coagulation defects, history of previous abortion/miscarriage, abruption placentae, placenta previa and maternal depressive symptoms.

APPENDICES 7a-7b:

Results of sensitivity analyses by utilization of GEE analyses (paper IV)

Appendix 7a: Association (adjusted OR, 95% CI) between the exposure groups and vaginal bleeding in early and midpregnancy according to GEE analyses (n=57,279)*

Vaginal bleeding in early pregnancy		**Any type of bleeding No. (%) 11,456 (20.0)**		**Trace of blood No. (%) 6,869 (12.0)**		**Medium blood loss or clots No. (%) 4,136 (7.2)**		**>1 episode No. (%) 4,704 (8.2)**	
	n	**n (%)**	**aOR† (95% CI)**	**n (%)**	**aOR‡ (95% CI)**	**n (%)**	**aOR§ (95% CI)**	**n (%)**	**aOR¶ (95% CI)**
Non-exposed in pregnancy	55,411	11,037 (19.9)	Reference	6,631 (12.0)	Reference	3,974 (7.2)	Reference	4,524 (8.2)	Reference
Disease comparison	1,282	293 (22.9)	**1.22 (1.06;1.39)**	158 (12.3)	1.10 (0.93;1.30)	121 (9.4)	**1.32 (1.09;1.60)**	130 (10.1)	**1.33 (1.10;1.60)**
Non-exposed (1st trimester)	55,533	11,066 (19.9)	Reference	6,654 (12.0)	Reference	3,980 (7.2)	Reference	4,535 (8.2)	Reference
SSRIs/SNRIs (1st trimester)	427	90 (21.1)	0.91 (0.72;1.16)	54 (12.6)	0.96 (0.72;1.30)	31 (7.3)	0.79 (0.28;2.26)	35 (8.2)	0.81 (0.57;1.17)
TCAs/OADs (1st trimester)	37	7 (18.9)	0.83 (0.35;1.94)	3 (8.1)	0.61 (0.18;2.07)	4 (10.8)	1.25 (0.85;1.83)	4 (10.8)	1.16 (0.40;3.41)
Vaginal bleeding in mid pregnancy		**Any type of bleeding No. (%) 5,395 (9.4)**		**Trace of blood No. (%) 3,495 (6.1)**		**Medium or large blood loss No. (%) 1,798 (3.1)**		**>1 episode No. (%) 1,580 (2.8)**	
	n	**n (%)**	**aOR†† (95% CI)**	**n (%)**	**aOR‡‡ (95% CI)**	**(%)**	**aOR§§ (95% CI)**	**n (%)**	**aOR¶¶ (95% CI)**
Non-exposed in pregnancy	55,411	5,176 (9.3)	Reference	3,355 (6.1)	Reference	1,724 (3.1)	Reference	1,512 (2.7)	Reference
Disease comparison	1,282	158 (12.3)	**1.28 (1.07;1.55)**	98 (7.6)	**1.24 (1.00;1.55)**	56 (4.4)	1.20 (0.90;1.60)	49 (3.8)	1.33 (0.98;1.81)
Non-exposed (2nd trimester)	55,750	5,212 (9.3)	Reference	3,379 (6.1)	Reference	1,735 (3.1)	Reference	1,522 (2.7)	Reference
SSRIs/SNRIs (2nd trimester)	222	22 (9.9)	0.89 (0.55;1.42)	15 (6.8)	0.97 (0.56;1.70)	7 (3.2)	0.83 (0.53;1.29)	9 (4.1)	1.09 (0.71;1.68)
TCAs/OADs (2nd trimester)	25	3 (12.0)	0.96 (0.26;3.50)	3 (12.0)	1.73 (0.50;5.95)	-	-	-	-

Abbreviations: GEE=Generalized Estimating Equations; aOR=adjusted odds ratio; CI=confidence interval; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin–norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants; OADs=other antidepressants.

Statistically significant results are in bold.

*The non-exposed group is the reference group in all models. The disease comparison group includes women using no antidepressants during pregnancy but with symptoms of depression at both gestational weeks 17 and 30.

In all models the disease comparison group is adjusted for all confounders as SSRI/SNRI and TCA/OAD groups, except for maternal depressive symptoms ("SCL-5" at gestational week 17).

†Adjusted for: Maternal age, parity, BMI, educational level, NSAIDs and antithrombotic use, smoking, previous abortions and/or miscarriages and depressive symptoms.

‡Adjusted for: Maternal age, parity, BMI, educational level, NSAIDs use, smoking, previous abortions/miscarriages and depressive symptoms.

§Adjusted for: Maternal age, marital status, BMI, NSAIDs and antithrombotic use, smoking, previous abortions/miscarriages and depressive symptoms.

¶Adjusted for: Parity, BMI, smoking, previous abortions/miscarriages, educational level and depressive symptoms.
††Adjusted for: Maternal age, marital status, BMI, smoking, placenta previa, bleeding episode in first trimester, depressive symptoms.
‡‡Adjusted for: Maternal age, marital status, BMI, smoking, bleeding episode in first trimester, depressive symptoms.
§§Adjusted for: Maternal age, educational level, BMI, placenta previa, bleeding episode in first trimester, depressive symptoms.
¶¶Adjusted for: Maternal age, BMI, placenta previa, bleeding episode in 1st trimester, history of previous abortion/miscarriage, depressive symptoms.

Appendix 7b: Association (adjusted OR, 95% CI) between exposure groups and postpartum hemorrhage according to GEE analyses (n=57,279)*

Postpartum hemorrhage (>500 ml blood loss at delivery)		**Any type of delivery No. (%) 8,242 (14.4)**		**Stratum 1: Cesarean section No. (%) 2,607 (4.6)**		**Stratum 2: Vaginal delivery No. (%) 5,635 (9.8)**	
	n	**n (%)**	**aOR† (95% CI)**	**n (%)**	**aOR† (95% CI)**	**n (%)**	**aOR† (95% CI)**
Non-exposed in pregnancy	55,411	7,937 (14.3)	Reference	2,485 (4.5)	Reference	5,452 (9.8)	Reference
Disease comparison	1,282	211 (16.5)	1.14 (0.98;1.34)	84 (6.6)	1.18 (0.89;1.58)	127 (9.9)	1.05 (0.86;1.28)
Non-exposed (week 30-childbirth)	55,862	8,009 (14.3)	Reference	2,515 (4.50)	Reference	5,494 (9.83)	Reference
SSRIs/SNRIs (week 30-childbirth)	123	18 (14.6)	0.97 (0.55;1.69)	6 (4.88)	1.47 (0.53;4.13)	12 (9.76)	0.90 (0.44;1.83)
TCAs/OADs (week 30-childbirth)	12	4 (33.3)	**3.75 (1.07;13.21)**	2 (16.67)	-	2 (16.67)	-

Abbreviations: GEE=Generalized Estimating Equations; aOR=adjusted odds ratio; CI=confidence interval; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin–norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants; OADs=other antidepressants.

Statistically significant results are in bold.

*The non-exposed group is the reference group in all models. The disease comparison group includes women using no antidepressants during pregnancy but with symptoms of depression at both gestational weeks 17 and 30.

In all models the disease comparison group is adjusted for all confounders as SSRI/SNRI and TCA/OAD groups, except for maternal depressive symptoms ("SCL-8" at gestational week 30).

†Adjusted for: Maternal age, parity, BMI, educational level, smoking, coagulation defects, history of previous abortion/miscarriage, abruption placentae, placenta previa and maternal depressive symptoms.