Diabetes, preeclampsia and infant death –

The associations with placental weight

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Lørenskog 2018

AKERSHUS UNIVERSITY HOSPITAL

UiO : Institute of Clinical Medicine
University of Oslo

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-8377-363-7

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

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Acknowledgements

The present work has been carried out at Department of Obstetrics and Gynecology, Akershus University Hospital and the Institute of Clinical Medicine, University of Oslo with funding from the South-Eastern Regional Health Authority in Norway. I am grateful for the financial support.

First of all, I would like to thank my primary supervisor, Professor Anne Eskild. It has been a great privilege to have a supervisor with such extensive knowledge when working in the comprehensive field of epidemiology. You gave me thorough answers when I asked naïve questions and you showed me patience when I needed time to understand. Your enthusiasm for research on women's health has been a great motivation trough these years. Thank you.

Second, Professor Lars Vatten, my secondary supervisor, your epidemiologic knowledge has guided me through some tough questions. Thank you for your contributions.

When working day in and day out with one study question, the opportunity of listening to what goes on in the Department of Obstetrics and Gynecology has been a welcomed break. I have also appreciated the opportunity of presenting our research to the Department and receiving questions and comments leading us to further on in our research. Dr. Pernille Schjønsby and the staff at the Department of Obstetrics and Gynecology, Akershus University Hospital, thank you.

I am very thankful to my research fellows at the Department of Obstetrics and Gynecology. I have learned so much during these years and my knowledge could not have expanded in the same manner without you. Dr. Sandra Larsen, thank you for sharing successes and frustrations. Your temperament, work ethic and perseverance have been valuable to me. Dr. Camilla Haavaldsen, co-author of all three papers included in this thesis. Thank you for sharing your knowledge and experience with me.

To Dr. Ellen Marie Strøm-Roum, you taught me SPSS while being sleep deprived, an impossible task to most others. Thank you for critically revising my thesis. I am thankful for your ability of putting things into perspective, and laughing about it. Your clinical experience has been

invaluable to me. I will never forget the sound of your calm voice and the feeling of safety while undergoing my second cesarean section. Thank you.

To my friends, thank you for reminding me that there is a world outside of Medicine and thank you for cheering me on!

My dear parents, Mamma and Pappa, thank you for loving me and for always supporting me. I am grateful for you showing me that one can never have enough knowledge.

To Halvard, thank you for being interested, thank you for being interesting and thank you for arguing.

Marius, I love you. Thank you for loving me.

To Helmer and Vilma, you have given me the joy of motherhood. Although you don't understand it now, your contribution to this thesis has been substantial. You have given me the best reason to work systematically and efficiently in order to spend as much time as possible with you. I love you.

Lørenskog, August 2018
Johanne Dypvik

Abbreviations

CI	Confidence interval
GLUT	Glucose transporters
hCG	Human chorionic gonadotropin
MBRN	Medical Birth Registry of Norway
OR	Odds ratio
SD	Standard deviation

List of papers

I. Preeclampsia in pregnancies with and without diabetes: the associations with placental weight. A population study of 655 842 pregnancies. Dypvik J, Strøm–Roum EM, Haavaldsen C, Vatten LJ, Eskild A. Acta Obstet Gynecol Scand. 2016;95:217–24.

II. Placental weight in the first pregnancy and risk for preeclampsia in the second pregnancy: A population–based study of 186 859 women. Dypvik J and Larsen S, Haavaldsen C, Jukic AM, Vatten LJ, Eskild A. Eur J Obstet Gynecol Reprod Biol. 2017;214:184–189.

III. Placental weight and risk for infant death. Dypvik J, Larsen S, Haavaldsen C, Eskild A. *Submitted May 2018.*

1 Introduction

Fetal growth is dependent on exchange of gases and nutrients with the mother by the placenta. Insufficient transfer of oxygen and nutrients from the placenta to the fetus has been suggested to be a cause of fetal growth restriction and low birthweight.[1,2] A compound measure of placental to birthweight ratio has been assessed in order to estimate how much birthweight a given placental weight was expected to produce, and if this compound measure could provide information on the risk of adverse outcomes.[3-6] Consequently, high placental to birthweight ratio has been associated with an increased risk of low Apgar–score at birth, admission to a neonatal intensive care unit, hypertension in adulthood and death from cardiovascular disease.[3,4,7] On the other hand, low placental to birthweight ratio has been associated with a decreased risk of low Apgar–score at birth, admission to the neonatal intensive care unit and cesarean section,[3] but with an increased risk of fetal death and cerebral palsy.[8,9] However, the associations found for placental to birthweight ratio do not necessarily reflect the associations with the placental weight itself.

Placental weight has been studied previously, and studies have found associations of high maternal age, increased parity, high maternal body mass index, maternal diabetes mellitus and term preeclampsia with high placental weight.[10-19] High placental weight has also been associated with adverse outcomes such as low Apgar–score at birth and neonatal morbidity.[20-22] On the other hand, maternal smoking, chronic hypertension and preeclampsia have been associated with low placental weight,[18,19,23,24] and low placental weight has been associated with fetal death, neonatal morbidity, cerebral palsy in childhood and the development of cardiovascular disease in adulthood.[8,9,21,22,25,26]

Thus, we hypothesize that placental weight is an independent indicator of the uteroplacental function. We aimed to further explore the variation in placental weight and how placental weight may be associated with maternal disease (preeclampsia and diabetes) and consequences for the infant (infant death).

2 Background

2.1 Birthweight

Globally, the neonate is routinely measured and weighed shortly after birth. This makes the variable of birthweight readily assessable to research, as well as the clinical value of birthweight to the individual offspring. The monitoring of birthweight at a population level is an important assessment of public health.

The developmental origin of health and disease (DOHaD) is based on a theory in which the development of organs and organ systems may change to accommodate to exposures during intrauterine life.[1,27,28] If the exposures occur at a critical time during organ development, the change in organ structure may influence organ function throughout offspring life. For instance, poor maternal nutrition has been suggested to be a cause of fetal growth restriction and, consequently, low offspring birthweight.[1,29] Low birthweight has been associated with short–term consequences such as fetal and infant death,[30-34] and long–term consequences such as cardiovascular disease in adulthood, diabetes mellitus and end–stage renal disease.[35-39] Women born with low birthweight have an increased risk of hypertension during pregnancy.[40] However, high birthweight has also been associated with short– and long–term consequences for the offspring.[33,41] Thus, knowledge about factors that influence birthweight is important both at a population level and for the individual offspring.

2.1.1 Factors associated with birthweight

The most recognized cause of variation in birthweight is the gestational age at birth.[42,43] The mean birthweight is around 650 grams in gestational week 24 and around 3600 grams in gestational week 40.[43] Birthweight also varies with offspring sex, and boys are reported to have a higher birthweight than girls.[42,43] Besides gestational age at birth and offspring sex, birthweight has been associated with numerous maternal, paternal or pregnancy–related factors. A selection of factors is presented in Table 2–1.

Table 2–1. Factors associated with birthweight.

Low birthweight	High birthweight
High and low maternal age[13,44]	
High paternal age[45]	
	Increased parity[11,12,46]
Low body mass index[47]	High body mass index[47,48]
Maternal smoking[11,12]	
Assisted reproductive technology[49]	
Maternal pregestational diabetes mellitus[50,51]	Maternal diabetes mellitus[11,17,48,52-55]
High and low hemoglobin concentrations[56-59]	Low hemoglobin concentrations[11]
Preeclampsia[60-63]	Term preeclampsia[62,63]

2.1.2 Birthweight and associated outcomes for the offspring

Birthweight has been proposed as a marker of offspring health[29] and birthweight has been associated with numerous short– and long–term outcomes. A selection of outcomes is presented in Table 2–2.

Table 2–2. Birthweight and associated outcomes for the offspring.

Low birthweight	High birthweight
Fetal death[8,64]	
Low Apgar–score[31]	
Neonatal morbidity[31,65]	
	Shoulder dystocia[66]
Infant death[32-34,65,67,68]	Neonatal death in term born infants[33,69]
Cerebral palsy in childhood[70]	Cerebral palsy in childhood[70]
Hearing loss in childhood[71]	
Development of hypertension during pregnancy [40]	
Development of preeclampsia[72]	
Development of diabetes mellitus type–2[36,37]	

Low birthweight	High birthweight
Development of cardiovascular disease[35]	
Development of end stage renal disease[39]	
Death from all causes[35,38]	Death from cancer in men[38]

2.2 Placental weight

During pregnancy the fetus is dependent on exchange of gases and nutrients with the mother by the placenta. After birth of the offspring, the placenta detaches from the uterus (*decidua*), and is usually delivered with membranes and umbilical cord intact.[73] Most of the variation in placental weight remains unexplained.

2.2.1 Factors associated with placental weight

In pregnancies reported the Medical Birth Registry of Norway, placental weight at birth varies from 100 grams to more than 2000 grams.[74] The most important factor that influences this variation is the gestational age at birth. Placental weight increases with gestational age,[74-77] and in girls the mean placental weight is 255 grams in births at gestational week 24 and 678 grams in births at gestational week 40.[74] Placental weight is higher in boys as compared to girls[74,75] and in boys, the mean placental weight is 267 grams in births at gestational week 24 and 690 grams in births at gestational week 40.[74]

Placental weight has also been associated with maternal, paternal and pregnancy–related factors. A selection of factors is presented in Table 2–3.

2.2.2 Placental weight and associated outcomes for the offspring

Placental weight has been associated with short– and long–term consequences for the offspring. A selection of outcomes is presented in Table 2–4.

Table 2–3. Factors associated with placental weight.

Low placental weight	No association	High placental weight
	Maternal age[78]	High maternal age[13]
		High paternal age[79]
		Increased parity[10-12]
		High body mass index[11,14,15]
Maternal smoking[18,24]	Maternal smoking[11,12,80-82]	
Chronic hypertension[18]		
		Assisted reproductive technology[49]
		Maternal diabetes mellitus[16-18,53,83]
Low hemoglobin concentrations[84]	Hemoglobin concentrations[12,85]	Low hemoglobin concentrations[14,18,24,86]
		Chorioamnionitis[18]
Preeclampsia[18,19,23]	Preeclampsia[61,87]	Term preeclampsia[19]

Table 2–4. Placental weight and associated outcomes for the offspring.

Low placental weight	No association	High placental weight
Small for gestational age offspring[25,61,88]		
Fetal death[8,21,25]		
		Low Apgar–score[20,21]
Neonatal morbidity[22]		Neonatal morbidity[21,22]
	Neonatal death[21]	
Male genital anomalies[89]		
Cerebral palsy in childhood[9]		
Development of cardiovascular disease[26]		
	Sudden cardiac death[90]	

2.3 Placental to birthweight ratio

The placental to birthweight ratio is defined as the placental weight divided by birthweight in grams. The placental to birthweight ratio has been suggested to express the efficiency of the placenta independent of the absolute placental weight.[5,6,91] Thus, a high placental to birthweight ratio is thought to represent a placenta that has produced less birthweight than expected according to the placental weight. Knowledge of factors that influence the placental to birthweight ratio is important both at a population level and for the individual offspring, as the placental to birthweight ratio has been suggested as an indicator of adverse outcomes for the offspring.[3-6]

2.3.1 Factors associated with the placental to birthweight ratio

Placental and fetal growth curves are not identical. The fetal growth curve is reported as being gentle in the first trimester, increases in the second trimester, and is steepest during the third trimester.[92,93] The placental growth curve is believed to be at its steepest in the first and second trimesters and levels off in the third trimester.[74,75] Thus, the placental to birthweight ratio decreases with increasing gestational age and low gestational age at birth has been associated with a high placental to birthweight ratio.[11,74,75,94] The placental to birthweight ratio is also influenced by fetal sex, and girls are reported to have higher placental to birthweight ratios as compared to boys.[11,74,75,94]

Placental to birthweight ratio has been associated with numerous maternal, paternal or pregnancy–related factors. A selection of factors is presented in Table 2–5.

2.3.2 Placental to birthweight ratio and associated outcomes for the offspring

Placental to birthweight ratio has been associated with both short– and long–term outcomes for the offspring, and placental to birthweight ratio has previously been suggested as an indicator of short– and long–term consequences for the offspring.[3-6] A selection of outcomes is presented in Table 2–6.

Table 2–5. Factors associated with placental to birthweight ratio.

No association	High placental to birthweight ratio
	High maternal age[13]
	High paternal age[79]
Parity[11]	Increased parity[5]
	High body mass index[5,11]
	Maternal smoking[5,11,82]
	Assisted reproductive technology[49]
Maternal diabetes mellitus[11]	Maternal diabetes mellitus[5,16,17]
	Low hemoglobin concentrations[5,11,24]
	Preeclampsia[5]

Table 2–6. Placental to birthweight ratio and associated outcomes for the offspring.

Low placental to birthweight ratio	High placental to birthweight ratio
Small for gestational age born at term[5]	Small for gestational age born preterm[5]
Fetal death[8]	Preterm fetal death[8]
	Low Apgar–score[3,20]
	Neonatal morbidity[3]
Cerebral palsy in childhood[9]	Cerebral palsy in preterm born infants[9]
	Development of diabetes mellitus type–2[37]
	Development of cardiovascular disease[4,26]
	Death from cardiovascular disease[7]

2.4 Placenta

2.4.1 Development and growth

After fertilization of the ovum by spermatozoa, through the initial stages of embryogenesis, a blastocyst is formed.[73] The blastocyst consists of two layers of cells:

– The inner cell mass that will differentiate into embryoblasts, and form the fetus.

– The outer cell layer that will differentiate into trophoblasts, and form the placenta.

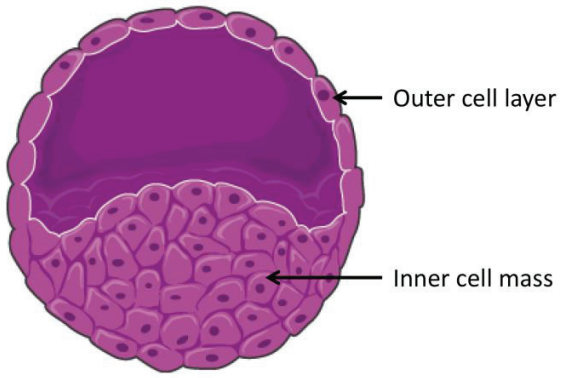

Figure 2–1. The blastocyst.

Adapted from https://smart.servier.com/smart_image/cellular–culture–5/

The formation of the placenta starts at the implantation of the blastocyst into the endometrium. In most successful spontaneous pregnancies, implantation occurs 8–10 days after fertilization.[95] At this stage of the menstrual cycle, the *corpus luteum* in the ovary has produced progesterone and estrogen that stimulates proliferation of the endometrium. The endometrium is rich in endometrial glands and spiral arteries, and is receptive to the blastocyst.

The outer layer of the blastocyst adheres to the primed endometrium and the trophoblasts invade the endometrium through cell proliferation. The trophoblasts differentiate into an outer layer of syntcytiotrophoblast and an inner layer of cytotrophoblasts. The cytotrophoblasts are single nucleated cells with cell borders, while the syncytiotrophoblast is a multinucleated cell mass that becomes a continuous syncytial lining.

When the blastocyst is enclosed within the endometrium, the trophoblasts continue to invade further. Lacunae can be observed in the syncytiotrophoblast later in the process. Eventually, these

lacunae are filled with maternal blood from the superficial endometrial capillaries that have been invaded by trophoblasts.[96] The development of the placenta continues as the cytotrophoblast primary villi protrude into the lacunae.[97] Some of these primary villi protrude through the syncytiotrophoblast and anchor the embryo to the endometrium, the anchoring villi. These anchoring villi establish the pole of the embryo that will form the placenta, the *chorion frondosum.* The endometrium directly below the *chorion frondosum* becomes the maternal side of the placenta, called the *decidua basalis*. At the opposite pole of the embryo, the trophoblastic villi degenerate and become the avascular *chorion laeve*.

Around 20–24 days after fertilization, the primary villi are invaded by mesenchymal cells derived from the inner cell mass of the blastocyst and the villi are now called secondary villi. Within days, the mesenchymal cells establish fetoplacental circulation by vasculogenesis.[97] The villi are now called tertiary villi.

As the invasion of the *decidua basalis* continues, the vascular endothelium in the spiral arteries is penetrated and eroded by trophoblasts. The spiral arteries are transformed from narrow, high–resistance uterine arteries into dilated, low–resistance uteroplacental arteries without vasomotor control.[98] However, 8–10 weeks after fertilization the trophoblasts form clots that block the entrance of maternal blood into the intervillous space. Thus, the embryogenesis and the initial development of the placenta takes place in a hypoxic environment.[98] At the end of the first trimester, the blood clots disintegrate and maternal arterial blood enters the intervillous space and surrounds the chorionic villi.[99]

The placenta grows as the villi continue to branch and become numerous.[73] The syncytiotrophoblast layer overlying the villi becomes thinner, and the distance between fetal blood and maternal blood is reduced. Each branch of the villi contains a fetal arteriovenous capillary system.[97] In the second trimester of pregnancy, there are three cell layers between the fetal blood and the maternal blood: the fetal vascular endothelium, villous connective tissue and the syncytium covering the intervillous space. This permits the exchange of oxygen, carbon dioxide, nutrients and hormones between maternal and fetal blood (Figure 2–2).

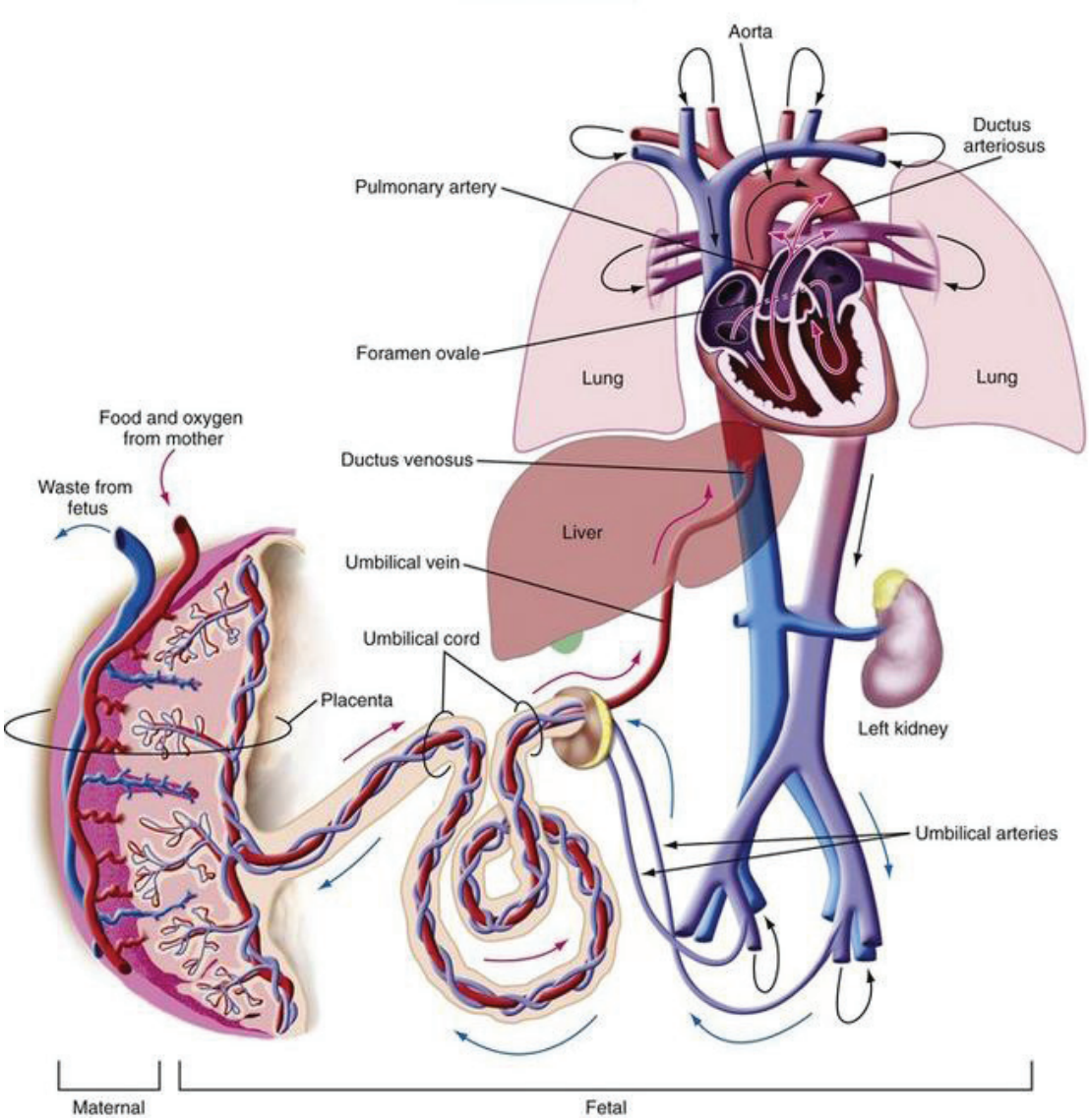

Figure 2–2. Fetoplacental circulation.

Adapted from https://clinicalgate.com/fetal–intervention–and–the–exit–procedure/

The parturition of the placenta, the third stage of labor, is initiated by birth of the offspring. The uterus spontaneously contracts due to diminished content.[73] The sudden decrease in uterine size causes deformation of the placenta and increased tension at the site of implantation. The placenta detaches at the weakest site of the *decidua*, the *stratum spongiosum.* Thus, the entire functional unit of the placenta is usually delivered with membranes and umbilical cord intact. This leaves the uterus with a endometrial lining similar to what is found after menstrual bleeding, although with a retroplacental hematoma at the site of implantation.

2.4.2 Placental functions

The placenta consists of functional tissue that ensures gas exchange, nutrient extraction and the production of growth regulating hormones. The placenta also acts as a barrier to protect the fetus from xenobiotics, infections and rejection by the maternal immune system.[73,100]

Gas exchange. Oxygen and carbon dioxide are exchanged as maternal arterial blood with a high oxygen concentration and low carbon dioxide concentration enters the intervillous space and wash over the villi containing fetal blood with a low oxygen concentration and high carbon dioxide concentration.[101] The countercurrent flow of maternal and fetal blood permits efficient passive diffusion of oxygen and carbon dioxide across the fetoplacental membrane.

The development of the placenta and fetus takes place in a hypoxic environment during the first trimester of pregnancy.[98,99] However, in the second and third trimester of pregnancy, oxygen becomes more important for placental and fetal growth.[102] Maternal hypoxia occurring in the second or third trimester of pregnancy may reduce the oxygen supply to the fetus and result in adverse pregnancy outcomes.[102] Hypoxia during pregnancy may be divided into three categories:[102,103]

- Preplacental hypoxia, recognized by reduced oxygen content in maternal blood, decreased maternal oxygen uptake or reduced oxygen supply to the fetus as seen in in pregnancies with preexisting maternal cardiovascular disease, maternal anemia, maternal diabetes mellitus or maternal smoking. Conditions causing preplacental hypoxia have been associated with changes in the placental structure that increase the oxygen supply to the fetus, such as increased trophoblast proliferation and increased placental angiogenesis.[24,104-107]
- Uteroplacental hypoxia, recognized by restricted flow of blood into placental tissues due to the occlusion of uterine arteries, defective trophoblast invasion or defective fetoplacental perfusion as seen in pregnancies with diabetes mellitus and preeclampsia. Conditions causing uteroplacental hypoxia have been associated with mechanisms that reduce the fetal oxygen demand, such as fetal growth restriction, preterm birth and fetal death.[55,107-112]

- Postplacental hypoxia, recognized by obstruction of the fetal circulation as seen in pregnancies with progressive fetal cardiac failure or congenital malformations. It is not clear whether conditions causing postplacental hypoxia induce placental compensatory mechanisms or if they have common underlying causes. However, fetuses with congenital malformations appear to have a deviating growth pattern as compared to fetuses without malformations,[113] and fetuses with congenital malformations have an increased risk of fetal death.[114]

Nutrient transport. Nutrients necessary for fetal development and growth are transported from maternal blood across the fetoplacental membrane with transport proteins, receptors, enzymes or endocytosis. Glucose is the primary source of energy for fetal growth. The glucose concentration of fetal blood is approximately 70% of the glucose concentration of maternal blood.[115] Glucose is transported from the maternal blood via glucose transport proteins expressed by the synctiotrophoblast.[116]

In the family of facilitated–diffusion glucose transporters (GLUTs), several isoforms have been found in placental tissues, but the most abundant isoform is GLUT–1.[116,117] GLUT–1 is found both on the microvillous membrane and on the basal membrane (facing the intervillous space) of the syncotiotrophoblast.[116] The expression of GLUT–1 appears to be higher in the microvillous membrane than in the basal membrane.[116] The expression of GLUT–1 in the basal membrane increases from the second to the third trimester, and contributes to fetal growth by increasing the glucose supply.[117] In pregnancies with diabetes mellitus, the expression and function of GLUT–1 is up–regulated in the basal membrane of the syncytiotrophoblast.[116,118] This facilitates a greater transport of glucose across the fetoplacental membrane in pregnancies with maternal diabetes mellitus as compared to non–diabetic pregnancies. In contrast, the expression and function of GLUT–1 is down–regulated in the basal membrane in pregnancies with chronic hypoxia.[117]

Lipids and amino acids are also required for fetal growth. Both amino acids and lipids are transported across the fetoplacental membrane via complex transport protein systems.[119] The transport of amino acids and lipids will not be further elaborated in this thesis.

Hormone production. The placenta produces hormones essential to placental and fetal growth. The syncytiotrophoblast produces two major hormones: human chorionic gonadotropin (hCG) and human placental lactogen. HCG promotes angiogenesis[96,120] and decreased serum levels of hGC have been associated with the development of preeclampsia.[121] HCG also promotes the production of relaxin[73] and stimulates the *corpus luteum* to maintain the production of progesterone and estradiol until the production of progesterone and estradiol by the placenta is sufficient. Both progesterone and estradiol act on maternal tissues to maintain pregnancy. After six to seven weeks of gestation, the placenta takes over the production of progesterone and estrogen from the *corpus luteum*.[73]

The biological functions of the human placental lactogen (hPL, also called chorionic somatomammotropin, hCS) comprise the promotion of vasculogenesis and angiogenesis of the fetal vasculature, maternal lipolysis to provide free fatty acids, inducing hypertrophy of the β–cells in the pancreas and promotion of insulin resistance in the second and third trimester.[73,122] Prolactin, produced in the *decidua basalis*, also induces hypertrophy of the β–cells in the pancreas, in addition to promoting angiogenesis and maintaining the amniotic fluid volume.[73,123]

The trophoblasts also synthesize the placental growth factor (PlGF) and vascular endothelial growth factor (VEGF). Both hormones are potent angiogenic factors, the latter also a vasculogenic factor.[96,97,106,124] Decreased serum levels of the placental growth factor have been linked to the development of preeclampsia.[125-127]

2.4.3 Indicators of placental function

Although placental functions have been explained to some extent, no gold standard for the assessment of placental functions exists.

During pregnancy, blood flow velocity in the umbilical arteries has been suggested as an indicator of the placental function (Figure 2–2). The umbilical vessels are not innervated. Thus, blood flow in the umbilical arteries may reflect the fetoplacental circulatory impedance. Doppler sonography detects the blood flow velocity and is therefore used to detect the presence and direction of blood flow, as well as volume and impedance. Accordingly, absent or reversed end–

diastolic velocity through the umbilical artery has been reported to predict adverse fetal outcomes in high–risk pregnancies.[128,129] Unfortunately, the same sonographic parameter has been unable to predict adverse fetal outcomes in low–risk pregnancies.[130] Various biochemical markers have also been suggested to reflect the placental function. However, none have shown consistent results in both high– and low–risk pregnancies.[131-133]

The placenta mainly consists of functional tissue and its purpose is to ensure fetal growth and survival. Accordingly, birthweight has been suggested as an indicator of placental function.[29] However, placental weight is closely related to birthweight and is a determinant for the achieved birthweight.[134-136] Thus, it is reasonable to assume that placental weight is also associated with placental function. Further, it is reasonable to assume that placental weight may serve as an indicator of placental function at a population level.

Other measurements of the placenta after parturition have also been suggested as indicators of placental function.[137] Accordingly, adverse outcomes such as being born small for gestational age, cardiovascular disease in adulthood and sudden cardiac death have been associated with the area of the placenta, length and breadth of the placenta, placental disc thickness and umbilical cord length.[90,138-142] However, these measurements have not been proven to serve as more reliable indicators of adverse outcomes than placental weight. Thus, until a gold standard for assessment of placental function is established, placental weight after parturition may serve as an indicator of placental function.

3 Background to the present studies

3.1 Diabetes mellitus

3.1.1 Definition and prevalence

Diabetes mellitus (hereinafter referred to as diabetes) is a group of metabolic disorders that are characterized by hyperglycemia caused by a lack of insulin secretion, insulin resistance or both.[143] Although the biological mechanisms behind the various subtypes of diabetes differ, the main treatment goal for all diabetic patients is glycemic control. The chronic hyperglycemia seen in diabetic patients predisposes to microvascular and macrovascular damage, and complications of diabetes comprise retinopathy, neuropathy, nephropathy, cardiovascular and cerebrovascular complications.[144,145] During pregnancy, diabetes has been associated with both maternal and fetal complications.[112,146] Maternal diabetes influences placental development and function,[105,106] and the placental weight in pregnancies with diabetes has been reported as being higher than in non–diabetic pregnancies.[16-18,53,83]

In 2014, the global prevalence of diabetes was estimated to be 8.5% and 422 million adults were estimated to live with diabetes.[147] In 2012, diabetes caused 1.5 million deaths and hyperglycemia caused an additional 2.2 million deaths.[147] In Norway, 200–300 women with diabetes type–1 and 100–200 women with diabetes type–2 give birth every year.[148] The prevalence of gestational diabetes differs greatly between populations due to varying ethnicity, indications for screening and diagnostic criteria, but has been estimated to be in the range of 5.8% to 12.9%.[149] In Norway, the prevalence of gestational diabetes has been estimated at 10%.[150]

3.1.2 Gestational diabetes

Diagnostic criteria. The current diagnostic criteria for gestational diabetes are glycemic values of 5.3–6.9 mmol/l in a fasting plasma glucose test, or 9.0–11.0 mmol/l in an oral glucose tolerance test (two–hour value), but below the diagnostic threshold of overt diabetes diagnosed during pregnancy.[150,151]

Biological mechanisms. In some women, insulin secretion is not increased sufficiently to overcome the physiological insulin resistance during the second and third trimesters of pregnancy, or the insulin resistance is more pronounced than in other pregnant women.[152] These women have

impaired glucose tolerance, which is called gestational diabetes when diagnosed during pregnancy.

Risk factors: Maternal obesity, high maternal age and maternal smoking increase the risk of gestational diabetes.[146,153,154] Women who had gestational diabetes have an increased risk of developing diabetes type–2 later in life.[149]

Treatment: Treatment of gestational diabetes is directed at not exceeding the recommended weight gain during pregnancy, maintaining a healthy diet and daily exercise. Treatment with insulin or antidiabetic medications is indicated when the glycemic values are above 5.2 mmol/l in a fasting plasma glucose test, or above 6.6 mmol/l two hours after the onset of a meal.[150]

3.1.3 Diabetes type–1

Diagnostic criteria. The diagnostic criteria for diabetes type–1 are glycemic values at or above 7.0 mmol/l in a fasting plasma glucose test, or above 11.0 in an oral glucose tolerance test (two hour value).[143,148]

Biological mechanisms. Diabetes type–1 is caused by an autoimmune destruction of the insulin secreting β–cells of the islets of Langerhans in the pancreas. The onset is most common during childhood or adolescence.[143] The cause is yet to be known, but genotypes, epigenetic changes and environmental factors have been suggested as etiologic agents.[155]

Treatment. Patients with diabetes type–1 are treated with exogenous insulin to achieve glycemic control, and the treatment goal during pregnancy is glycated hemoglobin (HbA_{1C}) levels under 6% in the second and third trimester.[148,156] As for other patients with diabetes, diet and life–style advice form part of the treatment for patients with diabetes type–1. Women with diabetes type–1 are advised to seek pregestational guidance in order to achieve optimal glycemic control, optimal pharmaceutical treatment, as well as dietary and life–style advice.

3.1.4 Diabetes type–2

Diagnostic criteria. The diagnostic criteria for diabetes type–2 are glycemic values at or above 7.0 mmol/l in a fasting plasma glucose test or above 11.0 in an oral glucose tolerance test (two hour value).[143,148]

Biological mechanism. Diabetes type–2 is characterized by insulin resistance and relative insulin deficiency.[143] The onset of diabetes type–2 is most common in adulthood.

Risk factors. Insulin resistance is linked to obesity,[157] and patients with diabetes type–2 often present with the metabolic syndrome of hyperglycemia, hypertension, dyslipidemia and visceral obesity.[158]

Treatment. Women with diabetes type–2 are treated with antidiabetic medications or exogenous insulin, and additionally dietary and life–style advice to counteract the insulin resistance associated with obesity.[159] The treatment goal during pregnancy is glycated hemoglobin (HbA_{1C}) levels of less than 6% in the second and third trimester.[148] Women with diabetes type–2 are advised to seek pregestational guidance in order to achieve optimal glycemic control, optimal pharmaceutical treatment, as well as dietary and life–style advice.

3.1.5 Diabetes and the placenta

The placental weight in pregnancies with diabetes is consistently reported as being higher than in non–diabetic pregnancies.[16-18,53,83] High placental to birthweight ratio has also been associated with pregestational and gestational diabetes.[5,16,17]

Maternal diabetes influences placental development and function.[105,106] Hyperglycemia may reduce trophoblast proliferation during placental development and invasion of the *decidua* during the first trimester.[106,160] This could delay placental development and growth. The increased risk of spontaneous abortions, preeclampsia and intrauterine growth restriction in pregnancies with pregestational diabetes has been linked to this effect of hyperglycemia.[161]

The diffusion distance across the placental membranes has been reported to be increased in diabetic pregnancies due to increased storage of collagen in the trophoblastic basement membrane.[162] In pregnancies with diabetes, up–regulation of GLUT–1 expression and function in the basal membrane of the syncytiotrophoblast facilitates a greater transport of glucose across the fetoplacental membrane.[116,118] In pregnancies with gestational diabetes, high fetal glucose concentrations and low fetal oxygen concentrations have been reported despite normoglycemia in the maternal blood.[163]

At term, the placentas from diabetic pregnancies have been associated with enlarged surface areas and altered villous morphology.[105,106,163] The mechanism behind this effect is not clear.

Both hyperglycemia and hyperinsulinemia have been suggested to induce hypervascularization and hyperproliferation of the villi in the second and third trimesters.[105,106]

Women with diabetes have an increased risk of endothelial dysfunction, including altered release of bioactive substances, increased tendency for vasoconstriction and increased risk of atherosclerosis.[164,165] The endothelial dysfunction is likely to increase with the duration of diabetes,[164] and is therefore more prominent in women with pregestational diabetes type–1 than in women with gestational diabetes. Vascular dysfunction may impair tissue oxygenation, thus causing preplacental and uteroplacental hypoxia.[106]

3.1.6 Complications in pregnancies with diabetes

Women with diabetes type–1 have reduced fertility and an increased risk of spontaneous abortions.[53,166] Women with diabetes have an increased risk of giving birth to a large for gestational age infant.[17,48,52-55,146] However, strict glycemic control in women with diabetes type–1 and women with diabetes type–2 has been associated with giving birth to a small for gestational age infant.[50,51] This association has not been found in gestational diabetes.[52] Women with diabetes type–1 and women with diabetes type–2 are at increased risk of giving birth to an infant with congenital malformations,[55,112,166] stillbirth[55,112,167] and infant death.[112,167] Women with diabetes type–1, diabetes type–2 and gestational diabetes are at increased risk of cesarean section[55,112,146,168] and increased risk of iatrogenic and spontaneous preterm birth.[55,110,146] Infants of diabetic mothers are associated with an increased risk of neonatal hypoglycemia and are at increased risk of neonatal morbidity.[168,169]

Women with diabetes type–1, diabetes type–2 and gestational diabetes are at increased risk of preeclampsia.[52,111,146,170] A systematic review found that the relative risk of preeclampsia was quadrupled among women with diabetes type–1 and diabetes type–2.[170] The increased risk of preeclampsia among women with diabetes type–1 and type–2 was confirmed in a large meta–analysis from 2016 (pooled relative risk 3.7 (95% CI 3.1–4.3)).[111] Women with gestational diabetes also have an increased risk of preeclampsia,[146] and in these women the risk of preeclampsia appears to increase further with high body mass index and in women with poorly controlled glycemic values.[171]

3.2 Preeclampsia

3.2.1 Definition and prevalence

Preeclampsia is a pregnancy complication defined as blood pressure ⩾140/90 mmHg and proteinuria after 20 weeks of gestation.[172] The placenta is necessary for the development of preeclampsia and the syndrome resolves by parturition of the placenta. More than 500 000 women die each year from pregnancy–related causes and 10–15% of these maternal deaths have been attributed to preeclampsia and eclampsia (preeclampsia with seizures).[173] In Norway, preeclampsia complicates 3–4% of all pregnancies.[174] Preeclampsia is associated with increased maternal mortality and morbidity[175-180] and increased offspring mortality and morbidity.[181-184]

3.2.2 Preeclampsia and the placenta

The placenta is both a necessary and sufficient cause of preeclampsia and the syndrome resolves, in most cases, by parturition of the placenta.[185] The biological mechanism of preeclampsia remains unclear, but some characteristic features of the placenta in preeclamptic pregnancies have been described.

In pregnancies with preeclampsia, the trophoblast invasions seem to be defective.[107,109,186] During trophoblast differentiation, the trophoblasts change their adhesion molecules from the epithelial phenotype to the endovascular phenotype in order to disintegrate the spiral arteries. In preeclamptic pregnancies the trophoblasts fail to express the adhesion molecules of the endovascular phenotype.[187] Thus, the spiral arteries are not transformed into the low resistance, dilated uteroplacental arteries in the myometrial segment of the uterus necessary for optimal placental function.[186,188] Instead, the spiral arteries remain narrow with high resistance in the myometrial segment causing uteroplacental hypoxia.[102] The degree of defective trophoblast invasion appears to be higher in the center of the placenta than in the periphery (shallow placentation). These characteristic placental features appear to be more pronounced in preeclamptic pregnancies with onset before gestational week 34 and in preeclamptic pregnancies with fetal growth restriction.[109,185,189]

Placentas in pregnancies with preeclampsia may also express signs of ischemia, possibly as a consequence of hypoperfusion. Signs of ischemia seen in placentas from pregnancies with

preeclampsia include acute atherosis, fibrinoid necrosis and placental infarctions.[185,190-193] It is not known whether the ischemia develops from underlying maternal conditions causing hypoperfusion (preplacental hypoxia) or whether the hypoperfusion is caused by the pathogenesis of preeclampsia itself (uteroplacental hypoxia). However, these findings have led to the hypothesis of a maternal origin of preeclampsia in women in which the placenta lacks the characteristic features of defective trophoblast invasion.[185,189]

A disruption of the balance between angiogenic and anti–angiogenic factors necessary to placental development and growth has also been linked to the development of preeclampsia. Decreased serum levels of the angiogenic factors placental growth factor and hCG in the first trimester have been linked to the development of preeclampsia.[121,125-127] Altered levels of these angiogenic factors in the second and third trimester have also been linked to development of preeclampsia.[125-127] On the other hand, altered serum levels of the antiangiogenic factors soluble fms–like tyrosine kinase 1 (sFlt–1) and soluble endoglin have been associated with development of preeclampsia.[125-127,194]

The clinical signs of preeclampsia have been attributed to generalized endothelial dysfunction;[109] disturbed endothelial control of vascular tone, which results in hypertension, increased endothelial permeability, which causes fluid retention, and abnormal endothelial expression of procoagulants, which may result in clotting dysfunction.[195] An intravascular inflammatory response has also been suggested as describing the clinical signs of preeclampsia, in which proinflammatory cytokines or leukocytes are activated by placental hypoperfusion and induce endothelial dysfunction.[196]

3.2.3 Placental weight in preeclamptic pregnancies; does maternal diabetes matter?

Preeclampsia has been associated with low placental weight.[18,19,23] However, there have also been studies reporting no association between preeclampsia and placental weight,[61,87] and a study reporting an association between preeclampsia and high placental weight in pregnancies delivered at term (after gestational week 37).[19] Preeclampsia has been associated with a high placental to birthweight ratio.[5]

Women with diabetes have an increased risk of preeclampsia[52,111,170] and maternal diabetes has consistently been associated with high placental weight.[16-18,53,83] However, placental weight in preeclamptic pregnancies with diabetes has previously not been reported. Nonetheless, it is reasonable to suggest that some of the variation of placental weight in preeclamptic pregnancies could, at least partially, be caused by maternal diabetes status. Consequently, the associations of preeclampsia with high placental weight could be attributed to maternal diabetes. These associations of preeclampsia with high placental weight may also vary with subtypes of diabetes. Knowledge about factors that influence placental weight in preeclamptic pregnancies could advance our understanding of the mechanisms that cause preeclampsia.

Both maternal diabetes and preeclampsia have been associated with a high placental to birthweight ratio, independent of the absolute weight of the placenta.[5,16,17] The placental to birthweight ratio in preeclamptic pregnancies with diabetes may also vary with the subtype of diabetes. Thus, the first objective of this thesis was to study placental weight and the placental to birthweight ratio in preeclamptic pregnancies according to maternal diabetes status.

3.2.4 Preeclampsia in the first and second pregnancy

The risk of preeclampsia is higher in the first pregnancy than in any subsequent pregnancy.[174,197] Among women with preeclampsia in the first pregnancy, the risk of preeclampsia in a subsequent pregnancy has been estimated at 15%.[174,198-200] However, higher recurrence risks have been reported among women with severe preeclampsia.[201] Women with preeclampsia in the first pregnancy also have an increased risk of developing gestational hypertension and HELLP (hemolysis, elevated liver enzymes and low platelets) in subsequent pregnancies.[200] Additionally, a previous study reported that women who gave birth to a small for gestational age baby in the first pregnancy had an increased risk of preeclampsia in the second pregnancy.[202]

3.2.5 Preeclampsia in the second pregnancy; does placental weight matter?

Prediction of the development of preeclampsia has proven to be difficult, independent of whether a previous pregnancy with preeclampsia is evident or not. However, the development of preeclampsia is associated with pregestational cardiovascular risk factors such as maternal diabetes, high maternal body mass index and chronic hypertension.[203-207] The same maternal

cardiovascular risk factors have been associated with placental weight: Chronic hypertension has been associated with low placental weight, whereas maternal diabetes and high maternal body mass index have been associated with high placental weight.[15,17,18]

Abnormal placental development appears to be part of the etiology of preeclampsia and preeclampsia has been associated with both high and low placental weight.[18,19,23,61,87] Thus, increased levels of underlying maternal risk factors may contribute to both the development of preeclampsia and abnormal placental development. If so, placental weight in the first pregnancy may serve as an indicator of the maternal risk factors predisposing to the development of preeclampsia in a subsequent pregnancy. Thus, the second objective of this thesis was to study the association of placental weight in the first pregnancy with the risk of preeclampsia in the second pregnancy in women with and in women without preeclampsia in the first pregnancy.

3.3 Infant death

3.3.1 Definition and prevalence

Infant death is defined as the death of a live–born infant within the first year of life. In 2016, 4.2 million infants died within their first year of life.[208] 2.6 million of these infants died during the first 28 days of life (neonatal death).[209] Infant mortality rate is the number of infant deaths per 1000 live births. In 2016, the infant mortality rate in Norway was 2.1 per 1000 live births, in comparison to the United States of America and Afghanistan, where the infant mortality rate was, respectively, 5.6 and 53.2 per 1000 live births.[208] Globally, the main causes of death in children under 5 years includes complications of preterm birth, intrapartum related events and neonatal sepsis.[209]

3.3.2 Risk factors for infant death

Several maternal and pregnancy–related factors have been associated with an increased risk of infant death, including low maternal age,[210-214] high maternal age,[214] increased parity,[211-213] maternal smoking,[211,213,214] high maternal body mass index,[211,215] maternal diabetes,[112,167] *in vitro* fertilization,[216,217] preeclampsia,[181] chorioamnionitis[218] and preterm birth.[214,219] Boys have an increased risk of infant death as compared to girls.[220,221] Low birthweight (defined as birthweight below the 3rd, 5th, 10th or 25th percentile) has been associated with an increased risk of infant death in preterm and term born infants.[31-34,65,67,68] Low Apgar–score at birth has also been associated with an increased risk of infant death.[222,223] The risk of infant death increases with the number of fetuses in the pregnancy: Twins have five times higher infant mortality than singleton infants, and triplets a ninefold higher infant mortality.[214] Infants with congenital malformations have an increased risk of infant death.[214] However, the risk varies with subtypes of malformations.[224,225]

3.3.3 Infant death; does placental weight matter?

The placenta is a determinant of fetal growth and being born small for gestational age has been associated with an increased risk of infant death in both preterm and term born infants.[31-34,65,67,68] The placenta is a determinant of the achieved birthweight,[134-136] and being born small for gestational age has been associated with low placental weight.[61] Thus, low placental weight could be an indicator of poor placental function. Low placental weight has been associated with fetal

death.[8,21] However, high placental weight has been associated with low Apgar–score at birth.[20] In a previous study, placental weight z–score was not associated with in–hospital neonatal death.[21]

Low placental to birthweight ratio has been associated with fetal death irrespective of gestational age at birth,[8] whereas a high placental to birthweight ratio has been associated with preterm fetal death[8] and low Apgar–score at birth.[20]

Taken together, it appears that placental weight and the placental to birthweight ratio may provide information about unfavorable intrauterine conditions that could predict an increased risk of adverse outcomes for the infant, such as infant death. Thus, the third objective of this thesis was to study the association of placental weight and placental to birthweight ratio with the risk of infant death.

4 Objectives of the thesis

Paper I. To study placental weight and the placental to birthweight ratio in preeclamptic pregnancies according to maternal diabetes status. We also studied placental weight and placental to birthweight ratio in preeclamptic pregnancies according to sub–types of diabetes.

Paper II. To study the association of placental weight in the first pregnancy with the risk of preeclampsia in the second pregnancy in women with and in women without preeclampsia in the first pregnancy. We also studied the association of placental weight in the first pregnancy with the risk of preterm and of term preeclampsia in the second pregnancy in women with and in women without preeclampsia in the first pregnancy.

Paper III. To study the association of placental weight and placental to birthweight ratio with the risk of infant death. We also studied the association of placental weight and the placental to birthweight ratio with the risk of neonatal death, and the association of placental weight and the placental to birthweight ratio with the risk of infant death in infants with and in infants without congenital malformations.

5 Material and methods

5.1 The Medical Birth Registry of Norway

We used data from the Medical Birth Registry of Norway (MBRN). This registry has obtained data on all births in Norway after 16 weeks of gestation since 1967 and after 12 weeks of gestation since 2002.[226,227] It is mandatory for the doctor or midwife attending the delivery to report births on a standardized form (See Appendix). Since 1999, information on placental weight has also been reported to the MBRN.[228] The MBRN is routinely linked to the National Registry of Norway to obtain information about vital status and emigration status.[227,229] It is a statutory requirement for all deaths in Norway to be reported by the doctor who confirmed the death.[230]

5.2 Study populations

5.2.1 Placental weight, preeclampsia and diabetes – Paper I

In this study we used data from the MBRN from 1999–2010 (Figure 5–1). A total of 716 024 births were recorded during this period. In the analyses, we excluded multiple pregnancies (N =25 928), deliveries before gestational week 20 (N =8701), and pregnancies with missing information on offspring sex (N =824). We considered pregnancies with a recorded offspring birthweight of less than 250 grams or 6500 grams or above (N =257) as having outlying values. Thus, these and pregnancies with missing information on birthweight (N =1475) were excluded. For the same reason we excluded pregnancies with a recorded placental weight of less than 25 grams or 2500 grams or above (N =740) and pregnancies with missing information on placental weight (N =24 621). Some pregnancies had missing or outlying values for more than one of these variables and, in total, 655 842 pregnancies could be included in the analyses.

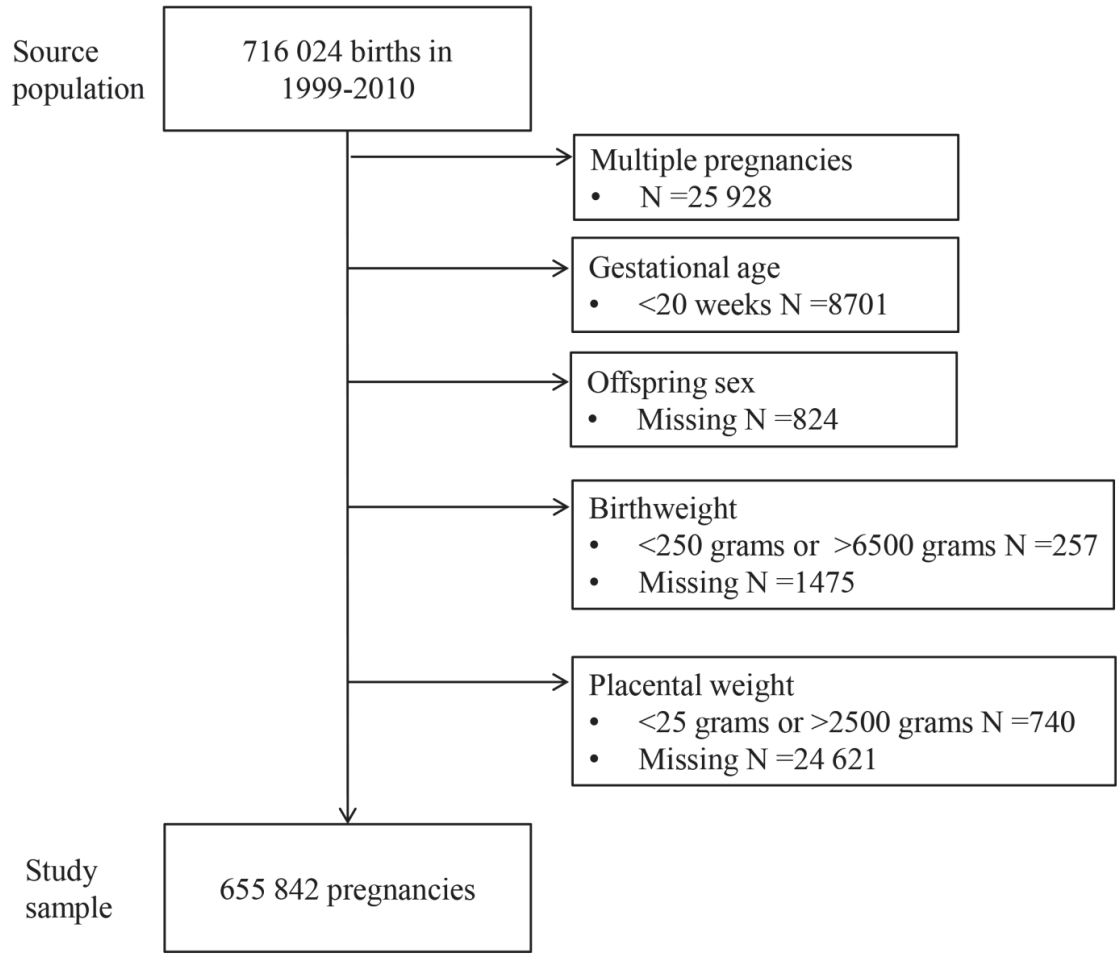

Figure 5–1. Study sample, Paper I. Some pregnancies had missing or outlying values for more than one variable.

5.2.2 Placental weight and preeclampsia in the second pregnancy – Paper II

We included women with two consecutive singleton births after the 20th gestational week recorded in the MBRN from 1999–2012 (N =193 637). We excluded women with missing information on placental weight (N =6599), birthweight (N =170) or offspring sex (N =9). A total of 6778 women were therefore excluded, leaving 186 859 women for statistical analyses.

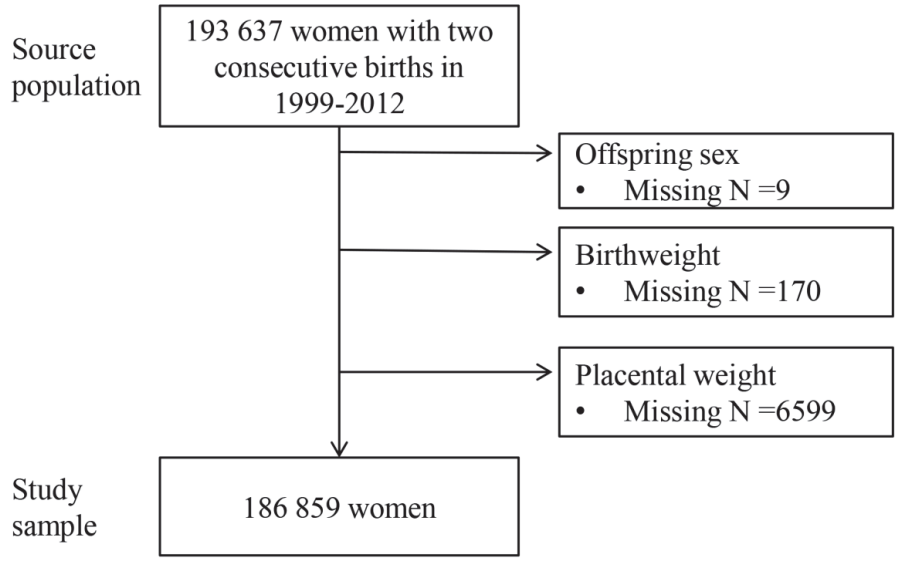

Figure 5–2. Study sample, Paper II.

5.2.3 Placental weight and infant death – Paper III

We used data from the MBRN from 1999–2015. During this period there were 981 044 singleton births in Norway. We excluded stillborn infants (N =6738), and infants with missing information on gestational age at birth (N =6166). We also excluded infants with a gestational age of less than 23 weeks at birth (N =3086). Infants with a gestational age above 42 weeks (N =2571) were excluded since the gestational age of some of these infants was erroneously recorded and we could not with certainty determine for whom. Furthermore, we excluded infants with missing information on birthweight (N =647), or with outlying birthweight values (<250 grams or >6500 grams) (N =5). Additionally, we excluded infants with missing information on placental weight (N =22 003) or with outlying placental weight values (<25 grams or >2500 grams) (N =7368).

Some infants had missing information or outlying values for more than one of these study factors. We also excluded infants if they had emigrated from Norway (N =20 674) or if vital status one year after birth was unknown (N =5260). Thus, our study sample comprised 909 750 infants.

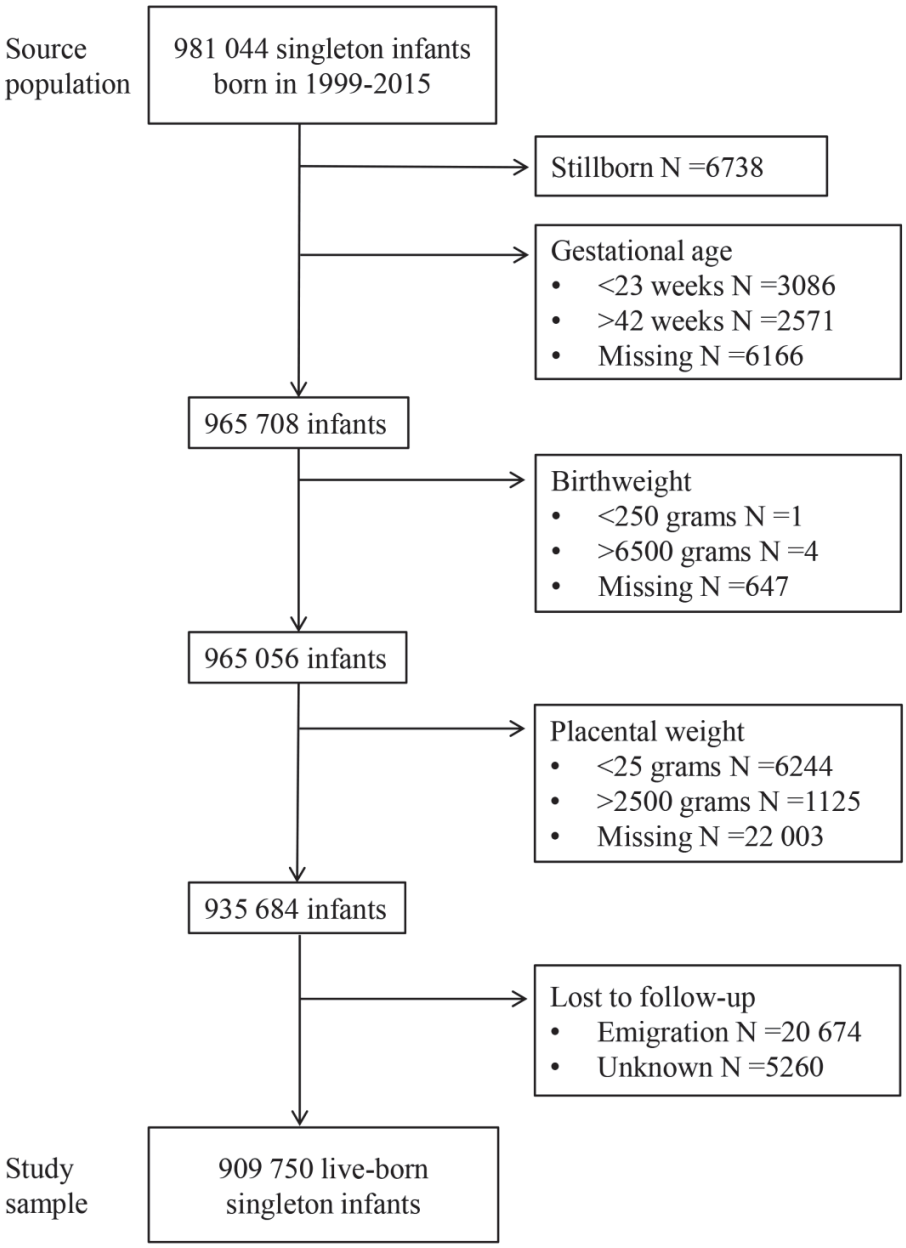

Figure 5–3. Study population, Paper III. Some infants had missing or outlying values for more than one variable.

5.3 Variables

Table 5–1. Variables used in Papers I–III.

	Exposure	Outcome	Other variables
Paper I	Preeclampsia, preeclampsia and diabetes, diabetes and none of the conditions	Placental weight Birthweight Placental to birthweight ratio	Gestational age at birth Offspring sex Parity Maternal age Maternal smoking *In vitro* fertilization Placenta previa Placental abruption
Paper II	Placental weight in the first pregnancy	Preeclampsia in the second pregnancy	Gestational age at birth* Offspring sex* Preeclampsia* Birthweight* Maternal age* Maternal smoking* Maternal diabetes* Interval between pregnancies
Paper III	Placental weight Birthweight Placental to birthweight ratio	Infant death	Gestational age at birth Offspring sex Parity Maternal age Maternal smoking *In vitro* fertilization Preeclampsia Maternal diabetes Congenital malformations

*in the first pregnancy

Placental weight was reported in grams. According to obstetric standards in Norway, the placenta is weighed in the obstetrics ward shortly after birth with membranes and umbilical cord attached.[228,231] Birthweight was reported in grams. The placental to birthweight ratio was calculated by dividing placental weight by birthweight in grams. Placental weight, birthweight and placental to birthweight ratio were used differently in Papers I–III, and further use of these variables is described in the statistical analyses (Chapter 5.4).

Gestational age at birth was based on term date estimates by routine fetal ultrasonographic examination in gestational weeks 17–19. If ultrasonographic examination had not been performed, term date was estimated on the basis of the first day of the last menstrual period.

Preeclampsia (yes/no) was defined as blood pressure ≥140/90 mmHg and proteinuria (protein dip–stick 1+ or >0.3 grams/24 hours) after 20 weeks of gestation.

Diabetes included women with diabetes type–1, diabetes type–2, non–specified diabetes prior to pregnancy, use of oral anti–diabetic medication during pregnancy, and gestational diabetes as reported to the Medical Birth Registry of Norway. Diabetes was used as a dichotomous variable (yes/no), and as a categorical variable (diabetes type–1, diabetes type–2, gestational diabetes and none of the above). Gestational diabetes was diagnosed through screening in antenatal care and was defined as a plasma glucose value ≥7.8 mmol/liter and <11.1 mmol/liter two hours after a 75 mg oral glucose tolerance test.[150]

Infant death was defined as death of a liveborn offspring within the first year of life (yes/no). In additional analyses, neonatal death (defined as death within the first 28 days of life) was used as a dichotomous variable (yes/no).

The following variables were used as dichotomous variables: Offspring sex (male/female), parity (0 or ≥1), pregnancy after *in vitro* fertilization (yes/no), placenta previa (yes/no), placental abruption (yes/no). Maternal smoking (yes/no) included daily and occasional smoking as reported by the mother at the first antenatal visit in the first trimester. Congenital malformations (yes/no) as diagnosed during the neonatal period included anencephaly, encephalopathy, spina bifida,

spinal cord defects, heart defects, cleft lip and/or cleft palate, hypospadias, omphalocele, gastroschisis, pes equinovarus, and chromosomal abnormalities. We had no information about groups or subtypes of congenital malformations.

Maternal age (in years) and interval between pregnancies (year of second birth − year of first birth, in years) were used as continuous variables.

5.4 Statistical analyses

The statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS Version 20.0, 22.0 and 24.0).

5.4.1 Placental weight, preeclampsia and diabetes – Paper I

The outcomes were deciles of placental weight z–scores, birthweight z–scores and placental to birthweight ratios. Placental weight and birthweight are closely related to gestational age at birth,[42,43,74-77] and both preeclampsia and diabetes are associated with preterm birth.[55,110,146,181,182] We therefore decided to use z–scores to adjust for differences in gestational age in pregnancies with preeclampsia and/or diabetes to pregnancies with none of the conditions. We calculated z–scores of placental weight and birthweight using the following equation:

$$Z - score = \frac{actual\ weight - mean}{standard\ deviation}$$

We used means and standard deviations of placental weight and birthweight at each gestational week in the study population as a whole. Z–scores were calculated separately for male and female offspring as the placental weight and birthweight differ with sex.[42,43,74,75]

We divided z–scores into deciles, indicating that 10% of the pregnancies would be expected to fall within each decile, assuming a normal distribution for each of our pregnancy groups. Placental to birthweight ratios were also divided into deciles.

The exposure was pregnancies with preeclampsia only, pregnancies with preeclampsia and diabetes, pregnancies with diabetes only and pregnancies with none of the conditions.

We compared means of placental weight, placental weight z–score, birthweight, birthweight z–score, placental to birthweight ratio and gestational week at delivery between pregnancies with and without preeclampsia according to maternal diabetes status. Differences in means between groups were tested by ANOVA–test using Bonferroni correction. We repeated these analyses in pregnancies with preterm (before gestational week 37) and term delivery (at or after gestational week 37). We also compared the mean maternal age and proportions of parity, maternal smoking, *in vitro* fertilization, placenta previa and placental abruption in pregnancies with and without preeclampsia according to maternal diabetes status.

We presented the proportions of pregnancies with and without preeclampsia according to maternal diabetes status within each decile of placental weight z–scores, birthweight z–scores and placental to birthweight ratios. A chi–squared test was used to test for differences in proportions in deciles between the pregnancy types. Corresponding analyses were repeated in preeclamptic pregnancies according to sub–types of diabetes (diabetes type–1, diabetes type–2 and gestational diabetes).

5.4.2 Placental weight and preeclampsia in the second pregnancy – Paper II

The primary outcome was preeclampsia in the second pregnancy (yes/no). Preterm (delivery before gestational week 37) and term preeclampsia (delivery in gestational week 37 or later) were used as secondary outcomes in additional analyses.

The exposure was quintiles of placental weight z–scores in the first pregnancy. Placental weight is closely related to gestational age,[74-77] and preeclampsia has been associated with preterm birth.[181,182] We therefore decided to use z–scores of placental weight in order to compare placental weight in pregnancies with preeclampsia to pregnancies without preeclampsia despite differences in gestational age at birth in the first pregnancy. We calculated z–scores of placental weight by using means and standard deviations of placental weight for each gestational week at

birth in the sample as a whole. Z–scores were calculated separately for male and female offspring as the placental weight differs with sex.[74,75]

The distribution of placental weight z–scores in the first pregnancy was divided into quintiles, indicating that 20% of the pregnancies would be expected to fall within each decile assuming a normal distribution for each of our pregnancy groups.

Differences in the distribution of study factors in the first pregnancy according to the development of preeclampsia in the second pregnancy were tested by using the Student's t–test for continuous variables and the chi–squared test for categorical variables.

The risk of preeclampsia in the second pregnancy according to quintiles of the placental weight z–score in the first pregnancy were estimated as crude and adjusted ORs with 95% CI separately for women with and without preeclampsia in the first pregnancy. Women with placental weight z–scores in the 3rd quintile were used as the reference group. In additional analyses, we estimated the crude and adjusted ORs with 95% CI of preterm and of term preeclampsia in the second pregnancy. Women who delivered preterm (before gestational week 37) in the second pregnancy were not included in the analyses of risk of term preeclampsia in the second pregnancy. We made adjustments for maternal diabetes, maternal smoking and maternal age in the first pregnancy and interval between pregnancies.

5.4.3 Placental weight and infant death – Paper III

The outcome was infant death (yes/no). In additional analyses neonatal death (yes/no) was used as the outcome.

The exposure variables were placental weight, birthweight and placental to birthweight ratio. Placental weight and birthweight are closely related to gestational age at birth,[42,43,74-77] and preterm birth is a risk factor for infant death.[219] We decided to conduct gestational age specific analyses in order to study the associations of placental weight, birthweight and placental to birthweight ratio with infant death across all gestational weeks of birth. We calculated mean placental weight, birthweight and placental to birthweight ratio according to infant vital status

one year after birth, within two–week intervals of gestational age at birth: 23–24, 25–26, 27–28, 29–30, 31–32, 33–34, 35–36, 37–38, 39–40 and 41–42 weeks. Differences in means were tested by applying the Student's t–test.

Placental weights, birthweights and placental to birthweight ratios were also grouped into quartiles of the distributions among all infants who were born within the above two–week intervals of gestational age at birth. Thus, 25% of the infants were expected to fall into each quartile, assuming normal distribution. Differences in proportions were tested with the chi–squared test. The proportions of infants in the 1st quartile and 4th quartile according to vital status one year after birth were presented in figures.

We estimated the associations of infant death with low (1st quartile) and high (4th quartile) placental weight, birthweight and placental to birthweight ratio as crude and adjusted ORs with 95% CI within intervals of gestational age. The reference group was 2nd–3rd quartile combined. In these analyses, we grouped gestational age at birth into larger intervals: 23–28, 29–32, 33–36 and 37–42 weeks. We made adjustments for factors that are known to be associated with infant death and placental weight: Offspring sex, parity, pregnancy after *in vitro* fertilization, maternal age, maternal smoking, preeclampsia and maternal diabetes.

In additional analyses, we estimated the OR for infant death in infants with and without congenital malformations separately.

5.5 Ethical aspects

Paper I. The MBRN is approved by the Norwegian Data Inspectorate and the use of data for research is regulated by law.[226,232] The study was recommended by the Advisory Committee of the MBRN (Assignment 08–1136/652).

Paper II. The MBRN is approved by the Norwegian Data Inspectorate and the use of data for research is regulated by law.[226,232] The use of data for this study was approved by the Regional Committee for Ethics in Medical Research (Reference number 2014/131).

Paper III. The MBRN is approved by the Norwegian Data Inspectorate and the use of data for research is regulated by law.[226,232] The study was recommended by the Advisory Committee of the MBRN (Assignment 08–1136/652).

6 Synopsis of the studies

6.1 Paper I

Preeclampsia in pregnancies with and without diabetes: the associations with placental weight. A population study of 655 842 pregnancies. Dypvik J, Strøm–Roum EM, Haavaldsen C, Vatten LJ, Eskild A. Acta Obstet Gynecol Scand. 2016;95:217–24.

Objective. To study the placental weight and the placental to birthweight ratio in preeclamptic pregnancies according to maternal diabetes status.
Design. Population–based cross–sectional study.
Material and methods. Information on all singleton births from 1999 through 2010 (N =655 842) were obtained from the MBRN. We used z–scores of placental weight to adjust for differences in gestational age at birth between deliveries, and compared the distribution of placental weight z–scores, in deciles, in preeclamptic pregnancies with and without diabetes, and in non–preeclamptic pregnancies with and without diabetes.
Results. Overall, the prevalence of preeclampsia was higher in pregnancies with diabetes than in pregnancies without diabetes (9.9% vs. 3.6%). Among preeclamptic pregnancies, having a placental weight in the highest decile was nearly three times more frequent (28.8%) in pregnancies with diabetes than in pregnancies without diabetes (9.8%). In the lowest decile, preeclamptic pregnancies with diabetes were underrepresented (7.5%), and preeclamptic pregnancies without diabetes were overrepresented (13.6%). Among pregnancies with preterm delivery, the above patterns were more pronounced, with 30.1% of the placentas in preeclamptic pregnancies with diabetes in the highest decile, and 19.5% of the placentas in preeclamptic pregnancies without diabetes in the lowest decile.
Conclusions. These results suggest that women with diabetes who develop preeclampsia have a higher placental weight than other women with preeclampsia or non–preeclamptic women.

6.2 Paper II

Placental weight in the first pregnancy and risk for preeclampsia in the second pregnancy: A population–based study of 186 859 women. Dypvik J and Larsen S, Haavaldsen C, Jukic AM, Vatten LJ, Eskild A. Eur J Obstet Gynecol Reprod Biol. 2017;214:184–189.

Objective. To study the association of placental weight in the first pregnancy with the risk for preeclampsia in the second pregnancy in women with and in women without preeclampsia in the first pregnancy.
Design. Population–based cohort study.
Material and methods. We included all women with two consecutive singleton pregnancies reported to the MBRN during 1999–2012 (N =186 859). Placental weight in the first pregnancy was calculated as z–scores, and the distribution was divided into five groups of equal size (quintiles). We estimated crude and adjusted ORs with 95% CI for preeclampsia in the second pregnancy according to quintiles of placental weight z–scores in the first pregnancy. The 3rd quintile was used as the reference group.
Results. Among women without preeclampsia in the first pregnancy, 1.4% (2507/177 149) developed preeclampsia in the second pregnancy. In these women, the risk for preeclampsia in the second pregnancy was associated with placental weight in the first pregnancy in both lowest (crude OR 1.30, 95% CI 1.14–1.47) and highest quintile (crude OR 1.20, 95% CI 1.06–1.36). The risk associated with the highest quintile of placental weight was confined to term preeclampsia. Among women with preeclampsia in the first pregnancy, 15.7% (1522/9710) developed recurrent preeclampsia, and the risk for recurrent preeclampsia was associated with placental weight in lowest quintile in the first pregnancy (crude OR 1.30, 95% CI 1.10–1.55). Adjustment for interval between pregnancies, maternal diabetes, age, and smoking in the first pregnancy did not alter these estimates notably.
Conclusion. Placental weight in the first pregnancy might help to identify women who could be at risk for developing preeclampsia in a second pregnancy.

6.3 Paper III

Placental weight, birthweight and risk for infant death. Dypvik J, Larsen S, Haavaldsen C, Eskild A. *Submitted May 2018.*

Objective. To study the association of placental weight and the placental to birthweight ratio with the risk for infant death.
Design. Population–based cohort study.
Material and methods. We followed all singleton infants in Norway during the years 1999–2015 until one year after birth. The risk for infant death was studied within intervals of gestational age at birth, and we estimated the odds ratio (OR) with 95% confidence intervals (CI) for infant death associated with having low (1st quartile) or high (4th quartile) placental weight and placental to birthweight ratio. The 2nd and 3rd quartile combined was used as the reference.
Results. Among the 909 750 infants, 2200 infants (0.24%) died during the first year after birth. For most infants, low placental weight increased the risk for infant death. The results differed for infants born in gestational weeks 29–32, and in these infants high placental weight increased the risk for death (OR 2.37, 95% CI 1.69–3.33). High placental to birthweight ratio increased the risk for death in all infants, but the strength of the association decreased by gestational age at birth. For infants born in gestational weeks 29–32 the OR was 2.47 (95% CI 1.77–3.45) and it was 1.37 (95% CI 1.19–1.57) for infants born in gestational weeks 37–42.
Conclusion. In most infants, low placental weight increased the risk for infant death. However, for infants born in gestational weeks 29–32, high placental weight increased the risk.

7 Discussion

7.1 Main findings

Paper I. We found that in pregnancies with preeclampsia, placental weight was higher in pregnancies with diabetes and lower in pregnancies without diabetes than in non–preeclamptic pregnancies. The high placental weight in preeclamptic pregnancies with diabetes was particularly pronounced in pregnancies with diabetes type–1.

Paper II. We found that low placental weight in the first pregnancy increased the risk of preeclampsia in the second pregnancy in women with and without preeclampsia in the first pregnancy. Additionally, in women without preeclampsia in the first pregnancy, high placental weight increased the risk of developing term preeclampsia in the second pregnancy.

Paper III. We found that in most infants, low placental weight increased the risk of infant death. However, the results differed for infants born in gestational weeks 29–32 and, in these infants, high placental weight increased the risk of infant death.

7.2 Methodological considerations

7.2.1 Strengths

The MBRN collects data on all births in Norway with close to 100% completeness.[226] This meticulous mandatory data collection provided the major strength of our studies; the sample size. The large population–based samples in our studies provide sufficient observations of rare pregnancy outcomes. The statistical estimations become more accurate as the confidence intervals become narrower with increasing numbers of observations. However, the statistical power may be decreased in the sub–analyses of the samples. Nonetheless, the potential error of reporting no association when there actually *is* an association between the exposure and the outcome (type II error) becomes less likely with a large sample size.

7.2.2 Errors

Errors in epidemiological studies are classified into two types: random error and systematic error.

Random error is variability in the data that remains after systematic errors have been eliminated.[233] Random errors tend to decrease with increasing sample size[233] and are therefore unlikely to affect the studies presented. Systematic errors may be divided into selection bias, confounding and information bias.[233] A description of the systematic errors will be given first, and the possible errors will be described for each paper subsequently.

Selection bias occurs when the association between the exposure and outcome differs between the study sample and the individuals excluded from the study sample.[233] Or it can occur if the study sample is not representative of the source population.

Confounding of the association between exposure and outcome may occur when a factor is associated with both the exposure and the outcome.[233] If confounding factors are not accounted for, the estimated associations may be biased. We identified potential confounding factors *a priori* based on associations found in previous studies. We could only make adjustments for factors available to us in the MBRN. Thus, inadequate control for confounding by unmeasured factors may have occurred in our studies.

Information bias occurs when the information collected is erroneous.[233] The erroneous information is referred to as misclassified.[233] If the misclassification of information is related to other variables, it is referred to as differential misclassification.[233] Misclassification of information according to exposure or outcome is of particular concern.[233]

Non–differential misclassification. If the misclassification of information is unrelated to other variables, it is referred to as non–differential misclassification.[233] Placental weight could be subject to such misclassification. There is no gold standard for weighing the placenta after parturition. According to the National Guidelines for Obstetrics published by the Norwegian Society for Obstetrics and Gynecology in 2014, macroscopic examination of the placenta should take place shortly after parturition and preferably within 30 minutes.[231] Macroscopic examination of the placenta includes weighing.[231] A validation study of the data regarding the placenta, cord and membranes in the MBRN concluded that the data on placental weight was of good quality for

epidemiological studies.[228] Validation studies on other variables recorded in the MBRN have also shown results that are satisfactory for epidemiological studies.[234-238]

7.2.2.1 Placental weight, preeclampsia and diabetes – Paper I

Selection bias. We excluded 8.4% of the pregnancies recorded in Norway from 1999–2010 (Figure 5–1). It is possible that the main reason for not reporting placental weight to the MBRN was delayed implementation of the new reporting procedures for placental weight. The reporting of placental weight started in 1999,[228] and in that year information about placental weight was missing for more than 4000 pregnancies (7.1%). In subsequent years, the number of pregnancies with missing information on placental weight decreased to 2750 (4.8% in 2000) and to 2250 (4.1% in 2001), until it reached 1250 (2.1%) in 2010. We assume that delayed implementation of the new procedures has occurred independent of absolute placental weight. Thus, it is most likely that pregnancies excluded due to missing information on placental weight have not introduced selection bias to our study.

We performed additional descriptive analyses of the study sample and pregnancies excluded due to missing information on placental weight (Table 7–1). The means and distribution of other study factors were similar in the excluded pregnancies compared to those that were included. Thus, we do not suspect that the pregnancies excluded due to missing information on placental weight have introduced selection bias to our study.

Table 7–1. Descriptive statistics on pregnancies excluded or included in the study sample (Paper I).

	Preeclampsia		Non–preeclampsia	
	Diabetes	**Non–diabetes**	**Diabetes**	**Non–diabetes**
Study sample (N =655 842), N (%)	**1173 (0.2)**	**22 847 (3.5)**	**10 660 (1.6)**	**621 162 (94.7)**
Birthweight in grams, mean (SD)	3406.0 (897.7)	3117.5 (884.3)	3705.4 (656.4)	3565.0 (566.4)
Gestational week, mean (SD)	36.8 (2.7)	37.8 (3.2)	38.5 (2.1)	39.5 (1.9)
Maternal age in years, mean (SD)	30.3 (5.5)	29.0 (5.4)	31.1 (5.2)	29.5 (5.1)
Parity ≥1, yes (%)	551 (47.0)	9114 (39.9)	6862 (64.4)	368 200 (59.3)
Pregnancy after IVF, yes (%)	34 (2.9)	543 (2.4)	331 (3.1)	10 243 (1.6)
Smoking, yes (%)	201 (20.8)	3307 (17.3)	1852 (20.7)	102 538 (19.8)
Pregnancies with missing placental weight (N =24 621), N (%)	**38 (0.2)**	**779 (3.2)**	**301 (1.2)**	**23 503 (95.5)**
Birthweight in grams, mean (SD)*	3315.5 (1256.4)	2998.2 (957.5)	3605.9 (776.9)	3501.4 (707.8)
Gestational week, mean (SD)	36.4 (4.3)	37.2 (3.8)	38.1 (3.2)	38.5 (4.3)
Maternal age in years, mean (SD)**	30.6 (4.9)	29.2 (5.4)	31.2 (5.0)	29.5 (5.2)
Parity ≥1, yes (%)	19 (50)	314 (40.3)	183 (60.8)	14 534 (61.8)
Pregnancy after IVF, yes (%)	1 (2.6)	12 (1.5)	12 (4.0)	326 (1.4)
Smoking, yes (%)	12 (41.4)	96 (16.8)	47 (19.7)	3989 (22.3)

*Missing information on birthweight N =835.
**Missing information on maternal age N =7.

Differential misclassification. Differential misclassification could have occurred if placental weight was erroneously reported in pregnancies with preeclampsia and diabetes. For instance, placental weight could be rounded down in pregnancies with preeclampsia and rounded up in pregnancies with diabetes. Such misclassification may have influenced the distribution of placental weights found in our study, and may have caused overestimation of the distribution of placental weights. However, since placental weight in preeclamptic pregnancies with diabetes had previously not been reported, we do not know if placental weight was most likely to be rounded up or down in these pregnancies. Our distribution of placental weights may have been underestimated if placental weight has been rounded down in preeclamptic pregnancies with diabetes. Also subtypes of diabetes could be erroneously reported.[235] Notably, the associations of maternal diabetes with placental weight are in accordance with studies using data sources other than the MBRN.[16,18,53,83]

Confounding. We identified the following factors that have previously been associated with preeclampsia and placental weight: Parity,[10-12,174,197] maternal age,[13,239] maternal smoking[18,240] and *in vitro* fertilization.[49,241] We reported the mean maternal age and proportions of women with parity ≥1, women who smoked and pregnancies after *in vitro* fertilization according to pregnancies with preeclampsia only, preeclampsia and diabetes, diabetes only and none of these conditions (Table 7–1). We also performed supplementary analyses to address whether the risk of preeclampsia according to placental weight was confounded by parity, maternal smoking, maternal age and pregnancy after *in vitro* fertilization (Table 7–2). The ORs for preeclampsia according to placental weight in pregnancies with and without diabetes did not change after adjustment by these factors. Thus, we do not suspect that our results were confounded by parity, maternal smoking, maternal age or pregnancy after *in vitro* fertilization.

Maternal body mass index could have confounded our results since high body mass index has been associated with high placental weight,[11,14,15,242] diabetes type–2 and gestational diabetes,[153,157] and risk of preeclampsia.[205-207] However, maternal body mass index could also be considered to be a mediating factor on the pathway to the development of gestational diabetes and diabetes type–2. Thus, the adjustment for body mass index could introduce errors into the analyses. Also, we found that the high placental weight in preeclamptic pregnancies with

diabetes was particularly pronounced in pregnancies with diabetes type–1. In pregnancies with diabetes type–1, high body mass index has not been reported to increase placental weight.[242] Thus, the pronounced findings in pregnancies with diabetes type–1 are most probably not confounded by maternal body mass index.

Table 7–2. The odds ratios for preeclampsia according to deciles of placental weight z–scores in singleton pregnancies with diabetes and pregnancies without diabetes.

	Preeclampsia				
Placental weight z–scores	Yes (%)	cOR	95% CI	aOR[a]	95% CI
Pregnancies with diabetes (N =11 833)					
1st decile	88 (13.4)	4.43	3.5–5.54	4.07	3.18–5.21
2nd to 9th decile	747 (9.2)	2.88	2.67–3.11	2.85	2.61–3.10
10th decile	338 (11.1)	3.58	3.19–4.01	3.85	3.40–4.37
Pregnancies without diabetes (N =644 009)					
1st decile	3111 (4.8)	1.44	1.38–1.49	1.32	1.26–1.37
2nd to 9th decile	17 496 (3.4)	1.00	Reference	1.00	Reference
10th decile	2240 (3.6)	1.06	1.01–1.11	1.13	1.08–1.19

cOR – crude odds ratio; aOR – adjusted odds ratio; 95% CI – 95% confidence interval

[a] adjusted for parity, maternal smoking, maternal age and pregnancy after *in vitro* fertilization.

7.2.2.2 Placental weight and preeclampsia in the second pregnancy – Paper II

Selection bias. We excluded only 3.5% (N =6778) of women with two consecutive singleton births after the 20th gestational week from 1999–2012 (Figure 5–2). Most women were excluded due to missing information on placental weight in the first pregnancy (N =6599). In additional analyses, the descriptive statistics were similar in women included in our study sample and in women excluded due to missing information on placental weight (Table 7–3). Mean birthweight, mean gestational age, prevalence of preeclampsia in the first pregnancy and the prevalence of preeclampsia in the second pregnancy were similar in the study sample and the women excluded due to missing information on placental weight. Thus, we do not suspect that selection bias has occurred.

Table 7–3. Descriptive statistics on women excluded or included in the study sample (Paper II).

	Study sample		Missing placental weight	
N (%)	186 859	(96.5)	6599	(3.5)
First pregnancy				
Birthweight in grams, mean (SD)	3471	(572)	3408	(675)*
Gestational age in weeks, mean (SD)	39.5	(2.1)	39.1	(2.9)
Maternal age in years, mean (SD)	26.9	(4.5)	26.7	(4.6)
Diabetes, yes (%)	2575	(1.4)	84	(1.3)
Maternal smoking, yes (%)	26 817	(17.3)	980	(14.9)
Preeclampsia, yes (%)	9710	(5.2)	342	(5.2)
Second pregnancy				
Interval between pregnancies in years, mean (SD)	3.1	(1.7)	3.2	(1.8)
Preeclampsia, yes (%)	4029	(2.2)	150	(2.3)

*Missing information on birthweight N =37.

Differential misclassification. Erroneous reporting of placental weight could have occurred if reporting of placental weight differed according to occurrence of preeclampsia in the first pregnancy. The distribution of women in quintiles of placental weight z–scores in pregnancies with preeclampsia in the first pregnancy is U–shaped in accordance with previous studies[19,61] and Paper I. Erroneous reporting of placental weight in the first pregnancy related to occurrence of preeclampsia in the second pregnancy is unlikely. Therefore, we do not suspect that the differential misclassification of placental weight has biased our results.

Confounding. We identified the following potentially confounding factors: Parity,[10-12,174,197] maternal diabetes,[17,18,52,111,170] maternal smoking[18,240] and maternal age[13,239] in the first pregnancy. We also included the interval between pregnancies in our analyses.[241,243] Parity was taken into account by our study design. After adjustment for the other potentially confounding factors, our estimated associations did not notably change. Thus, we do not suspect that our results were confounded by these factors.

However, there could be other factors that have confounded our results. The associations of high placental weight in the first pregnancy and increased risk of term preeclampsia in the second pregnancy are of particular concern. As mentioned above, high body mass index has been associated with high placental weight[11,14,15] and increased risk of preeclampsia.[205-207] Women with high body mass index could therefore be contributing to the association found with high placental weight in the first pregnancy. Women may even have increased their risk of preeclampsia in the second pregnancy if their body mass index was higher in the second pregnancy.[244,245] Consequently, inter–pregnancy weight change could be the most reasonable factor to include in the analyses. The reporting of maternal body mass index to the MBRN was introduced in 2006. Thus, information about body mass index is incomplete in our data material, and further analyses on these potential associations were not possible.

7.2.2.3 Placental weight and infant death – Paper III

Selection bias. We excluded 7.2% of the singleton infants recorded in Norway from 1999–2015 due to missing information on study factors (Figure 5–3). We excluded 2.9% (N =29 372) of the infants due to missing or outlying information on placental weight. In additional analyses we compared the infants in our study sample to the infants who were excluded due to missing information on placental weight or lost to follow–up (Table 7–4). Among the infants excluded due to missing or outlying values of placental weight, the proportion of infants who died was somewhat higher than among the included infants (0.39% versus 0.24%). However, among the excluded infants who died, 40% (46/115) were born in gestational weeks 23–28. The corresponding percentage was 24% (536/2200) among the infants included in the study sample. It is therefore likely that extremely preterm births could explain the higher risk of infant death, and possibly also the non–reporting of placental weight. There is little reason to believe that these relatively few infants, who were excluded due to missing information, would have altered our estimates had they been included.

Infants with unknown vital status one year after birth (2.6%, N =25 934) were also excluded from our study sample, and most of these infants (80%, N =20 674) had emigrated from Norway. As mentioned previously, selection bias occurs when the association between the exposure and outcome differs between the study sample and the individuals excluded from the study sample.

Thus, the association among the infants excluded from our study would tend toward high mean placental weight, high mean birthweight and similar mean gestational age at birth. The supplemental data analyses show that the infants lost to follow–up had a lower mean placental weight and lower mean birthweight as compared to the infants included, but similar gestational age at birth (Table 7–4). Therefore, skewed selection of our study sample has most probably not occurred.

Table 7–4. Descriptive statistics on infants excluded or included in the study sample (Paper III).

	Study sample	**Missing placental weight**	**Lost to follow–up**
N	909 750	29 372	25 934
Infant death yes, N (%)	2200 (0.24)	115 (0.4)	Unknown
Placental weight in grams, mean (SD)	673 (151)	Unknown	662 (148)
Birthweight in grams, mean (SD)	3550 (568)	3538 (585)	3471 (554)
Maternal age in years, mean (SD)	29.6 (5.1)	29.6 (5.2)	29.2 (5.2)
Gestational age weeks, mean (SD)	39.4 (1.9)	39.3 (2.1)	39.4 (1.8)

Differential misclassification. Differential misclassification could have occurred if placental weight was erroneously reported in pregnancies in which the infant died shortly after birth as compared to infants who died within months after birth. The analyses of the associations of placental weight with neonatal death were essentially the same as the associations with infant death. Thus, we do not suspect that placental weight has been erroneously reported according to time of death.

Placental weight could also be erroneously reported in infants with congenital malformations as compared to infants without congenital malformations. We compared the associations of placental weight with infant death in infants with congenital malformations compared to infants without congenital malformations. In these analyses, the associations of placental weight with infant death appeared stronger in infants with congenital malformations born at term. Thus, differential misclassification of placental weight in infants with congenital malformations may,

to some extent, have influenced our results. Differential misclassification could also have occurred if congenital malformations were diagnosed more often in infants that succumbed to infant death. However, such misclassification would be hard to differentiate from the fact that infants with congenital malformations have an increased risk of infant death.[114,224]

Confounding. We identified the following potentially confounding factors: Offspring sex,[76,220] parity,[76,211] maternal age,[13,210] maternal smoking,[18,211] *in vitro* fertilization,[49,216,217] preeclampsia[18,181] and maternal diabetes.[17,18,112] Adjustments for these factors did not notably change any of the associations. Thus, we do not suspect that these factors have confounded our results.

Another factor that has been associated with high placental weight and increased risk of perinatal death is chorioamnionitis.[18,218] The reporting of chorioamnionitis to the MBRN has not been validated. We therefore decided not to include chorioamnionitis as a confounder. However, we performed supplementary analyses to address whether pregnancies with chorioamnionitis could have confounded our estimated associations. In our study sample, there were 584 (0.06%) pregnancies with chorioamnionitis. In gestational weeks 29–32, there were 39 pregnancies with chorioamnionitis (0.64%, 39 /6064). The mean placental weight in pregnancies with chorioamnionitis was similar to pregnancies without chorioamnionitis (Table 7–5). Also, adjustment for chorioamnionitis did not alter our estimated associations of high placental weight with infant death in infants born in gestational weeks 29–32 (Table 7–6). Thus, chorioamnionitis is not likely to have confounded the associations of high placental weight and infant death in infants born in gestational weeks 29–32.

High maternal body mass index (>25 kg/m^2) has been associated with high placental weight[11,14,15] and increased risk of infant death.[211,215] Maternal body mass index may therefore be a confounder in our study. However, the increased risk of infant death associated with high body mass index was reported to be confined to term births.[211] Thus, we do not suspect that maternal body mass index has confounded the associations of high placental weight with infant death among infants born in gestational weeks 29–32.

Table 7–5. Mean placental weight according to chorioamnionitis in 6064 singleton infants in Norway born from 1999–2015.

	Chorioamnionitis				
Gestational age at birth	**N (%) No**	**N (%) Yes**	**Placental weight, grams (SD) No**	**Yes**	**Student's t–test p–value**
29–30	2128 (98.3)	27 (1.3)	389 (134)	439 (101)	0.054
31–32	3897 (99.7)	12 (0.3)	452 (137)	504 (189)	0.193

Table 7–6. The odds ratio for infant death according to gestational age specific quartiles of placental weight.

	Infant death								
	Yes (%)	cOR	95% CI	aOR[a]	95% CI	aOR[b]	95% CI	aOR[c]	95% CI
Gestational age 29–32 weeks (N =6064)									
1st quartile of placental weight	44 (2.8)	1.32	0.89–1.94	1.32	0.90–1.95	1.60	1.08–2.38	1.61	1.08–2.38
2nd–3rd quartile of placental weight	65 (2.1)	Reference		Reference		Reference		Reference	
4th quartile of placental weight	73 (4.9)	2.37	1.69–3.33	2.36	1.68–3.32	2.08	1.48–2.94	2.08	1.48–2.94

cOR – crude OR; aOR – adjusted odds ratio; 95% CI – 95% confidence interval

[a] adjusted for chorioamnionitis.

[b] adjusted for maternal age, parity, maternal diabetes, preeclampsia, maternal smoking, pregnancies after *in vitro* fertilization and offspring sex.

[c] adjusted for maternal age, parity, maternal diabetes, preeclampsia, maternal smoking, pregnancies after *in vitro* fertilization, offspring sex and chorioamnionitis.

7.3 Interpretation of results

7.3.1 Placental weight, preeclampsia and diabetes – Paper I

We found that in pregnancies with preeclampsia, placental weight was higher in pregnancies with diabetes and lower in pregnancies without diabetes than in non–preeclamptic pregnancies. The high placental weight in preeclamptic pregnancies with diabetes was particularly pronounced in pregnancies with diabetes type–1.

Why does placental weight differ in preeclamptic pregnancies with and without diabetes?

Low placental weight has been associated with preeclampsia.[18,19,23] However, there have also been studies reporting no association between preeclampsia and placental weight,[61,87] and a study reporting an association of high placental weight with term preeclampsia (after gestational week 37).[19] The placental weight in pregnancies with diabetes has consistently been reported as being higher than in non–diabetic pregnancies.[16-18,53,83] In our study, the mean placental weight did not differ in preeclamptic pregnancies with diabetes and pregnancies with diabetes only. Based on our results, it is likely that the associations of high placental weight in preeclamptic pregnancies are attributable to maternal diabetes. Thus, it is possible that the biological mechanisms that cause preeclampsia differ according to maternal diabetes status.

Defective trophoblast differentiation and reduced invasion of the *decidua* have been reported in pregnancies with preeclampsia.[107,109,186] In pregnancies with diabetes, hyperglycemia may reduce trophoblast proliferation and invasion of the *decidua*.[106,160] Consequently, these changes have been linked to the increased risk of preeclampsia in pregnancies with diabetes.[161] However, these changes in the placental structure do not necessarily explain the high placental weight seen in preeclamptic pregnancies with diabetes.

Hypervascularization and hyperproliferation of the villi have been described in pregnancies with diabetes.[105,106] Such changes in the placental structure have also been described as compensatory mechanisms to preplacental hypoxia.[102,103] The high placental weight in pregnancies with diabetes may be interpreted as a result of these changes in the placental structure. Diabetes may also represent a maternal origin of preeclampsia.[185] Women with diabetes have an increased risk of vascular dysfunction which may impair tissue oxygenation and cause preplacental and

uteroplacental hypoxia.[106] Vascular dysfunction is likely to increase with the duration of diabetes[164] and may be more pronounced in women with pregestational diabetes as compared to gestational diabetes. Women with diabetes type–1 are likely to have had diabetes for the longest time, and sustained vascular dysfunction could partially explain why our results were most pronounced in preeclamptic pregnancies with diabetes type–1.

The diffusion distance across the placental membranes seems to be increased in pregnancies with diabetes due to the accumulation of collagens in the placental villi.[162] Such changes in the placental structure have been associated with uteroplacental hypoxia, and may contribute to increased placental weight. Both vascular dysfunction and the increased diffusion distance across the placental membranes could explain the up–regulation of GLUT–1 transporters in the basal membrane of the syncytium reported in pregnancies with diabetes, which increase glucose transport across the placental membranes and ensure fetal growth.[116,118] A large placenta may also require a substantial amount of oxygen itself, which could contribute to deficient oxygen transfer to the fetus. Taken together, the high placental weight in preeclamptic pregnancies with diabetes may be a combination of pathological processes of diabetes causing hypoxia and the uteroplacental compensatory mechanisms to hypoxia.

Why does the placental to birthweight ratio differ in preeclamptic pregnancies with and without diabetes?

Preeclampsia has been associated with a high placental to birthweight ratio.[5] Maternal diabetes has also been associated with an increased placental to birthweight ratio.[5,16,17] However, there has also been a study reporting no association of maternal diabetes with placental to birthweight ratio.[11] In our study, the placental to birthweight ratio was higher in preeclamptic pregnancies with diabetes as compared to preeclamptic pregnancies without diabetes.

In preeclamptic pregnancies with diabetes, the high placental to birthweight ratio is likely to represent a high placental weight and a normal or high birthweight. Diabetes may represent a maternal origin of preeclampsia,[185] and high placental weight in preeclamptic pregnancies with diabetes may be a combination of pathological processes of diabetes causing hypoxia and the uteroplacental compensatory mechanisms to hypoxia. High placental to birthweight ratio has

been suggested to be an indicator of adverse intrauterine conditions.[3] Accordingly, the high placental to birthweight ratio seen in preeclamptic pregnancies with diabetes may serve as an indicator of decreased uteroplacental function and possibly preplacental and uteroplacental hypoxia. The percentage of low (1st decile) birthweights was higher in preeclamptic pregnancies with diabetes than the percentage of low (1st decile) birthweights in pregnancies with diabetes only. Consequently, the development of preeclampsia in women with diabetes may be an indicator of the severity of the uteroplacental hypoxia, and fetal growth restriction may be the result of a compensatory mechanism to hypoxia.

In preeclamptic pregnancies without diabetes, the high placental to birthweight ratio is likely to represent a low placental weight and a relatively even lower birthweight since placental weight was low in these pregnancies. GLUT–1 receptors are down–regulated in the microvillous membrane of the syncytium in preeclamptic pregnancies *in vitro*.[246] If this down–regulation also occurs *in vivo* it could contribute to decreased glucose transport across the placental membranes in preeclamptic pregnancies, and form part of the mechanism that causes fetal growth restriction. In preeclamptic pregnancies without diabetes, the percentage of low (1st decile) birthweights was higher than the percentage of low (1st decile) placental weights. Thus, fetal growth restriction as a compensatory mechanism to uteroplacental hypoxia and decreased glucose transport may be the cause of the relative difference in fetal and placental growth seen in preeclamptic pregnancies without diabetes.

7.3.2 Placental weight and preeclampsia in the second pregnancy – Paper II

We found that low placental weight in the first pregnancy increased the risk of preeclampsia in the second pregnancy in women with and without preeclampsia in the first pregnancy. Additionally, in women without preeclampsia in the first pregnancy, high placental weight was associated with an increased risk of developing term preeclampsia in the second pregnancy.

Why does low placental weight in the first pregnancy increase the risk of preeclampsia in the second pregnancy both in women with and in women without preeclampsia in the first pregnancy?
Implantation and placental growth depends on a well–functioning endometrium,[247] and placental weight could be interpreted as an expression of a woman's angiogenic ability. To give an

example, pregestational hypertension is a risk factor for preeclampsia.[200,203] Women with pregestational hypertension have also been associated with low placental weight.[18] Thus, an interpretation of this finding could be that women with pregestational hypertension express insufficient angiogenic ability. Consequently, low placental weight in the first pregnancy may be an expression of insufficient maternal angiogenic ability and thereby an indicator of an increased risk of preeclampsia in the second pregnancy.

An exaggerated maternal immune response to pregnancy has been suggested as a maternal cause of preeclampsia, and the clinical presentation of preeclampsia could be explained by a systemic immune response.[185] It is theoretically possible that underlying maternal factors that caused low placental weight in the first pregnancy induce an immune response and generate immune memory. Thus, a second pregnancy could induce an exaggerated maternal immune response and induce the development of preeclampsia. An accelerated immune response in the second pregnancy could also explain the associations of low placental weight with preterm preeclampsia.

Previous studies have shown that giving birth to a small for gestational age baby increases a woman's risk of preeclampsia in the second pregnancy,[202] but also the risk of cardiovascular disease and death from cardiovascular diseases.[177,248-253] The placenta is a determinant of the achieved birthweight.[134-136] Consequently, it is possible that low placental weight in the first pregnancy could also be an indicator of a woman's risk of cardiovascular disease and death from cardiovascular disease.

Why does high placental weight in the first pregnancy increase the risk of term preeclampsia in the second pregnancy?

It has been suggested that term preeclampsia is less severe than preterm preeclampsia.[63,254] The prevalence of maternal diabetes and small for gestational age offspring are lower among women with term preeclampsia as compared to women with preterm preeclampsia.[63,255] Women with term preeclampsia also have a lower long–term risk of death from cardiovascular diseases as compared to women with preterm preeclampsia.[176] Thus, high placental weight in the first pregnancy might be an expression of sufficient angiogenic ability in the woman, although close to the threshold of what might be biologically acceptable. Consequently, deterioration of the

cardiovascular risk factors from the first to the second pregnancy could lead to an increased risk of preeclampsia in the second pregnancy.

Acute atherosis of the spiral arteries has been associated with preeclampsia.[192,193] Acute atherosis, however, does not appear to be associated with the lack of trophoblastic remodeling of the spiral arteries typical for early onset preeclampsia.[192] Thus, underlying maternal factors known to predispose to high placental weight and acute atherosis, such as maternal diabetes and obesity,[11,14-18,192] could explain the association of high placental weight in the first pregnancy with the risk of preeclampsia in the second pregnancy. Also, interpregnancy weight gain may aggravate the systemic inflammation associated with diabetes type–2 and obesity,[256,257] and interpregnancy weight gain has been associated with an increased risk of gestational diabetes[245,258] and preeclampsia.[244,245] An interpretation of this may be that an aggravation of the conditions causing systemic inflammation could induce an exaggerated maternal immune response and thereby preeclampsia in the second pregnancy.[185]

A recent study reported that women who gave birth to a large preterm baby had an increased risk of death from cardiovascular diseases.[259] The study also reported that women who gave birth to a large for gestational age baby had an increased risk of diabetes in their next pregnancy,[259] a finding that has been reported by others.[248] The placenta is a determinant of the achieved birthweight.[134-136] Thus, it is possible that high placental weight in the first pregnancy could also be an indicator of a woman's risk of cardiovascular disease and death from cardiovascular disease.

7.3.3 Placental weight and infant death – Paper III

We found that in most infants, low placental weight increased the risk of infant death. However, the results differed for infants born in gestational weeks 29–32 and, in these infants, high placental weight increased the risk of infant death.

Why does low placental weight increase the risk of infant death?

Being born small for gestational age has been associated with increased risk of infant death in

both preterm and term born infants,[31-34,67] and small for gestational age offspring has been associated with low placental weight.[22,61,88] Low placental weight may therefore be an indicator of adverse intrauterine conditions, decreased uteroplacental function and possibly uteroplacental hypoxia. Low placental weight has previously been associated with fetal death.[8,21] Our findings suggest that the adverse intrauterine conditions indicated by low placental weight also increase the risk of death in the first year of life.

Among infants born at term, the association of low placental weight with infant death was significant only for infants with congenital malformations. Thus, it is possible that the underlying mechanisms that cause low placental weight also cause congenital malformations.[89] Consequently, these underlying mechanisms may also increase the risk of infant death.

In infants without congenital malformations born at term, placental weight was not associated with risk of infant death. It is possible that infants without congenital malformations born in gestational week 37–42 have had intrauterine conditions which do not show signs of pathology indicating iatrogenic preterm birth or intrauterine conditions causing spontaneous preterm birth. Thus, these infants may represent the most homogeneous group of placentas and infants in our study. However, we have compared the 25% lowest or highest placental weights with the 50% middle placental weights. Such analyses may not reveal all patterns of the association of placental weight with infant death. For example, it is possible that a division of placental weights in groups of less than 25%, for instance comparing the 10% lowest and highest placental weights (deciles) with the 20% (or 40%) in the middle could reveal an association of low placental weight with infant death among infants without congenital malformations born at term. It is also possible that analyses of placental weight as a continuous variable could reveal an association of placental weight with infant death in infants born at term.

Why does high placental weight increase the risk of infant death?

Similar associations of high placental weight have been found for preterm fetal death and spastic quadriplegia in preterm born infants.[8,9] Fetal death and severe cerebral palsy might share underlying mechanisms with infant death. However, the mechanisms causing high placental weight among infants born in gestational weeks 29–32 have not yet been discovered. The

associations of high placental weight with infant death appeared to be stronger among infants without congenital malformations. High placental weight may be a consequence of increased angiogenesis as a compensatory mechanism to preplacental hypoxia.[102,103] It is possible that the compensatory mechanisms that caused high placental weight also increased the risk of infant death.

The placenta is a determinant of the achieved birthweight,[134-136] and birthweight above the 90th percentile has been associated with increased risk of infant death in infants born in gestational weeks 28–31.[67] In our study, high birthweight did not increase the risk of infant death significantly in infants born in gestational weeks 29–32, however, the risk of neonatal death was significantly increased. An interpretation of this difference could be that the adverse intrauterine conditions associated with high birthweight are severe and increases the risk of death shortly after birth. The mechanisms behind the association of high birthweight with risk of infant death have not yet been discovered. However, it is likely that the discovery of the mechanisms causing high placental weight also could give information about the mechanisms causing high birthweight.

Among infants born at term, birthweight above the 97th percentile has been associated with an increased risk increased risk of perinatal and neonatal death.[33,69] Thus, it is possible that division of placental weight into in groups of less than 25% could reveal an association of high placental weight with infant death among infants born at gestational age 33–42 weeks.

Why does high placental to birthweight ratio increase the risk of infant death?

Among the infants with low placental weight who died, the placental to birthweight ratio was high. The high placental to birthweight ratio in these infants is likely to be an expression of a low placental weight and a relatively even lower birthweight. Consequently, it is possible that fetal growth restriction is the result of compensatory mechanisms induced by decreased uteroplacental function and uteroplacental hypoxia.[102,103] The association of high placental to birthweight ratio with infant death decreased with gestational age and, at term, the increased risk of infant death associated with high placental to birthweight ratio was only statistically significant in infants with congenital malformations. Thus, the compensatory mechanism induced by uteroplacental

hypoxia and decreased uteroplacental function could be more prominent in pregnancies with fetuses with malformations than in pregnancies with fetuses without malformations.

Among the infants born in gestational weeks 29–32 who died, the placental to birthweight ratio was high. The high placental to birthweight ratio in these infants is likely to be an expression of a high placental weight and an appropriate or high birthweight. High placental to birthweight ratio is most likely an expression of adverse intrauterine conditions among these infants. However, the mechanisms that cause disproportionate placental and fetal growth among infants born in gestational weeks 29–32 have not yet been discovered.

7.4 Clinical implications

7.4.1 Placental weight, preeclampsia and diabetes – Paper I

We identified that the associations of high placental weight in preeclamptic pregnancies could be attributable to maternal diabetes. Thus, we have contributed to increased knowledge about factors that influence placental weight. We also suggest that the mechanisms behind the development of preeclampsia may differ according to maternal diabetes status. This may have implications for future studies and future treatment of preeclampsia.

7.4.2 Placental weight and preeclampsia in the second pregnancy – Paper II

In women with low placental weight and preeclampsia in the first pregnancy, the absolute risk of preterm preeclampsia in the second pregnancy was 6.4%. Thus, knowledge of low placental weight in the first pregnancy may primarily be of clinical value to women with preeclampsia in the first pregnancy. However, prophylactic treatment for preeclampsia has been recommended for women at high risk of preeclampsia in the second pregnancy (for instance, previous early onset preeclampsia) in Norway since 2014.[260] The prophylactic treatment with acetylsalicylic acid for women at high risk of preeclampsia in the second pregnancy has hopefully lowered the recurrence risk of preeclampsia. However, it is not known whether prophylactic treatment has influenced the association of placental weight in the first pregnancy with recurrence risk of preeclampsia.

In women without preeclampsia in the first pregnancy, both high and low placental weight increased the risk of preeclampsia in the second pregnancy. Among the women without preeclampsia in the first pregnancy, the absolute risk of preterm preeclampsia associated with low placental weight was only 0.4%. However, women with low placental weight could benefit from the prediction of their increased risk of preterm preeclampsia in the second pregnancy, as women with preterm preeclampsia have an 8–fold increase in the risk of death from cardiovascular causes as compared to women with term preeclampsia or women without preeclampsia.[176] Consequently, the prevention of preterm preeclampsia in the second pregnancy could lower the risk of death from cardiovascular disease among these women.[253]

The absolute risk of term preeclampsia in the second pregnancy was 1.3% for both high and low placental weight in women without preeclampsia in the first pregnancy. Although the absolute risk is low, it is possible that both high and low placental weight in the first pregnancy may identify women without previous preeclampsia who could benefit from prophylactic treatment for preeclampsia in the second pregnancy. Also, women with preeclampsia have an increased risk of death from cardiovascular causes.[180] Thus, the risk of preeclampsia could potentially also predict the risk of subsequent cardiovascular disease. Consequently, it is possible that women at increased risk of development of preeclampsia could benefit from closer follow–up of their cardiovascular health later in life.[253]

7.4.3 Placental weight and infant death – Paper III

In most infants, low placental weight increased the risk of infant death and knowledge of placental weight among these infants could identify infants at increased risk of death. However, in infants born at term, the association of low placental weight with risk of infant death was confined to infants with congenital malformations. Consequently, knowledge of placental weight and the placental to birthweight ratio may primarily be of clinical value to preterm born infants.

Among the 6064 infants born in gestational weeks 29–32, the absolute risk of infant death was 4.9% in infants with high placental weight as compared to an absolute risk of 2.2% in infants with average placental weight. The absolute risk of infant death was 5.2% in infants with a high placental to birthweight ratio as compared to 2.2% in infants with average placental to

birthweight ratio. Neither high nor low birthweight was associated with infant death in infants born in gestational weeks 29–32. Consequently, high birthweight is not a sign of increased survival in these infants as it appears to be in infants born at other gestational ages. Infants born in gestational weeks 29–32 are most likely to be admitted to a neonatal intensive care unit immediately after birth, and their clinical parameters probably show signs of increased risk of death. However, information about placental weight and the placental to birthweight ratio could give additional information on the risk of infant death shortly after birth. Studies of causes of death could provide more information about the interventions needed to avoid adverse outcomes among these infants.

8 Future perspectives

Although we have contributed to increased knowledge about factors that influence placental weight, there is still a lack of knowledge regarding the factors that influence placental weight. The growth pattern of the placenta has been estimated on placental weight after parturition. Although placental weight is an indicator of placental growth, we do not know whether placentas after parturition in gestational week 24 are a representative sample of the placentas that continue to gestational week 25 and so on. Consequently, we do not know whether we can transfer our knowledge of placental weight after parturition to intrauterine placentas that cannot be weighed. If intrauterine placental growth could be estimated, signs of adverse intrauterine conditions could be detected. Thus, longitudinal studies on intrauterine placentas that use modalities capable of estimating placental weight with comparison to placental weight after parturition are warranted.

Prophylactic treatment for preeclampsia with acetylsalicylic acid has been recommended for women at high risk in Norway since 2014.[260] It should be studied whether the implementation of prophylactic treatment has lowered the recurrence risk of preeclampsia in Norway. Based on our findings in women without preeclampsia in the first pregnancy, a study of whether the risk of preeclampsia in the second pregnancy has been reduced by the use of acetylsalicylic acid in women with high or low placental weight in the first pregnancy could be conducted. Women with diabetes are not listed to be targeted for prophylactic treatment for preeclampsia, however prophylactic treatment may be indicated on other criteria. Nonetheless, since the mechanisms behind the development of preeclampsia may differ according to maternal diabetes status it could be well worth studying whether prophylactic treatment with acetylsalicylic acid is indicated or should be avoided in women with diabetes.

Also, pregnancy may be a missed opportunity to address women's cardiovascular health. If placental weight in the first pregnancy is an indicator of the risk of preeclampsia, placental weight in the first pregnancy may also be an indicator of the risk of cardiovascular disease. Thus, future studies could assess whether placental weight in the first pregnancy is associated with the risk of cardiovascular disease later in life.

It is possible that introducing placental weight as a predictor of the risk of infant death could improve the identification of infants at increased risk of death, especially in preterm born infants. Future studies could also address whether placental weight could identify infants at risk of other adverse outcomes. Studies of the morphology of placentas associated with adverse outcomes for mother and infant could potentially provide additional information about causes of high and low placental weight. However, future studies should address the gestational age–specific risk of adverse outcomes, as we have demonstrated that the associations of placental weight may differ according to gestational age at birth.

9 Conclusions

We found that both high and low placental weight were associated with maternal disease (preeclampsia and diabetes) and consequences for the infant (infant death).

- Placental weight was higher in preeclamptic pregnancies with diabetes and lower in preeclamptic pregnancies without diabetes than in non–preeclamptic pregnancies.

- Low placental weight in the first pregnancy increased the risk of preeclampsia in the second pregnancy in women with and in women without preeclampsia in the first pregnancy. Additionally, in women without preeclampsia in the first pregnancy, high placental weight increased the risk of developing term preeclampsia in the second pregnancy.

- In most infants, low placental weight increased the risk of infant death. However, in infants born in gestational weeks 29–32, high placental weight increased the risk of infant death.

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Appendix

II

European Journal of Obstetrics & Gynecology and Reproductive Biology 214 (2017) 184–189

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Placental weight in the first pregnancy and risk for preeclampsia in the second pregnancy: A population-based study of 186 859 women

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ARTICLE INFO

Article history:
Received 15 December 2016
Received in revised form 9 May 2017
Accepted 12 May 2017

Keywords:
Placental weight
Population study
Preeclampsia
Pregnancy

ABSTARCT

Objective: To study whether placental weight in the first pregnancy is associated with preeclampsia in the second pregnancy.
Study design: In this population-based study, we included all women with two consecutive singleton pregnancies reported to the Medical Birth Registry of Norway during 1999–2012 (n = 186 859). Placental weight in the first pregnancy was calculated as z-scores, and the distribution was divided into five groups of equal size (quintiles). We estimated crude and adjusted odds ratios with 95% confidence intervals for preeclampsia in the second pregnancy according to quintiles of placental weight z-scores in the first pregnancy. The 3rd quintile was used as the reference group.
Results: Among women without preeclampsia in the first pregnancy, 1.4% (2507/177 149) developed preeclampsia in the second pregnancy. In these women, the risk for preeclampsia in the second pregnancy was associated with placental weight in the first pregnancy in both lowest (crude odds ratio (cOR) 1.30, 95% confidence interval (CI); 1.14–1.47) and highest quintile (cOR 1.20, 95% CI; 1.06–1.36). The risk associated with the highest quintile of placental weight was confined to term preeclampsia. Among women with preeclampsia in the first pregnancy, 15.7% (1522/9710) developed recurrent preeclampsia, and the risk for recurrent preeclampsia was associated with placental weight in lowest quintile in the first pregnancy (cOR 1.30, 95% CI; 1.10–1.55). Adjustment for interval between pregnancies, maternal diabetes, age, and smoking in the first pregnancy did not alter these estimates notably.
Conclusion: Placental weight in the first pregnancy might help to identify women who could be at risk for developing preeclampsia in a second pregnancy.

Introduction

Preeclampsia is a pregnancy complication characterized by high blood pressure and proteinuria. The condition arises in about 3–6% of first pregnancies, and in 1–2% of second pregnancies [1,2] Preeclampsia is associated with increased risk for preterm delivery, intrauterine growth restriction, and perinatal mortality [3]. Despite its clear impact on maternal and infant health, the etiology of this condition is not well understood, and prediction of women who will develop preeclampsia is difficult.

Studies suggest that there is a strong correlation between pre-pregnancy cardiovascular risk factors and development of pre-eclampsia [4], and also between preeclampsia and cardiovascular disease later in life [5]. Several of the cardiovascular risk factors associated with preeclampsia such as high body mass index, diabetes and chronic hypertension have also been associated with placental weight [6–8]. Abnormal placental development is considered the prevailing cause of preeclampsia [9], and both small and large placentas are overrepresented in preeclamptic pregnancies [10].

Taken together, these studies suggest that factors that increase cardiovascular disease risk also contribute to the placental pathology that causes both abnormal placental weight and

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http://dx.doi.org/10.1016/j.ejogrb.2017.05.010

preeclampsia. If this is true, high or low placental weight may be a marker of a woman's underlying risk for preeclampsia. If placental weight is a marker of a woman's risk for preeclampsia, the placental weight from the first pregnancy could possibly predict the risk for preeclampsia in a subsequent pregnancy. If so, placental weight could be routinely measured and used to identify women at higher risk for developing preeclampsia in a future pregnancy. To our knowledge, the possible association of placental weight in the first pregnancy with the risk for preeclampsia in the second pregnancy has not been studied.

Among 186 859 women in Norway with their first and second singleton pregnancy during a 14 year period (1999–2012), we studied the association of placental weight in the first pregnancy with the risk for preeclampsia in the second pregnancy.

Materials and methods

We performed a population-based study using data from the Medical Birth Registry of Norway. The Medical Birth Registry contains information on all births after the 16th gestational week in Norway since 1967 [11]. The reporting is compulsory by law and is performed by the doctor or the midwife in charge of the delivery. Placental weight has been reported since 1999.

In this study, we included women with a first and second singleton delivery after the 20th gestational week during the period 1999–2012 (n = 193 637). We excluded women with missing information on placental weight (n = 6599), birthweight (n = 170) or offspring sex (n = 9). A total of 6778 women were thus excluded, leaving 186 859 women for statistical analyses.

Preeclampsia in second pregnancy was our outcome variable. Preeclampsia was reported to the Medical Birth Registry. The diagnosis was made by clinical examination in antenatal care and/or at the maternity ward [12] and defined as blood pressure ≥140/90 mmHg combined with proteinuria (protein dipstick 1+ or > 0.3 g/24 h) after the 20th gestational week. Almost all women in Norway attend the public antenatal health care program, and on average, each woman has attended twelve antenatal care visits before delivery, with increasing frequency as the pregnancy proceeds. Preeclampsia with preterm delivery is likely to be an indicator of early onset and severe preeclampsia [13], and we performed sub-analyses using preterm (delivery before pregnancy week 37) and term preeclampsia (delivery in pregnancy week 37 or later) as secondary outcomes.

Our main exposure variable was placental weight in the first pregnancy. The placenta was weighed within one hour after delivery at the obstetric ward, with membranes and umbilical cord according to obstetric standards in Norway.

The following variables from the first pregnancy were included in the data analyses as potentially confounding factors: birthweight (in grams) [14], preeclampsia (yes/no) [14], maternal diabetes (yes/no) [7], maternal age (in years) [15], maternal smoking (yes/no) [16], and the interval between pregnancies (in years) [17]. Diabetes included; diabetes type-1, type-2, gestational diabetes, non-specified diabetes prior to pregnancy, and use of oral anti-diabetic medication. Gestational diabetes was diagnosed in the antenatal screening program, and was defined as a plasma glucose concentration ≥7.8 − <11.1 mmol/l two hours after 75 mg oral glucose tolerance test. Smoking was reported as daily or occasional smoking at the first antenatal visit, typically pregnancy week 8–12.

Differences in the distribution of study factors in the first pregnancy according to development of preeclampsia in the second pregnancy were tested by using the Student's t-test for continuous variables and the Chi-square test for categorical variables.

Placental weight and birthweight are closely linked to gestational age at birth. To adjust for differences in gestational age between pregnancies, we calculated z-scores of placental weight by using means and standard deviations of placental weight for each pregnancy week at birth in the sample as a whole. Z-scores were calculated separately for male and female offspring. Gestational age at birth was estimated on the basis of a routine ultrasonographic fetal examination in pregnancy week 17–19. If ultrasonographic examination had not been performed (for 2.7%), gestational age at birth was based on the first day of the last menstruation. The distribution of placental weight z-scores in the first pregnancy was divided into quintiles. Thus, 20% of the pregnancies were expected to fall into each quintile, assuming normal distribution.

The risks for preeclampsia in the second pregnancy according to quintiles of placental weight z-score in the first pregnancy were estimated as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) separately for women with and women without preeclampsia in the first pregnancy. Women with placental weight z-scores in the 3rd quintile were used as the reference group. In additional analyses, we estimated the risks for preterm and for term preeclampsia in the second pregnancy. Women who delivered preterm were not included in the analyses of risk for term preeclampsia. All statistical analyses were conducted by using the IBM SPSS Statistics Version 22.0, (IBM Corp., Armonk, NY, USA).

The Medical Birth Registry of Norway is approved by the Norwegian Data Inspectorate. The use of data for this study was approved by the Regional Committee for Ethics in Medical Research (Reference number 2014/131).

Results

Characteristics of our study sample are presented in Table 1. In total, 5.2% (9710/186 859) of all women had preeclampsia in the

Table 1
Means and proportions of study factors in the first pregnancy among 186 859 women in Norway with their first and second singleton pregnancies during the years 1999–2012.

Study factors in first pregnancy	Total	Preeclampsia in first pregnancy		
		Yes	No	p-value
Total number (%)	186 859 (100)	9710 (5.2)	177 149 (94.8)	
Placental weight in grams (SD)	660 (185)	625 (201)	662 (184)	<0.001†
Birthweight in grams (SD)	3471 (572)	3134 (840)	3490 (547)	<0.001†
Gestational age in weeks (SD)	39.5 (2.1)	38.0 (3.1)	39.5 (2.0)	<0.001†
Maternal age years (SD)	26.9 (4.5)	26.7 (4.6)	26.9 (4.5)	<0.001†
Interval between pregnancies in years (SD)	3.1 (1.7)	3.2 (1.7)	3.1 (1.7)	<0.001†
Diabetes, number (%)	2575 (1.4)	325 (3.3)	2250 (1.3)	<0.001‡
Smoking, number (%)	26817 (17.3)	1230 (15.2)	25 587 (17.4)	<0.001‡

SD, standard deviation.
†Student's t-test.
‡Chi-square test.

first, and 2.2% (4029/186 859) had preeclampsia in the second pregnancy. Of the women with preeclampsia in the first pregnancy, the risk for recurrence was 15.7% (1522/9710), and 0.8% (1522/186 859) of all women had preeclampsia in both pregnancies. The women with recurrent preeclampsia represented 37.8% (1522/4029) of all cases of preeclampsia in the second pregnancy, and 62.2% (2507/4029) of the preeclampsia cases in the second pregnancy had no history of preeclampsia (Fig. 1).

Women without previous preeclampsia

Among women without preeclampsia in the first pregnancy, mean placental weight in the first pregnancy was 662 g (SD 184 g), and mean birthweight was 3490 g (SD 547 g) (Table 1). The overall absolute risk for preeclampsia in the second pregnancy was 1.4%, and the risk was 1.6% for women with low placental weight (1st quintile) and 1.5% for women with high placental weight (5th quintile) in the first pregnancy (Table 2). The OR for preeclampsia in the second pregnancy was increased for both low (cOR 1.30, 95% CI; 1.14–1.47) and for high placental weight (cOR 1.20, 95% CI; 1.06–1.36) in the first pregnancy as compared to women with placental weight in the 3rd quintile (reference). Low placental weight in the first pregnancy increased the risk both for preterm and for term preeclampsia in second pregnancy (Table 3, Fig. 2a and b). However, the increased risk for preeclampsia associated with high placental weight was confined to term preeclampsia (cOR 1.32, 95% CI; 1.15–1.53) (Table 3, Fig. 2b).

Women with previous preeclampsia

Among women with preeclampsia in the first pregnancy, mean placental weight in the first pregnancy was 625 g (SD 201 g), and mean birthweight was 3134 g (SD 840 g) (Table 1). The overall recurrence risk for preeclampsia was 15.7%, and the recurrence risk was 18.5% for women with low placental weight in the first pregnancy (Table 2). The OR for preeclampsia in the second pregnancy was increased for low placental weight in the first pregnancy as compared to the reference group (3rd quintile) (cOR 1.30, 95% CI; 1.10–1.55) (Table 2). Low placental weight increased the risk particularly for preterm preeclampsia in the second pregnancy. The absolute risk for preterm preeclampsia in the second pregnancy was 6.4% in women with low placental weight (cOR 1.58, 95% CI; 1.18–2.12) (Table 3, Fig. 2c). Adjustment for other study factors did not alter any of the above estimated ORs notably (Table 2, Table 3).

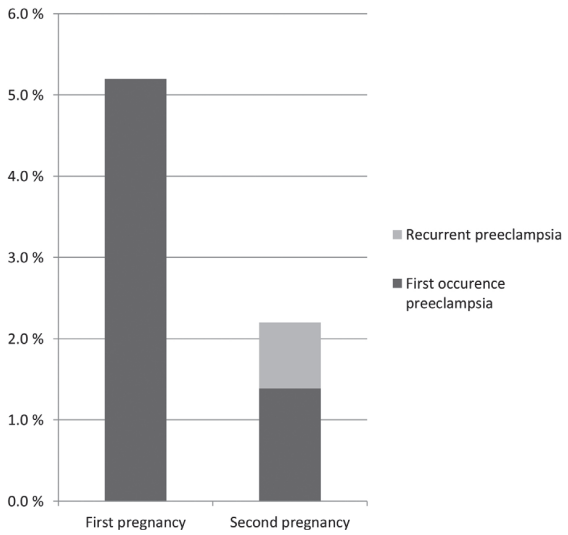

Fig. 1. Prevalence of preeclampsia in first and second pregnancy among 186 859 women in Norway with two consecutive singleton pregnancies during the years 1999–2012.

Comment

In this study of 186 859 women with two singleton pregnancies, we found that low placental weight in the first pregnancy increased the risk for preeclampsia in the second pregnancy. Additionally, in women without preeclampsia in the first pregnancy, high placental weight increased the risk for developing term preeclampsia in the second pregnancy.

We used data from the Medical Birth Registry of Norway, and the source population included all women in Norway with two singleton pregnancies during the years 1999–2012. Women with missing information on study variables were excluded (3.5%), of whom the majority (97%) were excluded due to missing information on placental weight in the first pregnancy. In separate analyses of women excluded due to missing placental weight, the prevalences of preeclampsia in first and second pregnancies were similar to the women included in our analyses. Also, mean offspring birthweight was similar, suggesting no selection bias.

Some women with severe preeclampsia in a first pregnancy may not have a second pregnancy. Thus, the women with severe preeclampsia in the first pregnancy may be underrepresented in our study, and it is possible that our estimated association of low placental weight with risk for recurrent preeclampsia represents an underestimate. It is also possible that the interval between pregnancies may be longer for women with previous preeclampsia as compared to women without previous preeclampsia [17]. However, adjustment for interval between pregnancies did not change the associations notably.

The diagnosis of preeclampsia in the Medical Birth Registry has high validity [12]. Also, the prevalence of preeclampsia in the first and in the second pregnancy in our study was similar to other studies [2,18]. Erroneous reporting of placental weight and other study factors in the first pregnancy may have occurred, but it is unlikely that such possible misclassifications differed by occurrence of preeclampsia in the second pregnancy.

Placental weight is strongly influenced by gestational age at birth, and pregnancies with preeclampsia may have shorter duration than pregnancies without preeclampsia. Therefore, we made adjustment for possible differences in gestational age at birth by using z-scores. We also made adjustments for maternal diabetes, age, smoking and interval between pregnancies, since preeclampsia and placental weight previously has been associated with these factors [7,15–17]. However, both in pregnancies with and pregnancies without previous preeclampsia, adjustments for these factors did not alter our estimates notably. Unfortunately, information on changes from first to second pregnancy in maternal body mass index, blood pressure or other risk factors of cardiovascular disease was not available. To study whether placental weight in preterm and in term preeclampsia in the first pregnancy is associated with preterm or with term preeclampsia in the second pregnancy was beyond the scope of this study.

To our knowledge, the association of placental weight in the first pregnancy with risk for preeclampsia in the second pregnancy has not previously been reported. However, low birthweight in the first pregnancy has been associated with increased risk for preeclampsia in the second pregnancy, independent of previous preeclampsia [14]. This previous finding supports our results since birthweight and placental weight are correlated [19].

We found that low placental weight in the first pregnancy was associated with preeclampsia in the second pregnancy in women without, and in women with previous preeclampsia. The

Table 2
Crude and adjusted odds ratios for preeclampsia in the second pregnancy according to quintiles of placental weight z-score in the first pregnancy- among women without preeclampsia (*n* = 177 149) and women with preeclampsia (*n* = 9710) in the first pregnancy in Norway during the years 1999–2012.

Placental weight z-score in first pregnancy	Mean placental weight, g (SD)	Preeclampsia in second pregnancy							
		Yes	%	No	%	cOR	95% CI	aOR	95% CI
Total	660 (185)	4029	2.2	182 830	97.8				
Without preeclampsia in first pregnancy									
1st quintile	482 (66)	560	1.6	34 272	98.4	1.30*	1.14- 1.47	1.28*	1.12- 1.47
2nd quintile	583 (46)	489	1.4	35 422	98.6	1.09	0.96- 1.25	1.03	0.90- 1.19
3rd quintile	646 (52)	444	1.2	35 184	98.8	Reference		Reference	
4th quintile	722 (56)	487	1.4	34 934	98.6	1.11	0.97- 1.26	1.07	0.93- 1.23
5th quintile	876 (262)	527	1.5	34 830	98.5	1.20*	1.06- 1.36	1.15	1.00- 1.33
Total	662 (184)	2507	1.4	174 642	98.5				
With preeclampsia in first pregnancy									
1st quintile	431 (95)	412	18.5	1816	81.5	1.30*	1.10- 1.55	1.26*	1.04- 1.52
2nd quintile	535 (96)	300	16.4	1531	83.6	1.13	0.94- 1.35	1.16	0.95- 1.41
3rd quintile	606 (87)	257	14.8	1476	85.2	Reference		Reference	
4th quintile	695 (75)	242	13.5	1556	86.5	0.89	0.74- 1.08	0.92	0.75- 1.13
5th quintile	861 (223)	311	14.7	1809	85.3	0.99	0.83- 1.18	0.93	0.77- 1.14
Total	625 (201)	1522	15.7	8188	84.3				

SD, standard deviation; cOR, crude odds ratios; 95% CI, 95% confidence interval; aOR, odds ratios adjusted for maternal diabetes, age and smoking in the first pregnancy and interval between pregnancies.
*Statistical significant OR.

Table 3
Crude and adjusted odds ratios with 95% confidence intervals for preterm and for term preeclampsia in the second pregnancy according to quintiles of placental weight z-score in the first pregnancy, among women without preeclampsia in the first pregnancy (n = 177 149) and women with preeclampsia in the first pregnancy (n = 9710).

Placental weight z-score in first pregnancy	n	Preterm preeclampsia in second pregnancy						Term preeclampsia in second pregnancy					
		Yes	%	cOR	95% CI	aOR	95% CI	Yes	%	cOR	95% CI	aOR	95% CI
Total	186 859	945	0.5					3084	1.7				
Without preeclampsia in the first pregnancy													
1 st quintile	34 832	144	0.4	1.42*	1.10–1.83	1.48*	1.13–1.95	416	1.3	1.27*	1.10–1.46	1.22*	1.05–1.43
2nd quintile	35 911	90	0.3	0.86	0.65–1.14	0.81	0.59–1.11	399	1.2	1.17*	1.01–1.35	1.10	0.93–1.29
3rd quintile	35 628	104	0.3	Reference		Reference		340	1.0	Reference		Reference	
4th quintile	35 421	97	0.3	0.94	0.71–1.24	0.90	0.67–1.23	390	1.1	1.15	1.00–1.33	1.13	0.96–1.32
5th quintile	35 357	82	0.2	0.79	0.59–1.06	0.77	0.56–1.05	445	1.3	1.32*	1.15–1.53	1.30*	1.12–1.52
Total	177 149	517	0.3					1990	1.2				
With preeclampsia in the first pregnancy													
1 st quintile	2228	143	6.4	1.58*	1.18–2.12	1.62*	1.17–2.26	269	13.6	1.20	0.98–1.46	1.12	0.90–1.40
2nd quintile	1831	97	5.3	1.29	0.94–1.76	1.42*	1.01–2.01	203	12.4	1.07	0.87–1.33	1.08	0.86–1.36
3rd quintile	1733	72	4.2	Reference		Reference		185	11.7	Reference		Reference	
4th quintile	1798	47	2.6	0.62*	0.43–0.90	0.71	0.47–1.07	195	11.6	0.99	0.80–1.23	0.96	0.79–1.26
5th quintile	2120	69	3.3	0.78	0.55–1.09	0.84	0.58–1.22	242	12.4	1.07	0.87–1.31	1.01	0.81–1.26
Total	9710	428	4.4					1094	12.3				

cOR, crude odds ratios; 95% CI, 95% confidence interval; aOR, odds ratios adjusted for maternal diabetes, age and smoking in the first pregnancy and interval between pregnancies.
*Statistical significant OR.

mechanisms underlying this association are unknown, but could involve several pathways. Preeclampsia and cardiovascular disease share several risk factors [4,5]. Our finding may therefore suggest that the biology underlying placental growth is also related to preeclampsia and to cardiovascular disease. For example, pre-pregnancy hypertension [8] and thrombophilia [20] are associated with low placental weight and also with the development of preeclampsia [20–22]. Arterial stiffness and arteriosclerosis could be other maternal vascular conditions that could possibly restrict placental growth [23]. Thus, low placental weight in the first pregnancy may be an indicator of an underlying increased risk for hypertensive disorders.

Placental development depends on a well-functioning endometrium. Any anatomic, hormonal, or immunological abnormality of the endometrium could possibly cause sub-optimal endometrial function and thereby impair trophoblast proliferation and consequently placental development [24]. Several growth factors and angiogenic factors are synthesized in trophoblastic cells in the placenta. Low levels of placental growth factor, endoglin and human chorionic gonadotropin in early pregnancy are associated with increased risk for preeclampsia [25,26] and for low birthweight [27]. Thus, for some women, underlying factors that caused low placental weight, in the first pregnancy, such as impaired endometrial function or maternal vascular conditions, may still be present or have progressed by the second pregnancy and possibly be a cause of preeclampsia.

Placental growth is regulated by both maternal and paternal genes, and for most women in our study it is likely that both pregnancies have the same father [17]. Thus, both maternal and paternal genes may influence placental growth and also the risk for developing preeclampsia [28].

Among women without previous preeclampsia, both low and high placental weight in the first pregnancy increased the risk for preeclampsia in the second pregnancy. High placental weight was associated with preeclampsia at term only, and term preeclampsia may be less severe than early onset preeclampsia [1]. Our finding

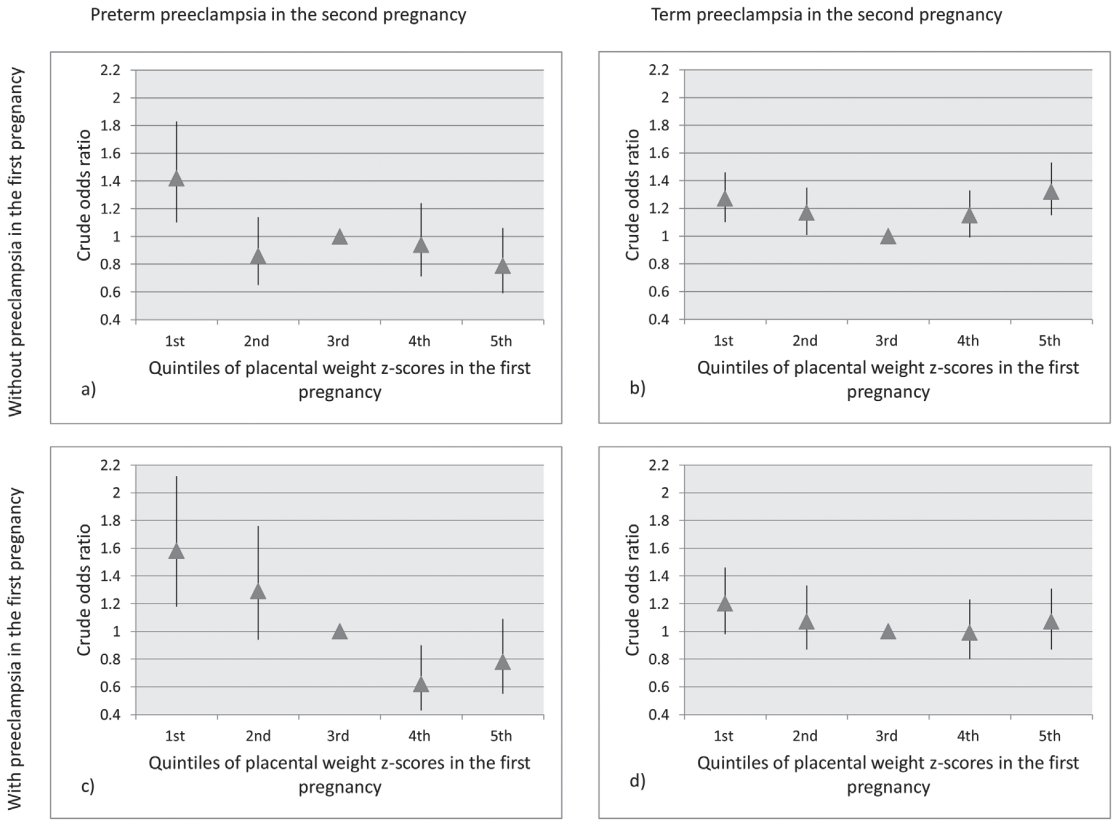

Fig. 2. Crude odds ratios (OR) with 95% confidence intervals for preterm (a, c) and for term (b, d) preeclampsia in the second pregnancy according to quintiles of placental weight z-score in the first pregnancy, among women without preeclampsia in the first pregnancy (n = 177 149) (a, b) and women with preeclampsia in the first pregnancy (n = 9710) (c, d).

may suggest different underlying maternal factors behind the development of preterm and term preeclampsia in a second pregnancy. High maternal body mass index has been associated with both high placental weight and with preeclampsia [6]. Hence, some women with high placental weight in the first pregnancy may have high maternal body mass index, and their body mass index may have increased from the first to the second pregnancy. Also, presence of other maternal factors associated with high placental weight, such as glucose concentrations [7] and blood pressure, may have increased in the interval between pregnancies. Thereby, their risk for preeclampsia may be higher in the second as compared to their first pregnancy [22,29].

Most cases of preeclampsia in second pregnancies were among women with no history of preeclampsia (62.2%). However, in women with no history of preeclampsia, the absolute risk for preeclampsia in a second pregnancy was low (1.4%), and the risk difference according to placental weight may not be of clinical importance (range 1.2–1.6%). In women with preeclampsia in the first pregnancy, a total of 15.7% developed recurrent preeclampsia, and 4.4% developed preterm preeclampsia. The women with low placental weight were at increased risk for recurrence, particularity for preterm preeclampsia. Such information may help to identify women who could be at risk for developing preeclampsia in a second pregnancy.

In conclusion, we found that low placental weight in the first pregnancy was associated with increased risk for developing preeclampsia in the second pregnancy. Additionally, in women without preeclampsia in the first pregnancy, high placental weight increased the risk for developing term preeclampsia in the second pregnancy.

Acknowledgment

The authors thank the South-Eastern Norway Regional Health Authority for funding our research (grant number 27408).

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Medical Birth Registry of Norway

Notification form December 1998 –December 2001

Notification form January 2002–present

Melding om avsluttet svangerskap etter 16. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

MFR

Statens helsetilsyn

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn

Fødsel utenfor institusjon: ☐ Hjemme, planlagt ☐ Hjemme, ikke planlagt ☐ Under transport ☐ Annet sted

Mors fulle navn og adresse

Pikenavn (etternavn):

Mors sivilstatus ☐ Gift ☐ Ugift/enslig ☐ Annet ☐ Samboer ☐ Skilt/separert/enke

Slektskap mellom barnets foreldre? ☐ Nei ☐ Ja Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato | Fars fulle navn | **Mors fødselsnr:**

B – Om svangerskap og mors helse

Siste menstr. 1. blødn.dag ☐ Sikker ☐ Usikker

Mors tidligere svangerskap/fødte Levende-fødte | Dødfødte (24. uke og over) | Spontanabort/Død-fødte (12.–23. uke) | Spontanaborter (under 12. uke)

Ultralyd utført? ☐ Nei ☐ Ja UL termin:

Annen prenatal diagnostikk? ☐ Nei ☐ Ja, angi type:

Patologiske funn ved prenatal diagnostikk? ☐ Nei ☐ Ja, hvis bekreftet – spesifiser

Spesielle forhold før svangerskapet: ☐ Intet spesielt
☐ Astma ☐ Allergi ☐ Tidligere sectio ☐ Res. urinveisinfeksjon ☐ Kronisk nyresykdom ☐ Kronisk hypertensjon ☐ Reumatoid artritt ☐ Hjertesykom ☐ Epilepsi ☐ Diabetes type 1 ☐ Diabetes type 2 ☐ Annet, spesifiser i «B»

Regelmessig kosttilskudd: ☐ Nei Før sv.sk. I sv.sk.
Multivitaminer ☐ ☐
Folat/Folsyre ☐ ☐

Spesifikasjon av forhold før eller under svangerskapet: B

Spesielle forhold under svangerskapet: ☐ Intet spesielt
☐ Blødning < 13 uke ☐ Blødning 13–28 uke ☐ Blødning > 28 uke ☐ Glukosuri ☐ Svangerskapsdiabetes ☐ Hypertensjon alene ☐ Preeklampsi lett ☐ Preeklampsi alvorlig ☐ Preeklampsi før 34. uke ☐ HELLP syndrom ☐ Eklampsi ☐ Hb < 9.0 g/dl ☐ Hb > 13.5 g/dl ☐ Trombose, beh. ☐ Infeksjon, spes. i «B» ☐ Annet, spesifiser i «B»

Legemidler i svangerskapet: ☐ Nei ☐ Ja – spesifiser i «B»

Røyking og yrke Forutsetter mors samtykke – se rettledning på baksiden

☐ Skriftlig orientering gitt til mor ☐ Samtykker ikke for røykeoppl.

Røykte mor ved sv.sk. begynnelse? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

- ved sv.sk. avslutning? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

Mors yrke ☐ Samtykker ikke for yrkesoppl. ☐ Ikke yrkesaktiv ☐ Yrkesaktiv heltid ☐ Yrkesaktiv deltid

Mors yrke

Bransje:

C – Om fødselen

Leie/presentasjon: ☐ Normal bakhode ☐ Sete ☐ Tverrleie ☐ Avvikende hodefødsel ☐ Annet, spesifiser i «C»

Fødselstart: ☐ Spontan ☐ Indusert ☐ Sectio

Ev. induksjons-metode: ☐ Prostaglandin ☐ Oxytocin ☐ Amniotomi ☐ Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon ☐ Komplikasjoner som beskrevet nedenfor ☐ Fostermisdannelser ☐ Overtid ☐ Annet, spesifiser i «C»

Inngrep/tiltak ☐ Ingen ☐ Utskj. tang, hodeleie ☐ Annen tang, hodeleie ☐ Vakuumekstraktor ☐ Episitomi

Fremhj. ved setefødsel: ☐ Vanlig fremhjelp ☐ Uttrekning ☐ Tang på etterk. hode

Sectio: Var sectio planlagt før fødsel? ☐ Nei ☐ Ja
☐ Utført som elektiv sectio ☐ Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner C

Komplikasjoner ☐ Ingen ☐ Vannavg. 12–24 timer ☐ Vannavg. > 24 timer ☐ Mekaniske misforhold ☐ Vanskelig skulderforløsning ☐ Placenta previa ☐ Abruptio placentae ☐ Perinealruptur (grad 1-2) ☐ Sphincterruptur (gr. 3-4) ☐ Blødn.> 1500 ml, transf. ☐ Blødning 500–1500 ml ☐ Eklampsi under fødsel ☐ Navlesnorfremfall ☐ Truende intrauterin asfyksi ☐ Risvekkelse, stimulert ☐ Langsom fremgang ☐ Uterus atoni ☐ Annet:

Anestesi/analgesi: ☐ Ingen ☐ Lystgass ☐ Petidin ☐ Epidural ☐ Spinal ☐ Pudendal ☐ Infiltrasjon ☐ Paracervical blokk ☐ Narkose ☐ Annet:

Placenta: ☐ Normal ☐ Hinnerester ☐ Ufullstendig ☐ Infarkter ☐ Koagler ☐ Utskrapning ☐ Manuell uthenting Placenta-vekt

Navlesnor ☐ Normal ☐ Velamentøst feste ☐ Marginalt feste ☐ Karanomalier ☐ Omslyng rundt hals ☐ Annet omslyng ☐ Ekte knute Navlesnor-lengde:

Fostervann ☐ Normal ☐ Polyhydramnion ☐ Oligohydramnion ☐ Misfarget ☐ Stinkende, infisert ☐ Blodtilblandet

Komplikasjoner hos mor etter fødsel ☐ Intet spesielt ☐ Feber > 38.5° ☐ Trombose ☐ Eklampsi post partum ☐ Mor overflyttet ☐ Mor intensivbeh. ☐ Sepsis ☐ Annet, spesifiser

D – Om barnet

Fødselsdato | **Klokken**

Pluralitet ☐ Enkeltfødsel ☐ Flerfødsel For flerfødsel: Nr. Av totalt

Kjønn ☐ Gutt ☐ Pike Ved tvil spesifiser i «D»
For dødfødte: ☐ Usikkert kjønn

Barnets vekt: Hode-omkrets:

Total lengde: Eventuelt sete–issemål:

Apgar score: 1 min 5 min

Barnet var: ☐ Levendefødt

For dødfødte: ☐ Dødfødt/sp.abort Oppgi dødsårsak i «D»
☐ Død før fødsel ☐ Død under fødselen ☐ Ukjent dødstidspunkt

For dødfødte, oppgi også ☐ Død før innkomst ☐ Død etter innkomst

Levendefødt, død innen 24 timer Livet varte: Timer Min.

Død senere (dato): | **Klokken**

Overfl. barneavd. ☐ Nei ☐ Ja Dato: | Overfl. til

Indikasjon for overflytting: ☐ Respirasjonsproblem ☐ Prematur ☐ Medfødte misd. ☐ Perinatale infeksjoner ☐ Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater) ☐ Intet spesielt
☐ Hypoglyk. (< 2 mmol/l) ☐ Medf. anemi (Hb < 13.5 g/dl) ☐ Hofteleddsdyspl. beh. m/pute ☐ Transit. tachypnoe ☐ Resp. distress syndr. ☐ Aspirasjonssyndrom ☐ Intrakraniell blødning ☐ Cerebral irritasjon ☐ Cerebral depresjon ☐ Abstinens ☐ Neonatale kramper ☐ Konjunktivitt beh. ☐ Navle./hudinf. beh. ☐ Perinat. inf. bakterielle ☐ Perinat. inf. andre ☐ Fract. claviculae ☐ Annen fraktur ☐ Facialisparese ☐ Plexusskade

Behandlingskoder: ☐ Systemisk antibiotika ☐ Respiratorbeh. ☐ CPAP beh.

Icterus behandlet: ☐ Lysbehandlet ☐ Utskifting
Årsak: ☐ AB0 uforlik. ☐ RH immunisering ☐ Fysiologisk ☐ Annen årsak

Tegn til medfødte misdannelser: ☐ Nei ☐ Ja

D Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege

☐ **Kryss av hvis skjema er oppfølgingsskjema**

Jordmor v/fødsel:

Jordmor v/utskrivning:

Lege:

Lege barsel/barneavd:

Utskrivningsdato Mor:

Barn:

Protokollnr.: /

IK-1002 Nr. 719424 Sem & Stenersen Prokom AS, Oslo 1-99

Melding om avsluttet svangerskap etter 12. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

Sosial- og helsedirektoratet

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn

Fødsel utenfor institusjon: ☐ Hjemme, planlagt ☐ Hjemme, ikke planlagt ☐ Under transport ☐ Annet sted

Mors fulle navn og adresse

Pikenavn (etternavn):

Mors sivilstatus: ☐ Gift ☐ Ugift/enslig ☐ Annet ☐ Samboer ☐ Skilt/separert/enke

Slektskap mellom barnets foreldre? ☐ Nei ☐ Ja Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato | Fars fulle navn

Mors fødselsnr:

B – Om svangerskap og mors helse

Siste menstr. 1. blødn.dag ☐ Sikker ☐ Usikker

Mors tidligere svangerskap/fødte: Levendefødte | Dødfødte (24. uke og over) | Spontanabort/Dødfødte (12.–23. uke) | Spontanaborter (under 12. uke)

Ultralyd utført? ☐ Nei ☐ Ja UL termin:

Annen prenatal diagnostikk? ☐ Nei ☐ Ja, angi type:

Patologiske funn ved prenatal diagnostikk? ☐ Nei ☐ Ja, hvis bekreftet – spesifiser

Spesielle forhold før svangerskapet:
☐ Intet spesielt
☐ Astma ☐ Allergi ☐ Tidligere sectio ☐ Res. urinveisinfeksjon
☐ Kronisk nyresykdom ☐ Kronisk hypertensjon ☐ Reumatoid artritt ☐ Hjertesykom
☐ Epilepsi ☐ Diabetes type 1 ☐ Diabetes type 2 ☐ Annet, spesifiser i «B»

Regelmessig kosttilskudd: ☐ Nei
Før sv.sk. / I sv.sk.
Multivitaminer ☐ ☐
Folat/Folsyre ☐ ☐

Spesifikasjon av forhold før eller under svangerskapet: B

Spesielle forhold under svangerskapet:
☐ Intet spesielt
☐ Blødning < 13 uke ☐ Blødning 13–28 uke ☐ Blødning > 28 uke ☐ Glukosuri ☐ Svangerskapsdiabetes
☐ Hypertensjon alene ☐ Preeklampsi lett ☐ Preeklampsi alvorlig ☐ Preeklampsi før 34. uke ☐ HELLP syndrom
☐ Eklampsi ☐ Hb < 9.0 g/dl ☐ Hb > 13.5 g/dl ☐ Trombose, beh. ☐ Infeksjon, spes. i «B»
☐ Annet, spesifiser i «B»

Legemidler i svangerskapet: ☐ Nei ☐ Ja – spesifiser i «B»

Røyking og yrke
Forutsetter mors samtykke – se rettledning på baksiden
☐ Skriftlig orientering gitt til mor ☐ Samtykker ikke for røykeoppl.

Røykte mor ved sv.sk. begynnelse? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

- ved sv.sk. avslutning? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

Mors yrke ☐ Samtykker ikke for yrkesoppl. ☐ Ikke yrkesaktiv ☐ Yrkesaktiv heltid ☐ Yrkesaktiv deltid

Mors yrke

Bransje:

C – Om fødselen

Leie/presentasjon: ☐ Normal bakhode ☐ Sete ☐ Tverrleie ☐ Avvikende hodefødsel ☐ Annet, spesifiser i «C»

Fødselstart: ☐ Spontan ☐ Indusert ☐ Sectio

Ev. induksjonsmetode: ☐ Prostaglandin ☐ Oxytocin ☐ Amniotomi ☐ Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon ☐ Komplikasjoner som beskrevet nedenfor ☐ Fostermisdannelser ☐ Overtid ☐ Annet, spesifiser i «C»

Inngrep/tiltak
☐ Ingen
☐ Utskj. tang, hodeleie ☐ Annen tang, hodeleie ☐ Vakuumekstraktor ☐ Episitomi

Fremhj. ved setefødsel: ☐ Vanlig fremhjelp ☐ Uttrekning ☐ Tang på etterk. hode

Sectio: Var sectio planlagt før fødsel? ☐ Nei ☐ Ja
☐ Utført som elektiv sectio ☐ Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner C

Komplikasjoner
☐ Ingen
☐ Vannavg. 12–24 timer ☐ Vannavg. > 24 timer ☐ Mekaniske misforhold ☐ Vanskelig skulderforløsning
☐ Placenta previa ☐ Abruptio placentae ☐ Perinealruptur (grad 1-2) ☐ Sphincterruptur (gr. 3-4)
☐ Blødn.> 1500 ml, transf. ☐ Blødning 500–1500 ml ☐ Eklampsi under fødsel ☐ Navlesnorfremfall
☐ Truende intrauterin asfyksi ☐ Risvekkelse, stimulert ☐ Langsom fremgang ☐ Uterus atoni ☐ Annet:

Anestesi/analgesi:
☐ Ingen
☐ Lystgass ☐ Petidin
☐ Epidural ☐ Spinal
☐ Pudendal ☐ Infiltrasjon
☐ Paracervical blokk ☐ Narkose ☐ Annet:

Placenta:
☐ Normal ☐ Hinnerester ☐ Ufullstendig ☐ Infarkter
☐ Koagler ☐ Utskrapning ☐ Manuell uthenting
Placenta-vekt:

Navlesnor
☐ Normal ☐ Velamentøst feste ☐ Marginalt feste ☐ Karanomalier
☐ Omslyng rundt hals ☐ Annet omslyng ☐ Ekte knute
Navlesnor-lengde:

Fostervann
☐ Normal ☐ Polyhydramnion ☐ Oligohydramnion
☐ Misfarget ☐ Stinkende, infisert ☐ Blodtilblandet

Komplikasjoner hos mor etter fødsel
☐ Intet spesielt ☐ Feber > 38.5° ☐ Trombose ☐ Eklampsi post partum
☐ Mor overflyttet ☐ Mor intensivbeh. ☐ Sepsis ☐ Annet, spesifiser

D – Om barnet

Fødselsdato | **Klokken**

Pluralitet For flerfødsel: ☐ Enkeltfødsel ☐ Flerfødsel Nr. Av totalt

Kjønn ☐ Gutt ☐ Pike Ved tvil spesifiser i «D»
For dødfødte: ☐ Usikkert kjønn

Barnets vekt:

Hode-omkrets:

Total lengde:

Eventuelt sete–issemål:

Apgar score: 1 min | 5 min

Barnet var: ☐ Levendefødt

For dødfødte: ☐ Dødfødt/sp.abort Oppgi dødsårsak i «D»
☐ Død før fødsel ☐ Død under fødselen ☐ Ukjent dødstidspunkt
For dødfødte, oppgi også ☐ Død før innkomst ☐ Død etter innkomst

Levendefødt, død innen 24 timer Livet varte: Timer Min.

Død senere (dato): | **Klokken**

Overfl. barneavd. ☐ Nei ☐ Ja Dato:

Overfl. til

Indikasjon for overflytting: ☐ Respirasjonsproblem ☐ Prematur ☐ Medfødte misd. ☐ Perinatale infeksjoner ☐ Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater)
☐ Intet spesielt
☐ Hypoglyk. (< 2 mmol/l) ☐ Medf. anemi (Hb < 13.5 g/dl) ☐ Hofteleddsdyspl. beh. m/pute
☐ Transit. tachypnoe ☐ Resp. distress syndr. ☐ Aspirasjonssyndrom ☐ Intrakraniell blødning
☐ Cerebral irritasjon ☐ Cerebral depresjon ☐ Abstinens ☐ Neonatale kramper
☐ Konjunktivitt beh. ☐ Navle./hudinf. beh. ☐ Perinat. inf. bakterielle ☐ Perinat. inf. andre
☐ Fract. claviculae ☐ Annen fraktur ☐ Facialisparese ☐ Plexusskade

Behandlingskoder: ☐ Systemisk antibiotika ☐ Respiratorbeh. ☐ CPAP beh.

Icterus behandlet: ☐ Lysbehandlet ☐ Utskifting

Årsak:
☐ AB0 uforlik.
☐ RH immunisering
☐ Fysiologisk
☐ Annen årsak

Tegn til medfødte misdannelser: ☐ Nei ☐ Ja

D Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege

☐ **Kryss av hvis skjema er oppfølgingsskjema**

Jordmor v/fødsel:

Jordmor v/utskrivning:

Lege:

Lege barsel/barneavd:

Utskrivningsdato Mor:

Barn:

Protokollnr.: /

IS-1002 23011. 07.06. Andvord Grafisk.