Haemodynamic changes during spinal anaesthesia for caesarean section

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Din veg

Ingen har varda den vegen
du skal gå
ut i det ukjende,
utt i det blå.
Dette er din veg.
Berre du
skal gå han. Og det er
uråd å snu.
Og ikkke varden du vegen,
du hell.
Og vinden stryk ut ditt far
i aude fjell.

Olav H. Hauge
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ABBREVIATIONS

AS Aortic stenosis
BP Blood pressure
CEMACH Confidential enquiry into maternal and child health
CO Cardiac output
C-section Caesarean section
CSE Combined spinal epidural
CVP Central venous pressure
GA General anaesthesia
GUCH Grown-up with congenital heart disease
HELLP Haemolysis, elevated liver enzymes, low platelets
HR Heart rate
IUGR Intrauterine growth restriction
MAP Mean arterial pressure
MMR Maternal mortality rate
MS Mitral stenosis
NYHA New York Heart Association Classification of cardiac disease
OR Odds ratio
PAC Pulmonary artery catheter
PDPH Post dural puncture headache
PE Preeclampsia
PPCM Peripartum cardiomyopathy
RR Relative risk
SAP Systolic arterial pressure
NOS Nitric oxide synthase
SV Stroke volume
SVR Systemic vascular resistance
PUBLICATIONS INCLUDED IN THE THESIS

The thesis is based on these four articles, which are referred to in the text by their roman numerals:


III. Langesæter E, Dragsund M, Rosseland LA: Regional anaesthesia for Caesarean section in women with cardiac disease. A prospective study (Acta Anaesthesiologica Scandinavica, In press)

IV. Langesæter E, Rosseland LA, Stubhaug A: Haemodynamic effects of oxytocin 5 units i.v in women with severe preeclampsia. (IJOA, submitted revision)
INTRODUCTION

Approximately 1500 women die every day due to pregnancy, and 99% of these women die in the developing countries (World Health Organization, 2007). The maternal mortality rate (MMR—deaths per 100,000 live births) has decreased in the developed countries the last century. Similar improvements are not observed in many developing countries. The MMR in developed countries is 9, compared to a MMR of 900 in sub-Saharan Africa (World Health Organization, 2007). To reduce the maternal mortality in the developing countries is the most important challenge in obstetric medicine. The World Health Organization (WHO) has a goal of reducing maternal mortality by 75% by 2015.

In the western world, there has been a tremendous improvement in aseptic, surgical, and anaesthetic techniques for caesarean section (C-section) from the early 1900 until today. From being an operation conducted on extreme medical indications to try to save the mother and the child, C-section has become a routine operation, not only conducted for medical reasons, but on maternal request. C-section is now one of the most commonly performed major operations in women throughout the world. Rates are escalating, with studies from the United Kingdom, the United States of America, and China reporting rates between 20–30% (Cheng et al., 2003; Betran et al., 2007).

The confidential enquiry into maternal and child health (Lewis, 2007) in the UK has published reports on maternal mortality for every three years since 1950. They register all maternal deaths and classify the deaths into direct or indirect causes. In the last report, cardiac disease was the main cause of maternal mortality. One half of the women who died were obese. The maternal age is increasing, the women are more obese, and the prevalence of cardiac disease (both congenital and acquired) is
increasing. These changes in the maternal population and the increasing number of C-sections have implications for the anaesthetic management of pregnant women (Cooper and McClure, 2005; Gomar and Errando, 2005; Clark et al., 2008).

In Norway, the C-section rate was 16.7% in 2007 (Dahl and Spreng, 2009), but at Oslo University Hospital - Rikshospitalet the rate of C-section is approximately 25%, and 50% of the C-sections are elective. Rikshospitalet is a tertiary centre for complicated pregnancies and for pregnant women with cardiac disease. The high rate of C-sections compared to other hospitals in Norway can be explained by the high percentage of pregnant patients with comorbidities as cardiac disease, diabetes, and preeclampsia.

**Anaesthesia for caesarean section**

The anaesthetic technique for C-section has changed the last 30 years (Lewis, 2007) from general anaesthesia to regional anaesthesia. Anaesthesia related mortality has decreased, and the main reason has been the change to regional anaesthesia for C-section. Neuraxial anaesthesia has become the main technique, both for elective and urgent C-section. There are several techniques for administering regional anaestheisa; spinal, epidural, combined spinal-epidural, and continuous spinal anaesthesia. A single-shot spinal technique is simple and reliable (Gogarten, 2003), provides a rapid onset of anaesthesia, and is the preferred choice of anaesthesia for both elective and non-elective C-section (Levy, 2006). Epidural anaesthesia has a slower onset, but has the advantage of titration of anaesthesia, and the option to extend duration by having a catheter inserted. Epidural anaesthesia for urgent C-section is increasing due to the large percentage of parturients receiving epidural for labour analgesia (Campbell and Tran, 2009). The use of epidural implies the use of higher volumes of local
anaesthetics and the risk of toxic reactions in case of an unintentional intravenous administration. A combined spinal-epidural technique, using a needle through needle technique (Rawal and Holmstrom, 2003), has the advantage of both a fast onset and the backup of an epidural catheter to extend the anaesthesia if needed. It also has the advantage of reducing the intrathecal doses of local anaesthetics. A continuous spinal anaesthesia provides reliable anaesthesia which can be titrated and continued (Bevacqua, 2003), and can be indicated in special cases to avoid general anaesthesia (extreme obesity), and has the possibility of a titrated spinal anaesthesia to avoid abrupt haemodynamic changes in pregnant women with high risk cardiac disease (Dresner and Pinder, 2009).

Contraindications to regional anaesthesia are patient refusal or patients not able to cooperate, increased intracranial pressure, coagulopathy, and local skin infection. The incidence of post dural puncture headache (PDPH) after spinal anaesthesia using small (25–27 G) pencil point needles is low (Halpern and Preston, 1994; Flaatten et al., 2000). Unintentional dura puncture with an epidural needle (18 G) has an incidence of 52% of PDPH (Choi et al., 2003; Thew and Paech, 2008). Long-lasting neurological deficit is extremely rare, estimated to 1:240 000. The incidence of spinal haematoma after obstetric epidural blockade has been estimated to 1:168 000 (Moen et al., 2004; Ruppen et al., 2006; Moen and Irestedt, 2008).

In non elective caesarean delivery, the risk of maternal morbidity is increased (Pallasmaa et al., 2008). This is important in planning the mode of delivery in high risk pregnant patients. General anaesthesia is reserved for patients with contraindications to regional anaesthesia, and for emergency C-sections where time does not permit the use of regional anaesthesia. Difficult intubation is a major concern in pregnant women and increasing airway oedema during pregnancy has been described (Pilkington et al., 1995). Recently, a publication demonstrated that the larynx oedema worsen during labour (Kodali et al., 2008). The parturient is prone to
aspiration due to low esophageal sphincter tonus and increased abdominal pressure. Preparation before general anaesthesia is to give sodium citrate 30 ml to neutralize gastric acid, preoxygenation with 8 deep breaths for a minute. In some obstetric units, the use of neuraxial anaesthesia exclusively has become a problem because residents are not getting experience giving general anaesthesia (Hawthorne et al., 1996; Barnardo and Jenkins, 2000; Lyons and Akerman, 2005).

The challenge for the anaesthetist during C-section is first of all to provide a high level of safety, but also make it a pleasant experience for the patient by giving good information ahead, short induction time to reduce anxiety, and a reduction of side effects such as nausea and vomiting.

**Prevention of hypotension during spinal anaesthesia for caesarean section**

The haemodynamic effects of spinal anaesthesia have previously been explained by the reflex bradycardia induced by reduced preload on the cardiovascular receptors in the vena cava, right atrium, and the left ventricle. These reflexes reducing HR has been the theoretical basis for assuming that CO decreases after spinal anaesthesia (Salinas et al., 2003). The decrease in SVR has been assumed moderate. As recent as 2008, a review article in obstetric anaesthesia stated that CO decreases after spinal anaesthesia (Reidy and Douglas, 2008).

Preventing hypotension during spinal anaesthesia for C-section has been referred to as the “Holy Grail” in obstetric anaesthesia (Macarthur, 2002; Macarthur and Riley, 2007). Even though the technique has improved, hypotension during spinal anaesthesia for C-section is still a major problem. Although, there is no exact definition of maternal hypotension, most publications define hypotension as a 20%
decrease in systolic blood pressure from baseline, or systolic blood pressure below 90 mmHg. Hypotension results in common maternal side-effects such as dizziness, nausea, and vomiting which makes the experience unpleasant for the mother. In severe cases, neuroaxially induced hypotension can result in unconsciousness, pulmonary aspiration, apnoea, and cardiac arrest. Severe and sustained hypotension can impair uteroplacental perfusion, and induce foetal hypoxia, acidosis, and neonatal depression or injury (Corke et al., 1982).

Numerous studies have been conducted to solve this problem. In the Cochrane Review (Cyna et al., 2006), 75 studies were included. Only eight of the studies included described adequate randomisation, and only 28 studies were blinded. Several interventions reduced the incidence of hypotension, but no single technique could effectively abolish hypotension.

To my knowledge, the haemodynamic effects of spinal anaesthesia for C-section in healthy pregnant women have not been investigated with continuous invasive monitoring before, and it would be interesting to investigate the effects of spinal anaesthesia on CO and SVR in relation to BP using beat-to-beat monitoring. Hypotension is always pathological, but a normal blood pressure does not necessarily reflect haemodynamic stability. Cardiac output is a primary determinant of global oxygen transport, and blood pressure has been used as a surrogate for cardiac output. Cardiac output is the product of heart rate and stroke volume, $CO = HR \times SV$. The relationship between blood pressure, cardiac output, and system vascular resistance can be expressed as $(MAP - CVP) \times 80 = CO \times SVR$. Increases in blood pressure can result from increases in system vascular resistance, and does not necessarily reflect an increase in cardiac output.

**Intrathecal doses.** Pregnant women require smaller doses of local anaesthetics for spinal anaesthesia because of a smaller CSF volume due to epidural venous
engorgement, and pregnant women have a higher sensitivity of the nerve fibres to local anaesthetics (Kestin, 1991). Local anaesthetics inhibit the propagation of the action potential in nerves by interfering with sodium-ion conductance. The most commonly used local anaesthetic for spinal anaesthesia during C-section is bupivacaine (both plain and hyperbaric solutions). During the last ten years, the doses of bupivacaine have been reduced due to the addition of an opioid such as fentanyl or sufentanil acting on spinal opioid receptors. Neuraxial opioids produce analgesia, but no loss of sensation or proprioception (Bernards et al., 2003).

Several studies (Vercauteren et al., 1998; Ben-David et al., 2000; Vercauteren et al., 2000; Vercauteren, 2003; Coppejans and Vercauteren, 2006; Van de Velde, 2006; Roofthooft and Van de Velde, 2008) have demonstrated the favourable effect of reducing the intrathecal bupivacaine doses on the incidence of hypotension, but this knowledge, however, seems to have little impact on clinical management.

**Lower limb compression.** In the last Cochrane Review by Cyna et al. (Cyna et al., 2006) seven studies using lower limb compression were included. The studies were small with methodical weaknesses (James, III and Greiss, Jr.; 1973; Bhagwanjee et al., 1990; Rout et al., 1993; Jorgensen et al., 1996; Sood et al., 1996; Sutherland et al., 2001; Adsumelli et al., 2003). The meta-analysis concludes that lower limb compression is more effective than no compression. The overall incidence of hypotension was only moderately reduced using lower limb compression. The rationale for using lower limb compression is to increase venous return. The amount of blood pooled in the lower limbs may be less than the blood volume redistributed to the splanchnic circulation (Stienstra, 2000), which makes this approach less effective. As commented in a recent editorial (Sharwood-Smith and Drummond, 2009), the focus on venous return and inferior vena cava compression may be overestimated in the discussion of important factors explaining the high incidence of neuraxially induced hypotension
during C-section in pregnant women, and that one should focus on the effects on the arterial side (Assali and Prystowsky, 1950).

Before recommending lower limb compression to prevent hypotension in clinical practice, this approach should be documented in methodologically better conducted studies.

**Volume loading.** Earlier, it was standard to give large volumes of crystalloids i.v. before giving spinal anaesthesia (prehydration) to prevent hypotension. The approach has until recently been standard routine at many hospitals. In the meta-analysis by Cyna et al. (Cyna et al., 2006), prehydration reduced hypotension, but was not proven very effective (Ngan Kee et al., 2001b). More recent publications (Jackson et al., 1995; Ngan Kee et al., 2001a; Dyer et al., 2004; Ngan Kee et al., 2005; Mercier et al., 2007) have shown that administering the volume load concomitantly with spinal anaesthesia (cohydration) may be a better approach.

Prehydration with 1.5 L of lactated Ringer’s solution or 0.5 L of HES (hydroxyethyl starch solution) 28% versus 100%, respectively, remained intravascular after 30 minutes (Ueyama et al., 1999). This demonstrates the importance of the timing of volume to prevent hypotension. Even though colloids stay longer intravascular, the use of colloids to prevent hypotension in healthy women may not be justified due to higher costs and the associated risk for allergic reactions (Rout and Rocke, 1999). Administering high volumes should be of concern because of release of atrial natriuretic peptid that can cause vasodilatation (Pouta et al., 1996) and the additional risk of volume overload in some patients.

**Vasopressor.** During pregnancy, there is an upregulation of nitric oxide synthase (NOS) in the uterine artery which makes the artery less sensitive to vasopressor (Li et al., 1996). The first choice of vasopressor in obstetric anaesthesia has been ephedrine
for many decades based on animal studies demonstrating that ephedrine had the least negative effects on the foetal circulation. Old studies in ewes (Ralston et al., 1974) showed that ephedrine protected uterine artery blood flow, but phenylephrine decreased it. Recent publications from animal studies in sheep (Erkinaro et al., 2004; Erkinaro et al., 2006; Erkinaro et al., 2007) show that in the compromised mother, ephedrine restored maternal haemodynamics without deterioration in foetal lactate concentration. The phenylephrine-group had a continued deterioration in foetal lactate even though maternal haemodynamics were restored. The findings from animal studies may not be applicable in humans, and clinical studies on the effects of vasopressors on the human foetus should be studied, in particular in the case of a compromised mother or foetus.

Newer studies in pregnant women the last five years by Ngan Kee et al. (Ngan Kee et al., 2004a; Ngan Kee et al., 2004b; Ngan Kee et al., 2005) using phenylephrine, have shown that phenylephrine gives less foetal acidosis than ephedrine. Studies have shown more acidosis when high doses of ephedrine have been used, probably due to stimulation of alpha-adrenergic receptors in brown fat increasing carbon dioxide production through an alteration of foetal metabolism (LaPorta et al., 1995; Cooper et al., 2002a).

Ephedrine has both a direct (alpha-and beta-receptor agonist) and an indirect mechanism of action (release of noradrenaline from presynaptic nerve terminals) (Reidy and Douglas, 2008) and has a slow onset of action. Ephedrine causes release of NOS. Phenylephrine is a short-acting, potent vasoconstrictor acting via alpha-adrenoceptors in the peripheral circulation. The potency ratio of phenylephrine to ephedrine has been shown to be 80:1 (Saravanan et al., 2006).

Studies in pregnant women have shown that a single, prophylactic, intravenous bolus of ephedrine is ineffective (Shearer et al., 1996; Ngan Kee et al., 2000). Studies looking at the combination of ephedrine and phenylephrine
demonstrated no effect on the incidence of hypotension compared to phenylephrine alone, only more side-effects when ephedrine was added (Cooper et al., 2002a).

Ngan Kee et al. (Ngan Kee et al., 2005) using high doses of prophylactic phenylephrine-infusion combined with cohydration, had an incidence of only 1.9% hypotension in the treatment group, but 47% hypertension. In my clinical practice, I have used low doses of spinal bupivacaine for C-section, individualized according to height, weight, and BMI. Study I (Langesaeter et al., 2008) was planned to investigate both the effects of bupivacaine doses and phenylephrine-infusion on CO and SVR in addition to BP.

**Oxytocin**

In addition to the cardiovascular changes induced by spinal anaesthesia, we wanted to investigate the haemodynamic changes after administering oxytocin. The effects of oxytocin have not previously been examined with an invasive beat-to-beat monitor evaluating the effects on CO, SVR, and blood pressure.

Oxytocin is the first-line drug for prophylaxis and treatment of uterine atony during delivery. Endogenous oxytocin is a polypeptide produced in the posterior pituitary. The exogenous form (Pitocin, Syntocinon) is a synthetic drug with a short half-life of 5–7 minutes (Sarna et al., 1997). Oxytocin receptors have been found in uterine, mammary, renal, cardiac and endothelial tissue. The vascular endothelial oxytocin receptors produce a calcium-dependent vasodilatory response via stimulation of the nitric oxide pathway (Yazawa et al., 1996; Thibonnier et al., 1999).

Weiss et al. showed the hemodynamic effects of oxytocin in 10 pregnant women (Weis, Jr. et al., 1975). This knowledge was paid little attention to until the publication of the CEMACH report from 1997–99 (Cooper et al., 2002b; Thomas and
Cooper, 2002). They reported a healthy parturient suffering cardiac arrest and dying after administration of oxytocin 10 units i.v. during a C-section complicated by uterine atony and bleeding. After this publication, the recommended dose of oxytocin was reduced from 10 to 5 units.

**Pregnant women with cardiac disease**

In the CEMACH-report (Lewis, 2007), cardiac disease was the main cause of maternal mortality. This was the first report where an indirect cause was the leading cause of mortality. The number of grown-ups with congenital heart disease (GUCH) is increasing due to improved cardiac surgery in the past decades. Many of these women are reaching fertile age. There is also an increasing incidence of cardiovascular disease in the maternal population due to increasing maternal age, obesity, diabetes, and smoking. This is a new challenge in obstetric anaesthesia.

Pregnant women with cardiac disease can be classified according to type of lesions into low, moderate, or high risk groups (Siu and Colman, 2001; Dob and Yentis, 2001; Lupton et al., 2002; Lewis et al., 2003; Dob and Yentis, 2006).
**Table 1.** Risk of death or severe morbidity resulting from certain cardiac lesions in pregnancy (Lupton et al., 2002, Dob and Yentis, 2006)

<table>
<thead>
<tr>
<th>Category</th>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (mortality 0.1–1.0%)</td>
<td>• Most repaired lesions</td>
</tr>
<tr>
<td></td>
<td>• Uncomplicated left-to-right shunts</td>
</tr>
<tr>
<td></td>
<td>• Mitral valve prolaps; bicuspid aortic valve; aortic regurgitation; mitral regurgitation; pulmonary stenosis and regurgitation</td>
</tr>
<tr>
<td>Intermediate risk (mortality 1–5%)</td>
<td>• Metal valves</td>
</tr>
<tr>
<td></td>
<td>• Single ventricles</td>
</tr>
<tr>
<td></td>
<td>• Systemic right ventricle; switch procedure</td>
</tr>
<tr>
<td></td>
<td>• Unrepaired cyanotic lesions</td>
</tr>
<tr>
<td></td>
<td>• Mitral stenosis; mild/moderate aortic stenosis; severe pulmonary stenosis</td>
</tr>
<tr>
<td>High risk (mortality 5–30%)</td>
<td>• NYHA III or IV</td>
</tr>
<tr>
<td></td>
<td>• Severe systemic ventricular dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Severe aortic stenosis</td>
</tr>
<tr>
<td></td>
<td>• Marfan’s syndrome with aortic valve lesion or aortic dissection</td>
</tr>
<tr>
<td></td>
<td>• Pulmonary hypertension</td>
</tr>
</tbody>
</table>
Cardiac risk can also be predicted with the use of a risk index based on a prospective multicenter study in 562 pregnant women with heart disease (Siu et al., 2001a).

**Table 2.** Predictors of primary cardiac events (pulmonary oedema and/or cardiac arrhythmia) (Siu et al., 2001b)

1. Prior cardiac events (heart failure, transient ischemic attack, or stroke) or arrhythmia
2. NYHA functional class >II or cyanosis
3. Systemic ventricular dysfunction (EF <40%)
4. Left heart obstruction (mitral valve area <2cm², aortic valve area <1.5cm², or peak left ventricular outflow tract gradient >30 mm Hg)

The estimated risk of a cardiac event in pregnancies with 0, 1, and >1 points was 5%, 27%, and 75%, respectively.

The NYHA classification based on symptoms is important for deciding risk. A cardiac lesion that normally is classified as low risk, could be classified into a higher risk group due to increasing symptoms during pregnancy. To describe every congenital heart disease in detail is beyond the aim of the thesis, but I will comment on some of the conditions. To understand the effects of pregnancy in women with cardiac disease, it is important to know about the normal physiological changes induced by pregnancy, with an approximately 50% increase in plasma volume, a 50% increase in CO secondary to increased HR and SV, and a 25% decrease in SVR.

Small atrial septal defects (ASD) and ventricular septal defects (VSD) are usually well tolerated during pregnancy, but could be symptomatic due to an increased shunt and the risk should be judged according to the NYHA classification.
The primary operation technique in patients with transpositions of the great arteries was previously an atrial switch (Senning or Mustard operation) (Drenthen et al., 2005). With this approach, the right ventricle is the systemic ventricle and prone to arrhythmias and cardiac failure. With the new arterial switch operation, the left ventricle is the systemic ventricle, and patients that have undergone this operation have less risk of complications.

Patients with Tetralogy of Fallot (TOF) represent about 5% of the GUCH. The risk in repaired lesions differs according to the degree of pulmonary regurgitation, arrhythmia, and right-sided heart failure, and should be treated according to the risk judged by the NYHA classification (Gelson et al., 2008).

Patients with Eisenmenger’s syndrome have an uncorrected left-to-right shunt producing right ventricular hypertrophy and elevated pulmonary artery pressures. Primary pulmonary hypertension is characterised by markedly elevated pulmonary artery pressures without a shunt. Pregnancy is contraindicated in women with primary pulmonary hypertension or Eisenmenger’s syndrome due to the high mortality associated with these conditions. Still, women with these lesions decide to get pregnant, even though the mortality is 30–50% (Bonnin et al., 2005).

Pregnant women with Marfan’s syndrome carry a risk of acute aortic dissection. The risk is based on the aortic diameter, and echo cardiography taken regularly during pregnancy is recommended (Meijboom et al., 2005). Both the haemodynamic changes during pregnancy and hormonal changes could increase the aortic diameter and make the patient more prone to dissection (Konishi et al., 1980).

Valve regurgitations are usually well tolerated during pregnancy, but could get symptomatic due to worsening of the regurgitation with the increased CO in pregnancy. A superimposed preeclampsia would increase afterload, and could precipitate pulmonary oedema.
The left sided obstructions (mitral stenosis and aortic stenosis) should be followed closely, and dependent on valve area and symptoms, treated as high risk patients. Pregnant women with hypertrophic obstructive cardiomyopathy (HOCM) have a decreased stroke volume due to a hypertrophic septum in the left ventricular outflow tract. These are high risk patients with the risk of sudden cardiac arrest (Autore et al., 2002).

Most arrhythmias are well tolerated in pregnancy. Patients with prolonged QT syndrome are treated with beta-blocker to reduce the risk of torsades de pointes and cardiac arrest (Viskin, 1999). Some women with severe bradyarrhythmias should have a pacemaker implanted before delivery.

Peripartum cardiomyopathy is defined as heart failure developing in the last month of pregnancy or in the first five months postpartum without underlying disease (James, 2004; Abboud et al., 2007). Elkayam et al. (Elkayam et al., 2005) suggest that the condition can be seen earlier in pregnancy, as well. The etiology is unknown, but viral myocarditis, immunological disease, and the stress of pregnancy are proposed mechanisms (Ansari et al., 2002; Sundstrom et al., 2002). Risk factors are multiple pregnancy, preeclampsia, multiparity, African origin, and advanced maternal age. A history of preeclampsia can be found in up to 70% of those who develop PPCM, but PPCM is an infrequent complication of preeclampsia (Bauer and Cleary, 2009). Recently, bromocriptine (a prolactin antagonist), has been suggested for treatment based on experimental studies in animals and some preliminary reports in humans (Hilfiker-Kleiner et al., 2008; Biteker et al., 2009). Cardiac performance may normalise in 50% of the patients (Elkayam et al., 2005), but a second pregnancy may not be advisable as the ventricles in these women may respond suboptimally to haemodynamic stress (Elkayam et al., 2001; Habli et al., 2008). A dobutamine challenge test may be advisable before planning a new pregnancy to see if the left ventricle has decreased contractile reserve (Lampert et al., 1997).
The incidence of ischemic heart disease is increasing because of increasing maternal age, the increased number of women smoking, and the use of contraceptives. Coronary dissection is uncommon in the whole population, but this is more common in pregnant women, with one survey finding that 16% of cardiac infarctions in pregnant women were caused by coronary dissection (Roth and Elkayam, 1996). Risk factors for ischemic heart disease in pregnancy are hypertension, diabetes mellitus, smoking, age > 35 years, thrombophilia, and African race (Hankins et al., 1985; Badui and Enciso, 1996; Roth and Elkayam, 1996). In addition, pregnancy related events such as preeclampsia, haemorrhage, and the need of transfusions increase the risk (James et al., 2006).

There are controversies on recommendations concerning both the mode of delivery and the choice of anaesthesia for C-section in this patient group (Brighouse, 1998; Whitfield and Holdcroft, 1998; McDonald, 2004). Data documenting the haemodynamic effects of spinal anaesthesia are sparse. The observational study in pregnant women with cardiac disease was initiated to examine both the need for a multidisciplinary approach and the risk classification in our population. In addition, we wanted to examine the haemodynamic changes during regional anaesthesia for C-section in intermediate and high risk patients by using continuous invasive monitoring of CO and BP.

**Pregnant women with preeclampsia**

Preeclampsia is a multisystem disease affecting approximately 5% of all pregnant women, and is a major cause of maternal and neonatal mortality and morbidity (Sibai et al., 2005). The aetiology is still not known. The asymptomatic first stage starts early, with a failure of trophoblastic invasion resulting in a decreased placental perfusion.
The symptomatic second stage is characterized by a maternal endothelial dysfunction. An antiangiogenic protein s-Flt-1 (soluble fms-like tyrosin kinase-1) produced by the placenta has been found to be upregulated in women with preeclampsia. This protein antagonises the angiogenic growth factors, vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). Another antiangiogenic protein, soluble endoglin (sEng), is elevated in patients with HELLP-syndrome (Maynard et al., 2003; Venkatesha et al., 2006).

Maternal predisposition results in a maternal syndrome (hypertension and proteinuria) with or without foetal growth restriction. Preeclampsia has been classified into the early form (before 34 weeks’ gestational age) with a genetic component (Redman and Sargent, 2005), and the late form (after 34 weeks’ gestational age) associated with a normal placenta and disposing maternal factors such as hypertension, diabetes, or obesity.

Preeclampsia is defined as the new onset of hypertension (140/90 mmHg) and proteinuria (300 mg/24 hr) after 20 weeks’ gestational age. Severe preeclampsia is defined as BP ≥ 160/110 mmHg and proteinuria > 5 g/24 hour, and elevated serum creatinine, pulmonary oedema, oliguria, intrauterine growth restriction, headache, visual disturbances, epigastric or upper quadrant pain, or signs of HELLP syndrome.

The decreased endothelium-dependent mechanisms of vascular relaxation and the enhanced mechanism of vascular smooth muscle contraction represent plausible causes of the increased vascular resistance and arterial pressure associated with preeclampsia (Khalil and Granger, 2002). Compared to a normal pregnancy characterized by an increased plasma volume and a decrease in SVR (Cotton et al., 1988; Schwarz, 1991), preeclamptic women are characterised by a lower plasma volume (Arnaudov et al., 1989) and an increase in SVR in addition to hypertension and proteinuria. Old studies using PA-catheters have shown different haemodynamic patterns in this patient group (Visser and Wallenburg, 1991). Discrepancy in the
haemodynamic findings could be due to treatment, but probably also due to individual differences (Visser and Wallenburg, 1991; Visser and Wallenburg, 1995; Young and Johanson, 2001).

There have been controversies (Howell, 1998; Santos and Birnbach, 2003; Santos and Birnbach, 2005) on the use of spinal anaesthesia in preeclamptic patients, but several studies have shown less hypotension in severe preeclampsia during spinal anaesthesia for C-section compared to healthy patients (Wallace et al., 1995; Aya et al., 2003; Clark et al., 2005; Aya et al., 2005; Visalyaputra et al., 2005) using non-invasive blood pressure monitoring. There are few publications of invasive monitoring during C-section in pregnant women. One old study using a PA-cathether during C-section in women with severe preeclampsia, demonstrates the abrupt increases in MAP after intubation and extubation, compared to minimal haemodynamic effects of epidural anaesthesia (Hodgkinson et al., 1980). General anaesthesia in these patients should be avoided unless neuraxial techniques are contraindicated due to HELLP and low platelets (Gogarten, 2009). There is only one study using invasive CO-monitoring during spinal anaesthesia for C-section in women with severe preeclampsia (Dyer et al., 2008). This study demonstrates the huge differences in baseline CO (ranging from 4 to 10 L/min), even though blood pressure was in the same range.

Measuring blood pressure using an automatic oscillatory technique has shown underestimation of blood pressure in preeclamptic patients compared to the auscultatory technique (Quinn, 1994). This discrepancy has been shown to be as much as 30 mmHg, and should be of concern in considering the start of antihypertensive treatment. Systolic blood pressure should be targeted and kept below 160 mmHg, and magnesium sulphate should be given prophylactically to prevent eclampsia (Belfort et al., 1999; Altman et al., 2002; Gogarten, 2009). The
CEMACH-report 2000–2002 (Lewis, 2007) focused on systolic instead of diastolic blood pressure and could be seen as a paradigm shift in obstetric medicine.

Several publications have linked PE to increased risk of cardiovascular disease (McDonald et al., 2008; Craici et al., 2008; Bauer and Cleary, 2009). Is PE predisposing for cardiovascular disease later in life, or is PE developing in women already at risk for cardiovascular disease? Some authors suggest (Mei et al., 2008) that patients developing early PE (<34 weeks of gestational age) may be at higher risk for complications during pregnancy and later in life.

Three important questions for the treatment of women with severe preeclampsia undergoing C-section emerge:
1. Can women with severe preeclampsia be treated as a homogenous group?
2. Is blood pressure alone enough to guide treatment?
3. Do women with severe preeclampsia differ from healthy pregnant women in their responses to haemodynamic challenges like spinal anaesthesia and oxytocin injection?
AIMS OF THE THESIS

1. Describe the haemodynamic changes induced by spinal anaesthesia for caesarean section in healthy pregnant women.

2. Compare the haemodynamic effects of two different doses of intrathecal bupivacaine (7 mg versus 10 mg) combined with or without a low dose intravenous phenylephrine-infusion (0.25μg/kg/min) for spinal anaesthesia in healthy pregnant women during caesarean section.

3. Describe the haemodynamic effects of a low-dose phenylephrine-infusion in healthy pregnant women during spinal anaesthesia for caesarean section.

4. Describe the haemodynamic effects of oxytocin in healthy pregnant women.

5. Describe the diversity of diagnosis and risk stratification in pregnant women with cardiac disease.

6. Describe the importance of a multidisciplinary approach in follow-up and deciding mode of delivery in pregnant women with cardiac disease

7. Describe the haemodynamic effects of spinal anaesthesia during caesarean section in pregnant women with cardiac disease.

8. Compare the cardiovascular response to a haemodynamic challenge in preeclamptic patients versus healthy women with the use of the response to oxytocin as a model.

9. Describe the implementation of invasive haemodynamic monitoring in pregnant women using a minimally invasive technique.
METHODS

All data in the four publications have been collected from pregnant patients delivering at the obstetric unit at Oslo University Hospital – Rikshospitalet.

Study design

Study I was a randomised double-blind, placebo-controlled study in healthy pregnant women scheduled for an elective C-section. The randomisation was performed by the senior author who was not involved with the drugs or the participants. The randomisation to four groups of equal size was in blocks of eight using a list of random numbers. The block size and the randomisation codes were not revealed to the investigators until all measurements and calculations had been entered into the database. The test drugs were prepared according to information in opaque, sealed envelopes marked with a randomisation number only. The syringes with test drugs for each patient were prepared on the morning of surgery by a colleague not involved in the study. This study was designed to compare different interventions for spinal anaesthesia close to clinical practice. All women had an arterial line, and continuous CO-monitoring. All data were downloaded from the CO-monitor. The haemodynamic changes after oxytocin 5 units in the first ten patients were analysed and published in Paper II.

Study III was an observational study of 113 pregnancies in 107 women with cardiac disease. All data were recorded prospectively. Descriptive data on mode of delivery and risk stratification were described and discussed. The haemodynamic changes during regional anaesthesia for C-section were analysed in 24 intermediate and high risk patients.
Study IV utilized data collected in from an ongoing observational study of
haemodynamic changes in women with severe preeclampsia. All data were recorded
prospectively. Data from 18 patients monitored during C-section and given oxytocin
5 units were analysed and compared with healthy pregnant women given the same
dose of oxytocin.

The LiDCOplus monitor
This is a cardiovascular monitor, providing continuous assessment of haemodynamic
status. This is achieved by two proprietary algorithms: a continuous arterial
waveform analysis system (PulseCO™) coupled to a single point lithium indicator
dilution cardiac output measurement system (LiDCO™) which can be used for
calibration of the PulseCO algorithm.

The PulseCO-algorithm utilized for this technique of arterial pulse power
analysis is not a pulse contour method. It is based on the assumption that the net
power change in a heartbeat is the balance between the input of a mass of blood
(stroke volume) minus the blood mass lost to the periphery during the beat. In taking
the whole beat period, and not a portion of the beat, the method is independent of the
position of the reflected wave (i.e. which artery the wave is recorded from). The
algorithm compliance corrects any arterial pressure signal to a standardized volume
waveform through the equation: $$\Delta V/\Delta bp = \text{calibration} \times 250 \times e^{k_{bp}},$$ where V is
volume, bp is blood pressure, and k is the curve coefficient. The number 250
represents the saturation value in mls, i.e., maximum additional volume above the
starting volume that the arterial tree can fill to. The calibration factor changes the
saturation value for the individual patient. The calibration factor is the ratio of the
PulseCO value for CO to the LiDCO value for CO at the time of calibration.
Autocorrelation is a time based method and thereby avoids using a frequency approach to measuring power (such as the Fourier transform) and, thus, the effects of arterial damping (which change frequency response) are limited (Pearse et al., 2004).

The LiDCO part of the monitor is based on the use of lithium as the indicator for the dilution technique for the estimation of cardiac output. By injecting a small dose of lithium chloride (0.3mmol) on the venous side, the concentration-time curve is detected on the arterial side by a lithium ion-sensitive electrode. The voltage response of the lithium electrode is proportional to the relative ion concentration change.

Cardiac output = Lithium dose (mmol) × 60/ Area × (1 – PCV) (mmol/s), where area is the integral of the primary lithium dilution curve, and PCV is the packed red cell volume. PCV is required because the lithium is dissolved in the plasma only.

The technique is not dependent on any special catheter insertion. It requires only peripheral venous and arterial cannulations. If a central venous catheter is inserted, one can in addition measure intrathoracic blood volume (ITBV) which gives more information about fluid status.

Limits of use include patients on lithium treatment, first trimester of pregnancy, and severe aortic regurgitation. The use of an intravenous muscle relaxant such as cisatracurium could influence the sensor and disturb calibration.

The monitor has been validated against the pulmonary artery catheter (Kurita et al., 1997). The LiDCOplus-monitor has been validated in other patient-groups (Costa et al., 2008; Marquez et al., 2008; Cecconi et al., 2009), but there is only one study (Dyer et al., 2008) of its use in pregnant women except for the studies included in this thesis.

Based on the experience using the LiDCOplus monitor in more than 200 pregnant women (Langesaeter, 2008), this minimally invasive technique has been implemented in our department as an alternative to more invasive techniques in this
patient group. Calibration is recommended every 12–24 hours, but this may be different in pregnant women. There is a tendency to differences in calibration factor before and after delivery, suggesting that calibration should be repeated after delivery.

A recent editorial (Pauca, 2008) was critical of the use of this monitor during C-section, but the arguments were based on incorrect assumptions. He referred to an old algorithm (Linton and Linton, 2001) that is not the algorithm utilised in the present monitor (Dyer and James, 2008).

**Statistical analysis**

All the haemodynamic data from the LiDCOplus monitor were organised in MatLab version 2007a (The MathWorks, Natick, MA) before analyses. The SPSS (Statistical Package for the Social Sciences) version 15 was used for all statistical analyses.

In study I, the beat-to-beat data set for all 80 women was transformed into average values every 10 seconds. Outliers were defined as extreme values and values more than 30% from the two previous values were considered erroneous and omitted from the data set. The Linear Mixed Model in SPSS® (ANCOVA) is an extension of regression analyses and ANOVA. The term “mixed” means that the statistical model contains both fixed effects and random effects. The data are permitted to be correlated and have changing variability. This is an advanced method for analysing repeated measurements for data that maybe independent or not. In study I, treatment groups and time were fixed factors, and baseline values were treated as a covariate. Rescue phenylephrine was included as a covariate since there was no correction for the use of rescue phenylephrine in the data set. The dependent variable was the 60 measured time intervals (mean every ten seconds for 10 minutes) for each variable.
Descriptive data were presented as mean and SD (standard deviation) for normally distributed data using ANOVA, a one-way analysis of variance comparing means of more than two independent groups of normally distributed observations.

In Paper II, descriptive statistics were used. The changes in cardiac output, systemic vascular resistance, and systolic blood pressure from the baseline after oxytocin in 10 pregnant women were presented as median and range. The haemodynamic changes in CO, SVR, and SAP were plotted in the figure as mean values with 95% confidential intervals every 10 seconds for 200 seconds.

In Paper III, descriptive statistics were used and the data were presented as median and range. The findings were presented in individual figures after organising the haemodynamic data in Matlab, omitting extreme values.

In Paper IV, an independent t-test was used to compare the mean differences in haemodynamic changes after oxytocin in healthy pregnant women and in women with severe preeclampsia. The data were presented as mean maximum changes with 95% confidential intervals.
SYNOPSIS OF RESULTS

Paper I

This study was a randomised double-blind placebo controlled study designed to compare haemodynamic changes induced by four different interventions for spinal anaesthesia during C-section. This was the first study conducted in healthy pregnant patients using a continuous invasive beat-to-beat monitoring of stroke volume, cardiac output, systolic arterial pressure, and systemic vascular resistance during C-section. Eighty healthy pregnant women scheduled for an elective caesarean section were randomised to four different interventions. Two groups were given 10 mg bupivacaine intrathecally with or without an intravenous phenylephrine-infusion (0.25µg/kg/min), and two groups were given 7 mg bupivacaine intrathecally with or without an intravenous phenylephrine-infusion. All groups had an addition of 4µg sufentanil intrathecally. Both the patients and the investigators were blinded to the group randomisation. The primary outcomes were group differences in cardiac output and systolic arterial pressure. The secondary outcomes were group differences in other haemodynamic variables, incidence of nausea, duration of motor block, and neonatal outcome (Apgar and umbilical blood gases).

There were clinically and statistically significant differences between the four groups in the primary outcomes, CO and SAP, and in all the other haemodynamic variables, except for SV. The group given 7 mg bupivacaine combined with a prophylactic phenylephrine-infusion had clinically and statistically significantly less haemodynamic changes from the baseline compared to the other groups.

By using continuous invasive monitoring during spinal anaesthesia for C-section, the study demonstrated the fast and prominent vasodilatory effect of
intrathecal bupivacaine. In less than two minutes after spinal injection, all four
groups had a marked decrease in SVR, and an increase in CO.

Comparing 10 mg bupivacaine to 7 mg bupivacaine shows that the higher dose
induces more hypotension than the lower dose (see figure 3–5, pages 42–43). The
relative risk of nausea was 2.4 in the high dose groups compared with the low dose
groups. Comparing the high dose group with placebo-infusion to the low dose group
with phenylephrine-infusion, RR for nausea was 4.3, RR for 20% reduction in SAP
was 2.5, and RR for 30% reduction in SAP was 3.7.

Comparing the groups receiving phenylephrine-infusion to the placebo-
infusion groups showed that the phenylephrine had a negative effect on CO and HR.

Three patients in the low dose groups, and one patient in the high dose groups
needed an epidural top up, but none of the women included in this study needed
general anaesthesia. The mean duration of motor blockade was 99 minutes in the low
dose groups, and 140 minutes in the high dose groups.

There was a statistically significant group difference in mean umbilical artery
and vein base excess, with the low dose groups having less acidosis.

**Paper II**

This paper showed the haemodynamic effects of oxytocin 5 units in ten healthy
patients included in study I.

After injection of 5 units oxytocin, cardiac index increased to 61% above the
baseline values, the systemic vascular resistance index decreased to 39%, and the
systolic blood pressure decreased to 67% of baseline values.

This is the first publication demonstrating the prominent haemodynamic
changes after oxytocin using invasive CO-monitoring. The mean time interval to
maximal haemodynamic changes was 45 seconds after the injection of oxytocin. The haemodynamic variables normalised to baseline values after approximately 2 minutes. These changes would not have been detected using non-invasive blood pressure measurements.

Based on the prominent haemodynamic changes induced by oxytocin 5 units, this paper recommended reducing the doses of oxytocin in healthy pregnant women during C-section.

Paper III

The data presented in this paper describe the management of 113 pregnancies in 107 women with cardiac disease. This survey demonstrates the huge spectre of diagnosis in our population. A high percentage (28.3%) of the patients was classified as high risk, 27.4% was intermediate risk, and 44.2% was low risk. One important topic in this paper is the mode of delivery in the high risk patients. The mode of delivery should be decided by a multidisciplinary team including an obstetrician, a cardiologist, and an anaesthetist. High risk patients should be delivered in a tertiary care centre with cardiac surgery available. We recommend a planned C-section in daytime with experienced staff, time for adequate monitoring, and the time for regional anaesthesia in high risk patients. Based on our experience with regional anaesthesia to all pregnant women with cardiac disease, we conclude that these patients tolerate the haemodynamic changes induced by regional anaesthesia. The haemodynamic changes during regional anaesthesia are shown in 24 intermediate and high risk patients using invasive CO-monitoring.
Paper IV

Eighteen women with severe preeclampsia were included in this paper. They were given oxytocin 5 units i.v. during C-section. The haemodynamic effects of oxytocin in these women with severe preeclampsia were compared to findings in the eighty healthy patients included in study I.

The haemodynamic changes after 5 units oxytocin in the women with severe preeclampsia were different from the findings in healthy pregnant women. The preeclamptic women had a smaller increase in SV (6% vs 38%), in HR (22% vs 42%), and in CO (35% vs 85) compared with healthy pregnant women. The preeclamptic women had less decrease in SVR (52% vs 62%). Both the healthy and the preeclamptic women had a decrease in SAP, but there were no differences in the mean percentage changes in SAP in the two groups. The cardiovascular response to oxytocin was less predictable in the preeclamptic patients than in the healthy patients, and five of the 18 women with severe preeclampsia (27.8%) had a decrease in CO after 5 units oxytocin. All the healthy pregnant women had an increase in CO. These findings suggest that women with severe preeclampsia respond differently to haemodynamic challenges compared to healthy pregnant women. Oxytocin should be administrated in small titrated doses to women with severe preeclampsia to avoid cardiac decompensation.
DISCUSSION

The first paper included in this thesis demonstrates the haemodynamic changes induced by spinal anaesthesia during C-section in healthy pregnant women. Publication II shows the haemodynamic effects of oxytocin in healthy pregnant women. Publication III is an observational study in pregnant women with cardiac disease, describing our recommendations for management concerning follow-up during pregnancy, mode of delivery, and demonstrating the haemodynamic effects of regional anaesthesia for C-section in the intermediate and high risk patients. Publication IV shows the haemodynamic effects of oxytocin in preeclamptic patients compared to healthy pregnant women.

Haemodynamic changes during spinal anaesthesia in healthy pregnant women

Paper I (Langesaeter et al., 2008) documents the prominent haemodynamic effects of spinal anaesthesia in healthy pregnant women using beat-to-beat monitoring. Independent of intervention, all 80 healthy pregnant women had a prominent decrease in SVR and an increase in cardiac output. In contrast to previous knowledge (Reidy and Douglas, 2008), we showed that CO increases after induction of spinal anaesthesia. This is new knowledge.
Figure 1. Mean differences in SVR between the four treatments groups. Baseline is marked on the y-axis. SE (standard error) for each group is marked as error bars. (Paper I).

Figure 2. Mean differences in CO between the four treatments groups. Baseline is marked on the y-axis. SE (standard error) for each group is marked as error bars. (Paper I).
Figure 1 and 2 demonstrate the prominent decrease in SVR and increase in CO in all four groups after spinal anaesthesia. The changes appear in less than two minutes. The group receiving 7 mg of bupivacaine and 4µg sufentanil combined with a low-dose intravenous phenylephrine-infusion of 0.25µg/kg/min had the least changes from baseline haemodynamics. The increase in cardiac output and the decrease in systemic vascular resistance were greatest in the group receiving 10 mg of intrathecal bupivacaine and an intravenous placebo-infusion. Comparing these two most haemodynamically different groups, RR for nausea was 4.3, RR for 20% hypotension was 2.5, and RR for 30% hypotension was 3.7.

To counteract these changes, the physiological approach is to give an alpha-agonist prophylactically. In study I, a prophylactic low-dose phenylephrine-infusion was started concomitant with intrathecal injection of anaesthesia. This could not prevent the rapid changes in SVR. Based on these results, we would recommend giving an initial bolus of 50µg phenylephrine to reduce the immediate changes in SVR.

A recent editorial (Sharwood-Smith and Drummond, 2009) comments on the dominant focus on venous return and the inferior vena cava compression theory to explain the haemodynamic effects of spinal anaesthesia. They refer to an old publication from 1950 (Assali and Prystowsky, 1950) demonstrating the larger effects of sympathetic block in healthy compared to preeclamptic pregnant women. The authors comment on these early findings suggesting that one should focus more on the effects on the arterial side induced by spinal anaesthesia. This is demonstrated in Paper I. The main effects of spinal anaesthesia are the rapid and prominent decrease in SVR, with a compensatory increase in CO.

Comparing the effects of 7 mg with 10 mg intrathecal bupivacaine, the high dose induced more hypotension (p=0.009) compared with the low dose. The relative
risk for 20% and 30% reduction in SBP between the two high-dose groups and the two low-dose groups were 1.6 and 2.1, respectively. RR for nausea was 2.4.

The haemodynamic changes in CO, SVR, and SAP in the high-dose versus the low-dose groups are shown in figures 3–5 below.

![Cardiac Output Graph](image)

**Figure 3.** Mean differences in CO between the two high dose groups and the two low dose groups. Baseline is marked on the y-axis. SE (standard error) is marked as error bars.
Figure 4. Mean differences in SVR between the two high dose groups and the two low dose groups. Baseline is marked on the y-axis. SE (standard error) is marked as error bars.

Figure 5. Mean differences in SAP between the two high dose groups and the two low dose groups. Baseline is marked on the y-axis. SE (standard error) is marked as error bars.
Ngan Kee et al. (Ngan Kee et al., 2005) published an interesting study in 2005. The healthy pregnant women (mean height 157 cm) were given 10 mg of intrathecal bupivacaine, combined with high doses of phenylephrine-infusion i.v., and with 2000 ml crystalloids as cohydration or no cohydration. Both groups had high doses of phenylephrine-infusion to keep systolic blood pressure at baseline. With this strategy, the incidence of hypotension with intermittent non-invasive measurements was only 1.9% in the group receiving 2000 ml of crystalloids as cohydration compared to 28.3% in the group with no cohydration. Their findings document the clinical relevance of cohydration. Their approach almost abolished hypotension, but they had 47% hypertension in both groups. Ngan Kee et al. measured heart rate and non-invasive blood pressure every minute. Both of their groups had an initial decrease in heart rate during the first minutes. All our patients had an initial increase in heart rate shown in figure 7 below. Figure 6 and 7 show the haemodynamic effects of a low dose phenylephrine-infusion (0.25μg/kg/min) compared to a placebo-infusion on cardiac output and heart rate. The administered dose of phenylephrine during the first ten minutes in our study equals 2.8μg/kg compared to 17μg/kg in Ngan Kee et al.’s study. The negative effect of phenylephrine on cardiac output and heart rate is dose dependent. By looking at the heart rate trends in Ngan Kee et al.’s study (Ngan Kee et al., 2005), one can assume that CO decreases the same way as heart rate (Dyer and James, 2009; Ngan Kee and Khaw, 2009; Langesaeter et al., 2009b).

Heart rate follows the same pattern as cardiac output (see figure 6 and 7), and the changes in HR could be used as a surrogate of CO. Administrating high doses of phenylephrine to sustain systolic arterial pressure at baseline by increasing SVR could result in a major reduction in CO. This is not an optimal strategy to prevent haemodynamic instability during C-section (Langesaeter et al., 2009b). The use of high doses phenylephrine with a decrease in CO may not be detrimental in healthy
women, but it is not a physiological approach. Spinal anaesthesia should be given in a balanced way taking into consideration all the factors which influence on haemodynamic instability, not focusing exclusively on blood pressure.

![Graph](image)

**Figure 6.** Mean differences in CO between the two phenylephrine groups and the two placebo groups. Baseline is marked on the y-axis. SE (standard error) is marked as error bars. (Paper I).
Figure 7. Mean differences in HR between the two phenylephrine groups and the two placebo groups. Baseline is marked on the y-axis. SE (standard error) is marked as error bars. (Paper I).

Many studies have used differences in umbilical arterial and venous pH as the main outcome when comparing different anaesthetic approaches during C-section (Cooper et al., 2002a; Ngan Kee et al., 2005; Cyna et al., 2006). Is umbilical pH a valid test to evaluate the effect of the anaesthetic technique on the foetus? A difference in pH of 0.03 has no clinical relevance, even though this small difference could be statistically significant. Compared to the lactate and the Apgar score, pH has a much lower predictive value in evaluating neonatal outcome (Lee, 1972; Hoffmann et al., 1991; Kruger et al., 1999; Casey et al., 2001). In Paper I, there were no clinically or statistically significant group differences in umbilical arterial or venous pH. There were statistically significant differences between low dose and high dose groups in umbilical arterial and venous base excess (BE) (p = 0.008, and p = 0.003, respectively), but the clinical implications are minimal as none of the newborn were acidotic. There
were no differences in umbilical blood gases comparing the phenylephrine-group to the placebo-group.

When discussing the anaesthetic improvements for C-section, one important factor is omitted from the discussion. That is the induction time; the time from spinal anaesthesia to delivery. Our department has introduced ‘a fast track procedure’. Before entering the operating theatre, the women have a urinary catheter and two peripheral lines in place. The women are positioned directly into the right lateral position on the operating table. The obstetricians arrive and spinal anaesthesia is given. The patient is turned into 15 degrees left lateral tilt, and surgery can begin in less than 10 minutes after the spinal injection. During study I using CSE-technique, the mean induction time (from spinal to delivery) was 18 minutes, and the mean surgery time in our study was less than 32 minutes. If induction time can be shortened, both the duration of hypotension and maternal anxiety can be reduced.

**Haemodynamic effects of oxytocin in healthy pregnant women**

Paper II (Langesaeter et al., 2006) was the first publication using continuous invasive monitoring of SV, SVR, and CO after administering of 5 units oxytocin during C-section. This demonstrated a mean decrease of 61% in SVR, a mean decrease of 33% in SAP, and a mean increase of 61% in CO, with a mean time to maximum changes of approximately 45 seconds. In less than two minutes the haemodynamic values were back to baseline.

Several studies have been published demonstrating the prominent and immediate hypotension after bolus administration of oxytocin (Secher et al., 1978; Munn et al., 2001; Pinder et al., 2002; Charbit et al., 2004; Thomas et al., 2007;
Svanstrom et al., 2008). But, as late as 2005, a publication on haemodynamic changes during C-section did not mention the effects of oxytocin (Tihtonen et al., 2005). The authors explained the hemodynamic changes as an effect of delivery itself. Their view did not change when the haemodynamic effects of oxytocin were commented on (Langesaeter and Rosseland, 2006). Swansvom et al. (Svanstrom et al., 2008) published an article showing the haemodynamic effects of 10 units oxytocin in pregnant and non-pregnant women. They demonstrated the same changes after oxytocin in non-pregnant women which documents that the haemodynamic effects are due to oxytocin and not to delivery.

There are still many hospitals using high doses of oxytocin 10 units when requested by the obstetricians. Even 5 units is an unnecessarily high dose (Vercauteran et al., 2009). Carvalho et al. (Carvalho et al., 2004; Balki et al., 2006) have shown that ED95% for oxytocin is 0.35 units for C-section in non-labouring women, and 3.0 units in labouring women. Based on these findings by Carvalho et al., the doses of oxytocin should be reduced. By giving small bolus doses of oxytocin, the effect will be recognised immediately. If oxytocin is not effective, one should change to misoprostol (prostaglandin) that acts on different uterine receptors (Robinson et al., 2003; Wise and Clark, 2008; Langesaeter et al., 2009a).

Oxytocin should be given with caution in pregnant women with cardiac disease, to avoid abrupt haemodynamic changes. Many recommend giving oxytocin as an infusion in both healthy and compromised pregnant women (Pinder et al., 2002; Thomas et al., 2007). A good alternative is to reduce the dose, and give an additional dose if needed. This also reduces the volume load to a minimum.
Management of pregnant women with cardiac disease

All current recommendations are based on expert consensus (Oakley et al., 2003) rather than evidence in this heterogeneous group (Oakley, 1997). Three main subspecialties are important in the decision making: the obstetrician, the cardiologist and the anaesthetist. Paper III describes the development of a multidisciplinary group for the management of pregnant women with cardiac disease, and the importance of a careful planning of the delivery in these patients. The paper focuses on the importance of the functional capacity for risk classification in addition to the specific cardiac lesion, the results of echo cardiography, and an evaluation of changes during pregnancy. In our department, we use a simple evaluation of functional capacity judged by climbing the stairs with monitoring of the heart rate and oxygen saturation.

Table 1 shows the different diagnoses and the risk groups of the 113 pregnancies included in our survey of pregnant women with cardiac disease. Many patients had several diagnoses. This demonstrates the huge spectre of different cardiac diseases. It shows the relatively high percentage (approximately 30%) of high risk patients in our survey compared to other surveys (Boyle, 2003; Ford et al., 2008; Curtis et al., 2008).
**Table 3.** (Paper III). Cardiac diagnosis and risk classification

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<th>Low risk</th>
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<td><strong>31</strong></td>
<td><strong>50</strong></td>
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HOCM, hypertrophic obstructive cardiomyopathy; HCM, hypertrophic cardiomyopathy; AS/AI/AVR, aortic stenosis; aortic insufficiency; aortic valve replacement; MI/MS, mitral insufficiency/stenosis; MVR, mitral valve replacement; PI/PS, pulmonary insufficiency/stenosis; PHT, pulmonary hypertension; ASD/VSD, atrial/ventricular septal defect; TAA, thoracic aortic aneurysm; CoA, aortic coarctation; TGA, transposition of the great arteries; LQTS, long QT-syndrome; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White Syndrome; Double-chamber RV, double-chamber right ventricle.
Vaginal delivery is recommended for pregnant women with cardiac disease unless there is an obstetric reason for C-section (Siu and Colman, 2001; Dob and Yentis, 2006). The arguments against C-section are the higher risk of thrombosis, bleeding, infections, and hemodynamic instability induced by anaesthesia (Oakley et al., 2003; Dob and Yentis, 2006; Uebing et al., 2006). This view can be questioned.

The risk of thrombosis is increased in pregnant women due to venous stasis and changes in the coagulation with an increased concentration of clotting factors. The risk of pulmonary thromboembolism is 0.01–0.05%, and the risk of deep vein thrombosis is 0.02–0.36% (Weiner, 1985; Gherman et al., 1999). Macklon (Macklon and Greer, 1996) found the incidence of DVT after C-section to be 0.424/1000 compared with 0.173/1000 following vaginal delivery, and the risk of VTE was doubled in case of an urgent C-section. James et al. (James et al., 2005) found the odds ratio for thromboembolism associated with C-section to be 2.1. In a recent publication, the incidence of DVT after C-section was 0.5% (Sia et al., 2009). The recently published guidelines (Bates et al., 2008) recommend pharmacological thromboprophylaxis combined with the use of compression stockings in pregnant women at risk of venous thromboembolism.

There is no documentation of increased risk of bleeding during C-section compared to vaginal delivery. In a retrospective study of 47 000 C-sections and 2.3 million vaginal deliveries (Liu et al., 2007), a lower risk of haemorrhage was reported in the C-section group (OR 0.4). In two randomised studies, there were no differences in bleeding as a secondary outcome (The European Mode of Delivery Collaboration, 1999; Hannah et al., 2000).

The risk of infection is increased after C-section compared to vaginal delivery (Blanco et al., 1981). A survey from Norway (Eriksen et al., 2009) found that 1 out of 12 women delivering by C-section had a wound infection. Prophylactic admini-
stration of antibiotics decreases the incidence of infection (Smaill F and Hofmeyr GJ, 2006). Many of the pregnant women with cardiac disease have antibiotic prophylaxis due to their cardiac lesions which may be preventive for endometritis and wound infections.

The hemodynamic changes associated with spinal anaesthesia for C-section has been a major concern in discussing the mode of delivery. The use of regional anaesthesia in high risk patients is still controversial. Numerous case reports have shown a successful anaesthesia with both general or regional anaesthesia in this patient group (Gandhimathi et al., 2002; Geohas and McLaughlin, 2003; Orme et al., 2004; Ferguson et al., 2006; Bilehjani et al., 2008; Smith et al., 2008; Toyama et al., 2009).

Paper III shows the haemodynamic changes during spinal anaesthesia for C-section in 24 intermediate and high risk pregnant women with cardiac disease. This was an observational study with individualized treatment of each patient. All patients had continuous invasive blood pressure and CO-monitoring during C-section, to guide the treatment and choice of vasopressor and fluid. The concern about giving regional anaesthesia is the vasodilatory effect induced by sympathetic block. Our survey shows that the vasodilatory effect was well tolerated when regional anaesthesia was titrated, and with guided vasopressor and fluid administration. By using continuous invasive monitoring, the haemodynamic changes were detected immediately. Regional anaesthesia should be chosen according to the cardiac lesion. Left sided obstructions (AS, MS, HOCM) are at risk to the haemodynamic consequences of vasodilatation after spinal anaesthesia. The degree of vasodilatation can be minimised by reducing spinal bupivacaine doses and administering a prophylactic alfa-agonist, as we have shown in Paper I in healthy pregnant women.
None of the 24 intermediate and high risk patients worsened symptomatically during C-section. Our figure demonstrates the changes in CO and SAP after spinal anaesthesia. One patient was challenging. The haemodynamic changes in this patient are not shown because she had no arterial line in place. This patient with a severe HOCM was scheduled for an elective C-section in daytime. She became bradycardic and lost consciousness before being given anaesthesia, and without an arterial line in place. An emergency C-section had to be conducted under general anaesthesia. She had a circulatory collapse and needed cardiac compression for five minutes. When an arterial line and CO-monitoring was in place, measurements showed an extreme vasodilation. The patient was haemodynamically stabilized after administering norepinephrine and fluids. This demonstrates the importance of continuous invasive monitoring. It also demonstrates the setting of an emergency C-section with no time for monitoring. A previous publication showed that a high number of pregnancies in high-risk cardiac patients attempting vaginal deliveries ended up with an urgent caesarean section (Dob and Yentis, 2001). General anaesthesia will induce autonomic responses with hypo- or hypertension and tachycardia, which may be less controllable. Positive pressure ventilation may be an important additional concern in some patients. Our conclusion is that high risk pregnant women with cardiac disease should preferably have an elective C-section in daytime, and not be exposed for the risk of emergency surgery. To avoid an urgent C-section in high risk patients, one should plan an elective C-section, as a vaginal delivery can not be planned.
The arguments for a planned C-section can be summarized as follows:

1. A planned C-section can be done in daytime
2. There is time for adequate invasive haemodynamic monitoring before giving anaesthesia
3. There is time for regional anaesthesia
4. Experienced staff
5. Available backup in case interventions like intra-aortic balloon pump or cardiac surgery are needed

In contrast, a vaginal delivery is difficult to plan, especially in nulliparous women. If the woman does not go into labour at term, should the labour be induced? An induction of labour in a nulliparous will significantly increase the risk of vacuum, forceps, or C-section (Vahratian et al., 2005; Cnattingius et al., 2005; Pevzner et al., 2009). Induction has been found to be a predictor of severe obstetric morbidity (Waterstone et al., 2001).

An issue which has not been investigated substantially is the haemodynamic effects of a vaginal delivery. Old studies conducted with different intermittent techniques for haemodynamic monitoring, show divergent measurements of cardiac output during the first stage of labour (Ueland and Hansen, 1969; Hansen and Ueland, 1974; Filippatos et al., 1997). Data on the continuous haemodynamic changes during the second stage is lacking, except for one case report of continuous invasive monitoring (Langesaeter, 2009). In this case report, SVR increased and CO decreased by 50% during each contraction. The effects of the haemodynamic changes during labour should be compared to the changes during a balanced anaesthesia for C-section. Haemodynamic stress during delivery is an important concern when discussing the mode of delivery in high risk patients.
The use of oxytocin in pregnant women with cardiac disease is controversial (Hamlyn et al., 2005; Tamhane et al., 2006). In paper III, the haemodynamic effects of small bolus doses of oxytocin 0.1–0.5 units are demonstrated. Even small doses have a significant haemodynamic effect, but the changes are smaller and short acting compared to higher doses. Oxytocin can be administered in small titrated doses, guided by invasive monitoring. In pregnant women with cardiac disease, the concern about giving an excessive volume load is greater. Our recommendation is to give titrated doses of 0.1 units oxytocin that induces short lasting and minimal haemodynamic changes.

It is important to continue the invasive monitoring in these high risk women in the postoperative period. The threshold for a chest x-ray and an echo cardiography in symptomatic pregnant women should be low. Even though dyspnoea could be judged as normal in late pregnancy, this should be investigated when the functional capacity is decreased. Undiagnosed valve regurgitations in pregnant women are usually well tolerated, but could become symptomatic with a superimposed preeclampsia due to the increased afterload. An echo cardiography is a simple, non-invasive diagnostic method to rule out cardiac pathology.

Management of pregnant women with severe preeclampsia

As shown in Paper IV, the haemodynamic effects of oxytocin in women in severe preeclampsia are different compared to healthy women. Eighteen women with severe preeclampsia were compared to 80 healthy pregnant women given the same dose of 5 units oxytocin. The preeclamptic women had higher baseline values in BP and SVR. There was no difference in changes in systolic blood pressure between the groups. The preeclamptic women had a smaller decrease in SVR. The most striking finding was the smaller increase in SV in the preeclamptic group of 6%, and the less increase
in CO of 32%, compared to 38% and 85%, respectively, in the healthy group. In fact, five of the 18 preeclamptic patients had a decrease in CO after administration of oxytocin, while all the 80 healthy pregnant women had an increase. The study was too small to do any subgroup analysis to look at risk factors for cardiac decompensation. Most of the preeclamptic patients were treated with antihypertensive medication, and some had magnesium sulphate before delivery. The differences in predelivery treatment could bias the search for haemodynamic risk factors. The different response to oxytocin in preeclamptic and healthy pregnant women is shown in figure 8.
**Figure 8.** The haemodynamic effects of oxytocin 5 units i.v. in 18 patients with severe preeclampsia compared to 80 healthy pregnant women. Oxytocin was given at time=0 seconds. CO=cardiac output. SVR=systemic vascular resistance. SBP=systolic arterial pressure. SV=stroke volume. (Paper IV).
The inability to increase SV after oxytocin could be due to a diastolic dysfunction. Andrietti et al. suggest a subclinical diastolic dysfunction in formerly preeclamptic women with a low plasma volume (Andrietti et al., 2008). The prevalence of a low plasma volume in this patient group is approximately 50% (Spaanderman et al., 2000). As shown by Ardenburg (Aardenburg et al., 2005), these women are not able to increase their SV with moderate exercise. Bamfo et al. (Bamfo et al., 2008) found that preeclamptic women with IUGR had impairment in diastolic function due to a reduction in both intrinsic contractility and diastolic filling.

Two recent publications (Mei et al., 2008; Vasapollo et al., 2008) have found a high SVR early in pregnancy as an independent factor for developing complications. Women with severe preeclampsia are considered hypovolemic characterised by relative plasma reduction compared to healthy pregnant women (Arnaudov et al., 1989; Bolte et al., 2001). The degree of dehydration may be a risk factor for cardiac decompensation.

Women with severe preeclampsia have an increased risk of preeclampsia in future pregnancies, and have an increased risk of cardiovascular and cerebrovascular disease (Bellamy et al., 2007; Gaugler-Senden et al., 2008), and cardiovascular mortality (McDonald et al., 2008). All these findings could be suggestive of a suboptimal cardiac function in some of the women with preeclampsia. Developing preeclampsia before gestational week 34 seems to give the highest risk of complications during pregnancy and later in life.

The unpredictable effects of oxytocin in some women with severe preeclampsia, is striking. Similar haemodynamic effects are seen after spinal anaesthesia and seem to be a common response to haemodynamic challenges. Preliminary data from an ongoing study in women with severe preeclampsia, demonstrate that the preeclamptic patients, as a group, behave differently from the
healthy group, with small haemodynamic effects after spinal anaesthesia. However, the preeclamptic group is heterogeneous, and the haemodynamic effects induced by spinal anaesthesia are unpredictable compared to healthy women. All healthy pregnant women had a prominent decrease in SVR and a concomitant increase in CO, SV, and HR (Langesaeter et al., 2008). In the preeclamptic group, the majority had minimal haemodynamic effects, but some had rapid and pronounced changes after spinal anaesthesia (data not shown). These changes mimic the data showing the effects after an oxytocin injection. The findings are in accordance with an early publication from 1950 (Assali and Prystowsky, 1950) demonstrating the homogenous effects of spinal anaesthesia in healthy pregnant women, and the less hemodynamic changes in women with severe preeclampsia, but four of 15 preeclamptic women had unpredictable haemodynamic changes.
MAIN CONCLUSIONS

1. Spinal anaesthesia for caesarean section in healthy pregnant women induces a prominent decrease in SVR and a concomitant increase in CO in less than 2 minutes, compared to baseline.

2. The intervention group given the lower dose spinal bupivacaine (7 mg) combined with a low dose intravenous phenylephrine-infusion (0.25μg/kg/min) had clinically, and statistically, significantly less haemodynamic changes from baseline. This group had a smaller decrease in SVR, SAP, MAP and DIA, and less increase in CO, HR, and SV, and less nausea compared to the other three groups.

3. A prophylactic phenylephrine-infusion of 0.25μg/kg/min increases SAP, but has a negative effect on CO and HR.

4. Oxytocin 5 units induced pronounced decreases in SVR and SAP, and an increase in SV, HR, and CO, with a maximal change after approximately 45 seconds in healthy pregnant women.

5. Pregnant women with cardiac disease include a huge spectrum of diagnoses. These patients should be classified into risk groups based on cardiac lesion, functional capacity, and echo cardiography. Intermediate and high risk patients should have a careful plan for delivery decided on by a multidisciplinary team including a cardiologist, an obstetrician, and an anaesthetist.

6. Pregnant women with high risk cardiac disease should be delivered in a tertiary centre with cardiac surgery available. These patients should preferably be delivered in an elective way in daytime by qualified persons with experience in managing this group of patients.
7. Pregnant women with intermediate and high risk cardiac disease tolerate the haemodynamic changes induced by spinal anaesthesia for C-section. Regional anaesthesia is recommended in these patients unless there is a contraindication, such as coagulopathy.

8. Women with severe preeclampsia had a different haemodynamic effect of 5 units oxytocin compared with healthy pregnant women. The preeclamptic women had a smaller increase in mean SV and CO, and less decrease in mean SVR, but there was no difference in mean decrease in SAP, compared with the healthy pregnant women. All the 80 healthy pregnant women had an increase in CO, while 5 of 18 women with severe preeclampsia had a decrease in CO after 5 units oxytocin. Women with severe preeclampsia should be treated with an individualized tailored approach due to their heterogeneity and unpredictable response to haemodynamic challenges during C-section.

9. Use of a new minimally invasive technique has given new knowledge about haemodynamic changes during C-section in healthy pregnant women, describing for the first time the immediate and prominent haemodynamic effects of spinal anaesthesia. This new technique is promising as a tool for haemodynamic research in pregnant women, and as a guide to treatment in pregnant women with cardiac disease or severe preeclampsia.
IMPLICATIONS FOR CLINICAL PRACTICE

The findings in paper I demonstrate the haemodynamic changes of spinal anaesthesia in healthy pregnant women during C-section with the use of continuous beat-to-beat monitoring. This has never been shown before, and has important implications for our understanding of how to treat neuraxially induced hypotension in pregnant women. Due to the rapid and pronounced decrease in systemic vascular resistance and the concomitant increase in cardiac output in less than 2 minutes, the physiological approach is to administer an alfa-agonist (such as phenylephrine) prophylactically to counteract these changes. Based on the findings in paper I, a low-dose prophylactic intravenous phenylephrine-infusion of 0.25µg/kg/min should be used in all healthy women to prevent hypotension during spinal anaesthesia for caesarean section. In addition, an initial bolus of 50µg phenylephrine i.v should be given at start of spinal anaesthesia to prevent the immediate and pronounced vasodilatation. By reducing the spinal bupivacaine dose, one can reduce the incidence of hypotension, nausea, and vomiting. This approach can safely be used with the combined spinal epidural technique.

Phenylephrine has a negative effect on cardiac output and heart rate. Giving high doses of phenylephrine to keep the blood pressure at baseline during spinal anaesthesia for caesarean section is not recommended because of its negative effects on cardiac output.

Based on the findings in paper II, showing the pronounced haemodynamic effects of oxytocin 5 units i.v., the doses should be reduced to avoid haemodynamic instability in healthy pregnant women.

Based on the findings in paper III, a balanced and individualized regional anaesthesia should be the choice of anaesthesia in pregnant patients with cardiac
disease. In intermediate and high risk patients, the treatment should be guided by invasive haemodynamic monitoring both during caesarean section and postoperatively. An elective caesarean section in day time with experienced staff, adequate invasive monitoring, and the time for regional anaesthesia is a safe method of delivery in pregnant women with high risk cardiac disease. Oxytocin should be given in small incremental doses of 0.1 unit to avoid abrupt haemodynamic changes in these high risk pregnant women.

Based on the findings in paper IV, invasive haemodynamic monitoring should be applied in women with severe preeclampsia during delivery. This heterogeneous group of patients, oxytocin has unpredictable responses, and probably to spinal anaesthesia. Therefore, an arterial line is mandatory in this patient group during C-section. While all healthy women have a predictable effect of oxytocin with an increase in cardiac output, approximately 30% of the preeclamptic patients had a decrease in cardiac output due to inability to increase their stroke volume. This could be due to a diastolic dysfunction in some of the preeclamptic patients. Oxytocin should be administered in small titrated doses to avoid cardiac decompensation in patients with severe preeclampsia.

The introduction of a minimally invasive monitor for haemodynamic assessment could be beneficial in pregnant women. The monitor utilised in this thesis requires only peripheral arterial, and venous, cannulation. It is a valuable tool for doing research in healthy pregnant women, and to guide treatment in pregnant women with severe preeclampsia and cardiac disease.
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