Maternal overweight and obesity;

**impact on obstetric outcomes in
adolescents and oxytocin in labor**

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To all of you who inspire me

“Don’t be afraid. Be focused. Be determined. Be hopeful. Be empowered.”

-Michelle Obama

PREFACE

Overweight and obesity in the pregnant population is increasing. It is well-known that an increased body mass index (BMI) is associated with increased risks for both the mother and the fetus. However, in pregnant adolescents the risks related to overweight and obesity have been sparsely studied. More knowledge regarding obstetric and neonatal outcomes based on age and BMI is needed to optimize management in clinical care.

Women with obesity have an increased risk for induction of labor and labor arrest. Despite the common use of oxytocin for stimulation of uterine contractions in labor, little is known about the relation between oxytocin and maternal BMI. Hopefully, with more knowledge, improvements can be made to the treatment of obese women with oxytocin infusion during labor.

ABSTRACT

Objectives

The overall aim of this thesis was to evaluate the impact of maternal body mass index (BMI) on obstetric and neonatal outcomes in adolescents as well as on treatment with oxytocin infusion during labor regarding cumulative oxytocin dose and plasma levels of oxytocin.

Material and Methods

Studies I and II were nationwide Swedish register studies including 31,386 primiparous adolescents subdivided in BMI groups and obesity classes according to early pregnancy BMI. Additionally, 178,844 low-risk normal weight adult women, called “the standard women” were included for comparison with the adolescents in the different BMI groups.

Study III was an observational study conducted at seven maternity wards in the southeast region of Sweden, including 1,097 nulliparous women with spontaneous start of labor receiving oxytocin infusion during labor. The study group was subdivided according to BMI on admission to the labor ward. Cumulative oxytocin dose was registered from the start of the oxytocin infusion until the neonate was born.

Study IV was an observational pilot study conducted at the maternity ward in Linköping, including 40 women in term labor receiving oxytocin infusion during the first stage of labor. The women were subdivided into obese and non-obese categories according to BMI on admission to the labor ward. Serial peripheral venous blood samples were taken during oxytocin infusion in the first stage of labor. The plasma oxytocin concentrations were analyzed with ultra performance liquid chromatography - Orbitrap tandem mass spectrometry at the Department of Chemistry Biomedical Centre, Uppsala University.

Results

Compared with their normal weight counterparts and compared with the standard women, overweight and obese adolescents had increased risks for adverse pregnancy and neonatal outcomes such as preeclampsia, stillbirth, post-term pregnancy, neonates large for gestational age and neonates with low Apgar score. In labor, compared with the normal weight adolescents, the overweight and obese adolescents had a decreased chance for a normal vaginal delivery (VD), increased risk for Cesarean section (CS) and postpartum hemorrhage (PPH). However, compared with the standard women, the overweight adolescents had increased chance for a normal VD, and decreased risk for instrumental VD, CS, obstetric anal sphincter injury (OASI) and PPH in VD. The obese adolescents had an increased risk for CS but a

decreased risk for instrumental VD and OASI and they had the same chance for a normal VD and no increased risk for PPH in VD.

The mean cumulative oxytocin dose increased in the BMI groups (normal weight 2278 [2748] mU, overweight 3108 [3839] mU and obese 4082 [4895] mU ($p<0.0001$)) and the mean maximum oxytocin infusion rate during the first stage of labor was higher in the obese group compared with the overweight group of women (15.5 [9.5] mU/min vs. 13.6 [9.1] mU/min ($p<0.05$)). When adjusting for birth weight, epidural analgesia, and cervical dilation at the start of oxytocin infusion, the statistically significant differences were no longer seen. The obese women had increased median levels of oxytocin in plasma at an oxytocin infusion rate of 3.3 mU/min compared with the non-obese women (19.55 ng/mL [IQR 10.61; 29.06 ng/mL] vs. 6.97 ng/mL [IQR 5.55; 13.70 ng/mL], $p=0.016$).

Conclusions

There are several adverse obstetric and neonatal outcomes associated with overweight and obesity in adolescents. It is important for clinicians to be aware of these outcomes in maternal health care. Nevertheless, overweight adolescents seemed to have better labor outcomes compared with low-risk adults, which is useful knowledge when risk-assessments are made in the labor ward.

In spontaneous onset of labor, the cumulative oxytocin dose and maximum oxytocin infusion rate were higher in women with obesity compared with lower BMI groups. One explanatory factor seems to be that women with obesity received the oxytocin infusion at an earlier cervical dilatation stage. Furthermore, obese women seemed to have higher levels of oxytocin in plasma at the beginning of the oxytocin infusion. The oxytocin-oxytocin receptor complex must be further investigated to gain more knowledge on how to optimize the treatment of obese women with oxytocin infusion during labor.

LIST OF SCIENTIFIC PAPERS

- I Obstetric outcomes in adolescents related to body mass index and compared with low risk adult women**
Anna Ramö Isgren, Preben Kjølhede, Marie Blomberg
J Womens Health (Larchmt). 2017;16(5):426-436
- II Adverse neonatal outcomes in overweight and obese adolescents compared with normal weight adolescents and low risk adults**
Anna Ramö Isgren, Preben Kjølhede, Marie Blomberg
J Pediatr Adolesc Gynecol. 2019;32(2):139-145
- III Maternal body mass index and oxytocin in augmentation of labour in nulliparous women: a prospective observational study**
Anna Ramö Isgren, Preben Kjølhede, Sara Carlhäll, Marie Blomberg
Submitted
- IV Serial oxytocin levels in labor, analyzed by mass spectrometry, in non-obese and obese women**
Anna Ramö Isgren, Mark Dennis Retrato*, Sara Carlhäll*, Chamali Kodikara, Kumari Ubhayasekera, Preben Kjølhede, Jonas Bergquist, Marie Blomberg
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In manuscript

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ABBREVIATIONS

ADH	Antidiuretic hormone
BIA	Bioelectrical impedance analysis
BMI	Body mass index
Ca	Calcium
CI	Confidence interval
CNS	Central nervous system
CS	Cesarean section
CSF	Cerebrospinal fluid
CV	Coefficient of variation
DM	Diabetes mellitus
EDA	Epidural analgesia
GA	Gestational age
HSD	Honest significant difference test
ICD	International Classification of Diseases and Related Health Problems
IOTF	International Obesity Task Force
IQR	Interquartile range
LGA	Large for gestational age
MS	Mass spectrometry
OASI	Obstetric anal sphincter injury
OLIV	<u>O</u> xytocin in <u>L</u> abor <u>I</u> n <u>V</u> ivo
OR	Odds ratio
PE	Preeclampsia
PPH	Postpartum hemorrhage
SD	Standard deviation
SGA	Small for gestational age
SMBR	Swedish medical birth register
UPLC	Ultra performance liquid chromatography
VD	Vaginal delivery
WHO	World Health Organization

BACKGROUND

OVERWEIGHT AND OBESITY IN WOMEN

Worldwide, overweight and obesity are of major concern due to the increased risks for adverse health outcomes in all age groups.¹ Women with overweight and obesity have increased risks for diabetes mellitus (DM), cardiovascular diseases and several forms of cancer.²⁻⁴ Young women with overweight and obesity have been shown to have increased risk for psychosocial problems, menstrual cycle irregularity and infertility.⁵⁻⁷ Furthermore, increased maternal body mass index (BMI) has been linked to several adverse outcomes in pregnancy and labor.^{8,9}

Definition and measurement by BMI

Overweight and obesity are, according to the World Health Organization (WHO), defined as “abnormal or excessive fat accumulation that may impair health”.¹ BMI has been shown to be correlated with adiposity and is the most common measurement to define overweight and obesity. It is calculated by dividing the weight in kilograms by the height in square meters (kg/m^2). According to the WHO the definition of pre-obesity is BMI 25.0-29.9 and obesity BMI ≥ 30.0 . The obesity group can be further subdivided into three obesity classes, class I (BMI 30.0-34.9), class II (BMI 35.0-39.9) and class III (BMI ≥ 40).¹⁰ The pre-obese group defined by WHO is known as the overweight group in this thesis, in accordance with the Public Health Agency of Sweden.¹¹ An overview of the BMI groups and obesity classes is shown in Table 1. The term ‘morbidly obese’ is commonly used in the literature to indicate either BMI ≥ 35 or ≥ 40 . The cut-off used in this thesis is set at BMI ≥ 35 .

In pregnancy

There are today no standard pregnancy-specific definitions for overweight and obesity. Most studies in the pregnant population use BMI according to the definitions by WHO. The weight used for calculation is either the woman’s weight measured before pregnancy, at the first antenatal visit or on admission to the labor ward. The latter is often referred to as admission BMI.

Table 1. WHO classification of body mass index (BMI) groups and obesity sub-classes

BMI (kg/m²)	BMI group	BMI (kg/m²)	Obesity class
< 18.5	Underweight	30.0-34.9	Class I
18.5-24.9	Normal weight	35.0-39.9	Class II
25.0-29.9	Overweight	≥ 30	Class III
≥ 30	Obese		

Adipose tissue

The white adipose tissue constitutes the major type of adipose tissue in mammals and is commonly called “fat”. It is composed of adipocytes, macrophages, fibroblasts, immune cells and other cell types.^{12, 13} The adipose tissue is an energy reservoir and, in addition, it acts as an organ with endocrine, metabolic, and inflammatory functions. Adipokines, such as leptin and apelin, are cytokines secreted by adipocytes with pro-or anti-inflammatory and weight/energy regulating properties. Adipose tissue also contains components that influence the coagulation and the fibrinolytic processes and it acts as a site for the metabolism of sex steroids and glucocorticoids.¹² Excessive adiposity can increase the inflammatory mediators (e.g. cytokines, macrophages and leukocytes), which may lead to local inflammation and can result in metabolic and vascular complications.¹⁴

In pregnancy

Maternal obesity has been associated with an inflammatory upregulation with higher levels of C-reactive protein and pro-inflammatory cytokines such as interleukin-6, leptin and monocyte chemotactic protein 1 in plasma.¹⁵⁻¹⁷ Obesity in pregnancy has also been associated with increased inflammation in the placenta, which has been suggested to lead to long-term negative effects such as obesity and insulin resistance in the fetus.¹⁷ Furthermore, obese pregnant women have a higher risk for hyperinsulinemia, dyslipidemia and endothelial dysfunction.¹⁶ Higher serum concentrations of apelin and leptin have been shown in obese individuals. Both apelin and leptin have an inhibitory effect on myometrial contractility in vitro, which has been suggested to play a part in dysfunctional labor in obese women.¹⁸⁻²⁰

Prevalence

Overweight and obesity increases in both children and adults. Globally, in the year 2016, 25% of adult women were overweight and 15% were obese (Figure 1). In adolescents 15-19 years old, 18% were either overweight or obese.¹

Figure 1. Mean BMI in adult females worldwide in 2016

Figure reproduced with permission from WHO. World: Mean body mass index (BMI) ages 18+, age standardized Female 2016 Copyright (2020). Accessed October 2020

http://gamapserver.who.int/mapLibrary/Files/Maps/Global_BMI_2016_Female.png

In pregnancy

The proportion of women with overweight and obesity in early pregnancy seems to be steadily increasing. Among women giving birth in the USA in 2015, 26% were overweight and another 26% were obese.²¹ The corresponding figures in Sweden in 2018, were 27% and 15%, respectively (Figure 2).²²

Figure 2. Proportion of women with overweight and obesity at the first visit to prenatal care in Sweden 1992-2018

Source: The Swedish Medical Birth Register, National Board of Health and Welfare

ADOLESCENT PREGNANCY

Prevalence

In 15-19-years-old adolescents, the estimated birth rate worldwide in 2018 was 4.4%. However, the incidence differed greatly around the world from approximately 20% in eastern Asia and western Africa to lower than 0.3% in Switzerland, South- and North Korea.^{23, 24} In 2018, around 1% of all women giving birth in Sweden were aged under 20. In absolute figures this equals a little over 1000 individuals. However, when looking at nulliparous women only, the rate of adolescents giving birth was 2%, i.e. approximately the same proportion as nulliparous women aged 40 or older (Figure 3).²²

Figure 3. Proportion of women giving birth to their first child in Sweden in 2018 according to age

Source: The Swedish Medical Birth Register, National Board of Health and Welfare

Pregnancy, obstetric and neonatal outcomes

Globally, maternal complications are reported as the most common cause of mortality in adolescents. Adolescents have shown higher risks for preterm delivery, eclampsia, endometritis, systemic infections and neonates with low Apgar score and low birth weight.²⁵⁻²⁷

In high-income countries, adolescents seem to be at higher risk for anemia and premature delivery compared with adults.²⁸⁻³⁰ However, they have also been shown to be more likely to have spontaneous onset of labor, and to have a lower risk for Cesarean section (CS), instrumental vaginal delivery (VD), major perineal lacerations and postpartum hemorrhage (PPH).^{28, 29} Neonates born to adolescent mothers seem to have a lower risk of being admitted to the intensive care unit, of showing fetal distress, and of suffering from meconium aspiration.^{26, 28, 29, 31, 32} Furthermore, it seems that there is no increased risk for a neonate that is small for gestational age (SGA).³¹ The risk for preeclampsia (PE) is ambiguous; studies have shown both increased and reduced risk compared with adults.^{26, 29}

The reasons for the adverse obstetric outcomes in adolescents have not been fully clarified. Biological factors related to age or factors such as smoking or insufficient maternal care during pregnancy have been suggested.^{29, 32} The favorable labor outcomes seen in the adolescents have been suggested to be due to better function in the myometrium and greater elasticity in the connective tissue.³³

OBSTETRIC AND NEONATAL OUTCOMES IN RELATION TO MATERNAL BMI

In adults

There are several well-known pregnancy and obstetric complications related to increasing maternal BMI. For many outcomes a linearly increased risk is seen. Women with overweight and obesity are more likely than normal weight women to be diagnosed with gestational DM and hypertension.³⁴ Furthermore, the risk for PE is nearly twofold in overweight women, around threefold in obese women and as high as five- to sixfold in obesity class III.^{9, 35-37} Due to the related maternal complications, overweight and obese women have an increased risk for induced preterm delivery.³⁸⁻⁴⁰ The risk for spontaneous preterm delivery seems to be related to obesity in the extremely preterm gestational weeks.^{38, 41}

Still birth is a rare but severe complication during pregnancy and the risk increases with rising BMI. Women with obesity class III have approximately a two- to threefold higher risk of being affected.^{37, 42} Shoulder dystocia is another rare but serious adverse outcome in obese women. The risk increases successively with rising obesity class and a three- to fivefold increased risk has been shown in women with obesity class III.^{37, 43, 44}

The rate of both elective and emergency CS gradually increases with maternal BMI.^{45, 46} For nulliparas, the risk for emergency CS is increased by 50% in overweight women, doubled in women with obesity and three- to fourfold in women with obesity class II.^{45, 47, 48} Additionally, perioperative complications, such as anesthesiology complications, prolonged time interval from skin incision to delivery, increased operative time and further increased risk for major bleeding, wound infections and thromboembolism have been shown to be more common in the obese women.⁴⁹⁻⁵⁴

PPH due to uterine atony has been shown to give a 10% increased risk in overweight women and more than twice the risk in women with obesity class III.^{49, 50} By contrast, the risk for obstetric anal sphincter injury (OASI) seems to be decreased in overweight and obese women.⁵⁵⁻⁵⁷ The reasons for this are speculative, but increased perineal thickness, more stretchable tissue due to adiposity or sub diagnostics caused by more difficult examination of the obese women have been suggested.⁵⁵⁻⁵⁸

Regarding neonatal outcomes, overweight and obesity have been associated with increased risks for large for gestational age (LGA) and macrosomia. On the other hand, neonates born to obese mothers have shown lower risk of being born SGA. Furthermore, maternal overweight and obesity have shown increased adverse outcomes in neonates with risk for fetal distress, low Apgar score and meconium aspiration.^{34, 37, 59}

In adolescents

In adolescents, the relationship between BMI and obstetric and neonatal outcomes has not been as well studied as in adults, and especially not in the higher classes of obesity. Overweight and obese adolescents seem to have a higher risk for gestational DM, hypertension, PE, induction of labor, CS and PPH.⁶⁰⁻⁶⁴ Interestingly, some studies have indicated a lower risk for spontaneous preterm birth in overweight and obese adolescents.^{60, 65, 66} The results of rare outcomes, such as stillbirth and shoulder dystocia, in relation to BMI in adolescents have not been studied before. Newborns of adolescents with overweight and obesity have shown increased risks for macrosomia and decreased risk for low birth weight and SGA.^{60-62, 64}

ONSET AND PROGRESS OF LABOR

The process of labor can be subdivided into three stages, the first stage (latent phase and active phase), the second stage (from fully dilated cervix until birth of the neonate) and the third stage (delivery of the placenta).

Onset of labor

The definition for the onset of the active phase of labor differs worldwide and has also changed over time. In Sweden, the current definition was set in 2015 by the Swedish Associations of Midwives and the Swedish Society of Obstetrics and Gynecology (Table 2).⁶⁷ This recommendation was a revision of the original guidelines from the National Board of Health and Welfare in Sweden published in 2001.⁶⁸ In line with the Swedish criteria, the National Institute for Health and Care Excellence (NICE) guidelines, from the United Kingdom, use a cervical dilatation of 4 cm as the threshold for established active labor. However, the American College of Obstetricians and Gynecologists changed their guidelines in 2014 to define the active start of labor at 6 cm cervical dilatation and since 2018 the WHO has recommended that the active phase starts for most women at cervix dilation of 5 cm.^{69, 70}

Table 2. The Swedish definition of spontaneous start of active labor⁶⁷

At least two out of following three criteria should be fulfilled:
<ul style="list-style-type: none">• Cervix dilated 4 cm or effaced and dilated more than 1 cm• Regular painful contractions (2-3/10 minutes)• Spontaneous rupture of the amniotic membranes
<i>In addition to the above, the labor should progress within the following two hours.</i>

Compared with normal weight women, women with obesity have a lower chance for spontaneous start of labor and have an increased risk for post-term pregnancy (>41 or ≥42 gestational weeks).^{7, 37, 71} The reason for this is unclear. One theory has proposed that obese women, when calculating from the last menstrual period, get a miscalculated date for delivery due to the increased frequency of irregular menstrual cycles.⁷² Others have speculated that inflammatory and metabolic changes related to obesity may negatively impact the onset of labor.^{15, 16, 73}

Normal progress of labor

To follow the progress of labor, the use of the partogram is part of the standard care when women give birth in Sweden. It is a graphical record and a tool for visualizing the progress of active labor (Figure 4). The partogram used in Sweden is based on the criteria for normal progress of labor from Friedman’s studies in the 1950s. His work showed a labor curve accelerating from 3-4 cm with an expected progress of labor with 1 cm dilatation of the cervix per hour.^{74, 75} Studies by Zhang (2010) and Oladapo (2018), have shown that labor might last longer and the progress of labor is slower until 5-6 cm and faster thereafter.^{76, 77} A recent labor progress research from Sweden showed, in line with the studies by Zhang and Oladapo, an acceleration of cervical dilatation at 5-6 cm; however, the median time in the first stage of labor was faster.⁷⁸ A large Norwegian study comparing labor outcomes in nulliparous women with spontaneous onset of labor managed according to either the partogram based on Friedman’s data or based on Zhang’s findings did not find any differences in adverse outcomes, including CS rate.⁷⁹

Overweight and obese women seem to have a slower first stage, but not second stage, of labor compared with normal weight women.⁸⁰⁻⁸⁴

Figure 4. The partogram

Labor arrest

As with spontaneous start of labor, there is no consensus globally on the definition of labor arrest. Labor arrest can also be referred to as labor dystocia, prolonged/delayed labor or failure to progress. The criteria determining when oxytocin infusion for stimulation of uterine contractions should be considered have changed over time, both worldwide and in Sweden. The current Swedish guidelines for augmentation with oxytocin are shown in Table 3.⁸⁵ The underlying cause for labor arrest can be related to ineffective uterine contractions, fetal malpresentation (e.g. occiput posterior, asynclitism) or cephalopelvic disproportion.⁸⁶ Labor arrest is related to higher risks for CS, instrumental VD, chorioamnionitis and postpartum bleeding.⁸⁷⁻⁸⁹

In obesity

Obesity is one of several known risk factors for labor arrest.⁹⁰ The risk of CS due to labor arrest after spontaneous onset of labor seems to increase with rising BMI.^{47, 91, 92} One theory addressing the increased risk for dysfunctional labor in obese women is an underlying pathobiology related to obesity leading to impaired myometrial contractility.^{47, 73, 91, 93} This is supported by the findings from a study analyzing myometrial strips from normal weight and obese women undergoing elective CS. The study showed that the strips from the obese women contracted with less frequency and with less force compared with the strips from normal weight women.⁹¹ Furthermore, the myometrium in obese pregnant women has shown an increased content of triglycerides and reduced myocyte content, which could impair uterine contractility. This has also been suggested to be a mechanism behind labor arrest in obese women.⁹⁴

OXYTOCIN

Function and treatment

Oxytocin is a hormone mostly known for its peripheral effects in parturition and lactation (Figure 5).⁹⁵ It was discovered by Henry Dale in 1906 when he found that it stimulated uterine contractions in cats.⁹⁶ The name derives from the Greek words meaning “quick birth”.⁹⁵ At the beginning of the 1950s the sequence of amino acids in oxytocin was discovered and in 1953 Vincent du Vigneaud succeeded in synthesizing oxytocin.⁹⁷ For his scientific achievements on the two pituitary hormones oxytocin and vasopressin and for his synthesis of these two hormones, du Vigneaud was awarded the Nobel Prize in chemistry in 1955.

Today, oxytocin is probably the most commonly used drug in the labor ward due to its effect on uterine contractility. There is still insufficient evidence for using oxytocin as a treatment to stimulate lactation.^{98, 99}

Recent research has revealed that oxytocin also has potential effects as a neuromodulator in the central nervous system (CNS), including an influence on social behavior, trust, bonding, pain perception and energy metabolism.¹⁰⁰⁻

¹⁰⁵ Oxytocin and its potential role in neuropsychiatric disorders (schizophrenia, autism, mood and anxiety disorders) has been studied frequently in recent years, as has its possibilities for use as a therapeutic drug in the psychiatric field.^{95, 106}

Figure 5. The oxytocin molecule

Source: PubChem Identifier: CID 439302 Accessed October 2020

<https://pubchem.ncbi.nlm.nih.gov/compound/439302#section=2D-Structure>

Structure, synthesis and secretion

Oxytocin is a nine-amino acid peptide hormone produced in the magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus. From the hypothalamus, oxytocin is transported by axons as a precursor protein and modified on its way to the posterior lobe of the pituitary gland. In the pituitary gland it is stored together with its carrier protein neurophysin. Oxytocin is then released into the peripheral circulation by exocytosis. Oxytocin-containing neurons in the hypothalamus also project to other areas of the brain, reaching different regions in the CNS.¹⁰⁷⁻¹¹²

The synthetic oxytocin has exactly the same structure as the endogenous oxytocin and it is therefore not possible to separate them in chemical analysis, if the exogenous oxytocin is not labeled.

It is unclear if a correlation exists between the oxytocin levels in plasma and in the cerebrospinal fluid (CSF) during intravenous oxytocin infusion. In animals, around 0.001-0.002% of the systemically administered oxytocin has been shown to pass the blood-brain barrier and reach the CSF.¹¹³⁻¹¹⁵

In pregnancy

During the time of parturition, oxytocin has been shown to be synthesized peripherally in the corpus luteum, decidua, amnion, chorion and the placenta.^{111, 116} In addition, the fetal pituitary glands secrete oxytocin during labor which may gain access to the decidua through the placenta or the amniotic fluid.¹¹⁷

Metabolism

Oxytocin circulates in the blood mostly as a free peptide. The half-life is short and ranges from 3-20 minutes.¹¹⁸ It appears to be inactivated and eliminated especially through the kidneys and to a lesser extent from the liver.¹¹⁹⁻¹²¹

In pregnancy

The enzyme placental leucine aminopeptidase (P-LAP), also called oxytocinase, is synthesized and expressed by the syncytiotrophoblasts in the placenta.¹²² Oxytocinase degrades several peptides including oxytocin and vasopressin.^{123, 124} The concentration of oxytocinase increases to a great extent in the maternal serum with advanced gestational age.¹²³ It has been suggested that oxytocinase maintains the homeostasis of pregnancy by regulating uterine contractions and vasoconstriction by degrading oxytocin and vasopressin on both the fetal and maternal sides.^{123, 124} The oxytocinase in humans seems to be distributed in other tissues than the placenta, but the physiological function is not well understood.¹²³ Whether the metabolic clearance during oxytocin infusion in pregnancy is affected seems unclear.^{119, 125}

Levels of oxytocin in plasma in pregnancy and labor

The oxytocin concentrations in plasma during pregnancy and labor have shown a wide numerical variability. The reason for the discrepancies could be individual differences but technical difficulties during extraction or problems related to the method of analysis must be taken into consideration.¹²⁶⁻¹²⁸ Oxytocin has been described as biologically complex and a challenge to measure. It has a short half-life and the oxytocin molecule can bind to other molecules in a matrix and also itself.¹²⁹

The plasma concentration of oxytocin seems to increase in some stages during pregnancy in most women, but the literature is not entirely consistent.^{127, 130-138} The majority of data does not support an increase in oxytocin in plasma as an initiator of labor.^{130, 131, 136, 139} In animal studies, a pulsatile release of oxytocin in plasma during labor with maximum peaks at the moment of birth has been shown.^{126, 140, 141} In humans, some studies have indicated secretion of oxytocin in plasma with discrete pulses (peaks) or fluctuation in plasma while others have not.^{130, 135, 136, 142, 143} Furthermore, no association has been found between the pulses of oxytocin and uterine contractions, and whether there are physiological functions of these pulses is still unknown.^{135, 136, 142} In humans, the oxytocin levels in plasma seem to increase in some parts of the second stage of labor.^{130-132, 135, 139, 144}

During oxytocin infusion, one study showed that the plasma levels of oxytocin increased at an infusion rate of 4-6 mU/min and the plasma levels were approximately twice as high at rates of 10-16 mU/min, compared with oxytocin concentrations before the infusion was started.¹³²

In overweight and obesity

There is one earlier study investigating the levels of oxytocin in plasma in obese and normal weight women in labor. The women were treated with oxytocin infusion due to induction of labor, and oxytocin in plasma was measured prior to start of the oxytocin infusion and at the supposed maximum infusion rate. No differences in plasma levels between the obese group and the normal weight group of women were seen.¹⁴⁵

The oxytocin receptor

Oxytocin initiates uterine contractions through activation of the oxytocin receptor, a G-protein-coupled receptor, in the myometrium. The activation stimulates and regulates different pathways and cellular processes leading to mobilization of intracellular calcium (Ca) from the sarcoplasmic reticulum and Ca-channels. When intracellular Ca increases, contractions in the smooth muscles occur through stimulation of the Ca-dependent calmodulin and activation of the myosin (Figure 6).^{111, 146} There are still knowledge gaps concerning the mechanisms of the oxytocin receptor.¹⁴⁶ The oxytocin receptor has, except from in the myometrium and the breast-tissue, been found in the chorion, the decidua and in endothelial cells in humans.^{112, 116, 147} In animals, the oxytocin receptor has been located in all four chambers of the heart.¹⁴⁸ The receptors increase considerably in number in the myometrium at term pregnancy and they seem to be located with higher concentrations in the corpus and the fundus compared with the lower segments of the uterus.^{126, 149}

Figure 6. Oxytocin and oxytocin receptor signaling in the myometrium leading to contraction

Ca: Calcium, *OTR*: Oxytocin receptor, *OT*: oxytocin, *SR*: Sarcoplasmic reticulum, *Ca-CaM*: Ca-calmodulin complex, *MLCK*: Myosin light chain kinase, *MLCP*: Myosin light chain phosphatase, *VOCC*: Voltage operated Ca-channels, *SOCE*: Store operated Ca entry. Red lines: Direct influence from Ca. Purple lines: Ca-independent pathways.

Dotted lines: Mechanisms not clarified

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Regulation

The uterotonic effect of oxytocin can be regulated by changes in expression or sensitivity in the oxytocin receptor. It seems that estrogen increases the amount of the receptor binding sites in the myometrium and progesterone inhibits the expression.¹¹¹ Cholesterol has been shown to stabilize the receptor against degradation or inactivation.¹⁵⁰ Stimulation of the oxytocin receptor can lead to desensitization and internalization of the receptor and full responsiveness has been shown to occur within four hours.¹⁵¹ Myometrial tissue from women undergoing emergency CS has shown a reduction of oxytocin receptor mRNA if the labor had progressed for more than 12 hours. The cause is unknown but a desensitization of the receptor after prolonged labor has been suggested.¹⁵²

In overweight and obesity

The oxytocin receptor expression has shown a positive correlation to maternal BMI in women undergoing primary elective CS. It was suggested to be caused by a compensative myometrial answer to impaired second messenger systems or to a lower concentration of oxytocin in obese women due to an increased volume of distribution.¹⁵³ Another similar study could not confirm the result.¹⁵⁴

As previously mentioned, the two adipokines, apelin and leptin, which are increased in obesity, seem to have inhibitory effects on myometrium contractility.¹⁸⁻²⁰ Leptin has been suggested to have an inhibitory effect on the myometrium through inhibition of the Ca channels in the receptor, reducing the Ca influx.¹⁵⁵ Furthermore, the intracellular calcium flux has shown to be lower in myometrial strips taken at CS from obese women compared with myometrial strips from normal weight women.⁹¹

OXYTOCIN INFUSION IN LABOR

Oxytocin infusion is administered to stimulate the uterine contractions in labor arrest and in induction of labor. The national Swedish clinical guidelines for oxytocin use are shown in Table 3. If the fetal membranes are still intact, amniotomy should be performed first and oxytocin infusion should be started after one additional hour if still required.⁸⁵

To lower CS rate and reduce the total cumulative dose of oxytocin, different regimes of administrating oxytocin have been studied (high or low dose, early or late onset, pulsatile vs. continuous administration).¹⁵⁶⁻¹⁵⁸ The regime in Sweden is considered a low-dose regime.

In overweight and obesity

Guidelines for oxytocin infusion in labor do not take BMI or weight into account, either in Sweden or worldwide. Studies conducted in the US have shown that women with increasing BMI seem to receive both higher cumulative oxytocin doses and higher oxytocin infusion rates in augmentation and induction of labor.¹⁵⁹⁻¹⁶⁴ Deliveries among women with class III obesity with induced and spontaneous labors have shown a higher maximum rate of oxytocin compared with normal weight women.¹⁶³ Furthermore, women with obesity class II, with spontaneous start of labor, required higher amounts of oxytocin during the first three hours after labor arrest had been diagnosed compared with lower BMI groups.¹⁵⁹

Table 3. Indication, regime and prerequisites for augmentation with oxytocin infusion according to the Swedish national guidelines

Indication for augmentation with oxytocin in active labor	<i>In first stage:</i> Labor prolonged for three hours from what is expected (expected 1 cm/hour)
	<i>In second stage:</i> No descent for one hour or active pushing for more than 30 minutes
Standard oxytocin solution	1 mL (8.3ug/mL=5 IU/mL) of oxytocin in 500 ml Sodium chloride (9 mg/mL) reaching a concentration of: $10 \text{ mU/mL} = 0.01667 \text{ ug/mL} = 16.67 \text{ ng/mL}$
Conversion of oxytocin rates and units	1 mU/min=1.67ng/min=60mU/h=6 ml/h 1 mU=1.67 ng, 1 ng=0.60 mU
Regime for oxytocin infusion	<ul style="list-style-type: none"> ○ Administered as an intravenous infusion through a peripheral venous catheter by an electronic infusion pump ○ Starts at an infusion rate of 3.3 mU/min ○ Increases with intervals of 20 minutes by 3.3 mU/min at a time until 4-5 contractions/ 10 min are achieved and/or normal progress of labor occurs according to the partogram
Prerequisites	<ul style="list-style-type: none"> ○ If intact fetal membranes: Amniotomy should be performed and oxytocin infusion should be started after one additional hour if still required ○ Continuous cardiotocography for registration of the fetal heart rate and monitoring the uterine contractions ○ Hyperstimulation defined as > 5 contractions /10 min

Potential risks of oxytocin

There are risks associated with the use of oxytocin infusion in labor and it should be used with great caution and systemic surveillance. Oxytocin given as intravenous injections during elective CS has been shown to decrease maternal vascular resistance and to cause hypotension followed by increased heart rate and cardiac output.^{165, 166} Oxytocin receptors have been found in the endothelial cells in humans and it is suggested that oxytocin may cause vasodilatation by activating the nitric oxide pathways in the receptor.¹⁴⁷ According to the Pharmaceutical Specialities in Sweden (FASS), commonly

reported side effects of oxytocin are headache, tachycardia, bradycardia, nausea and vomiting.¹¹⁸ The oxytocin molecule can also cause water retention due to activation of the antidiuretic hormone (ADH) receptor because of the similarity between oxytocin and ADH (vasopressin).¹⁶⁷ Furthermore, oxytocin infusion during labor entails a risk for uterine hyperstimulation and a risk for a negative impact on fetal heart rate. It is also associated with neonatal acidemia at birth and increased risk for postpartum bleeding.¹⁶⁸⁻¹⁷²

HYPOTHESES

BACKGROUND

The increased risk for adverse obstetric and neonatal outcomes among overweight and obese adults is recognized. However, the impact of BMI on obstetric and neonatal outcomes in teenagers has been far less investigated. In high-income countries, obstetric and neonatal outcomes in adolescents, compared with adults, have shown several favorable outcomes.^{28, 29} Based on this we wanted to evaluate the impact of BMI on obstetric and neonatal outcomes in adolescents. In addition, we wanted to compare the BMI groups of the adolescents with a low-risk group of normal weight, adult women, called “the standard women”. By using the group of standard women for comparison, we hoped to achieve wider knowledge to help when making risk assessments of overweight and obese adolescents in obstetric care. (Studies I and II)

Obese women seem to require a higher total amount of oxytocin during induction and augmentation of labor compared with normal weight women.^{159, 162, 163} Obese women also have an increased risk for CS due to labor arrest.^{47, 91, 92} With the theory that BMI has an impact on myometrial contractility in labor, we wanted to investigate the oxytocin levels in the first stage of labor in relation to obese and non-obese women during oxytocin infusion. We hypothesized that the obese women would have lower plasma oxytocin levels compared with non-obese women during oxytocin infusion. (Studies III and IV)

These considerations lead to a series of research questions that should test specific hypotheses.

SPECIFIC HYPOTHESES

- With rising BMI, adolescents have increased risks for adverse obstetric and neonatal outcomes compared with normal weight counterparts. (Studies I and II)
- Overweight and obese adolescents have better obstetric and neonatal outcomes compared with a low-risk group of adult women. (Studies I and II)
- In augmentation of labor, obese nulliparous women have an increased cumulative oxytocin dose in labor and experience a higher maximum oxytocin infusion rate in the first stage of labor than normal weight women do. (Study III)
- Obese women have lower plasma oxytocin levels, compared with non-obese women, during similar treatment with oxytocin infusion in the first stage of labor. (Study IV)

AIM

OVERALL AIM

The overall aim of this thesis was to evaluate the impact of maternal BMI on obstetric and neonatal outcomes in adolescents as well as on treatment with oxytocin infusion during labor regarding cumulative dose and plasma levels of oxytocin.

SPECIFIC AIMS

- To evaluate the association in adolescents between early pregnancy BMI and obstetric outcomes and to determine whether the outcomes in the BMI groups of adolescents differed from those of a low-risk population of adult women defined as “the standard women”. (Study I)
- To investigate if early pregnancy BMI among adolescents was associated with adverse neonatal outcomes compared with their normal weight counterparts and, in addition, to compare the neonatal outcomes in the different BMI groups among adolescents with a low-risk group of adult women. (Study II)
- The primary aim was to determine the cumulative oxytocin dose in relation to admission BMI in nulliparous women at term with spontaneous onset and augmentation of labor. The secondary aim was to analyze the association between maternal admission BMI and the maximum oxytocin infusion rate during the first stage of labor. (Study III)
- To examine the association between maternal admission BMI and levels of oxytocin in maternal plasma at different infusion rates of oxytocin in the first stage of labor and to validate tandem mass spectrometry as a reliable methodology to measure plasma oxytocin. (Study IV)

MATERIAL AND METHODS

An overview of the four studies included in the thesis is presented in Table 4.

Table 4. Overview of the four studies included in the thesis

Study	I	II	III	IV
Design	Retrospective cohort study	Retrospective cohort study	Prospective observational study	Prospective observational study
Time period for data collection	1992-2013	1992-2013	2017-2019	2019-2020
Data sources	The Swedish Medical Birth Register	The Swedish Medical Birth Register	Medical record: Obstetrix*	Medical record: Obstetrix*
Laboratory method				Mass Spectrometry
Setting	National, Sweden	National, Sweden	Seven hospitals in the Southeast health region of Sweden	The university hospital in Linköping, Sweden
Participants	31,386 singleton primiparous women < 20 years old; 178,844 standard women*	31,386 singleton primiparous women < 20 years old; 178,844 standard women*	1,097 nulliparous women with spontaneous onset of labor and oxytocin infusion in labor	40 women receiving oxytocin infusion in first stage of term labor
Exposures	Early pregnancy BMI	Early pregnancy BMI	BMI on admission to the labor ward	BMI on admission to the labor ward
Primary outcome measures	Obstetric (pregnancy and labor) outcomes	Neonatal outcomes	Cumulative oxytocin dose during labor	Levels of oxytocin in plasma during oxytocin infusion in first stage of labor
Statistics	Descriptive statistics, ANOVA, logistic regression analysis	Descriptive statistics, ANCOVA, Pearson's Chi-squared test, logistic regression analysis	Descriptive statistics, Pearson's Chi-squared test, ANOVA, Mann-Whitney U-test, Kruskal-Wallis ANOVA, ANCOVA	Descriptive statistics, t-test, Mann-Whitney U-test, Pearson's Chi-squared test. Fisher's exact test, Pearson's correlation coefficient

* Normal weight, non-smoking, primiparous women, 25-29 years old with singleton pregnancy and no known comorbidity.

BMI, body mass index; ANOVA, analysis of variance; ANCOVA, analysis of covariance

DATA SOURCES

The Swedish Medical Birth Register

Data in studies I and II were retrieved from the Swedish Medical Birth Register (SMBR). The SMBR started in 1973 and it is held by the National Board of Health and Welfare. The register is compulsory for all health care providers to report to and covers 97-99% of all births in Sweden. The information is reported by the health care providers in standardized medical records from prenatal, delivery and neonatal care. The information includes diagnoses classified according to the Swedish version of the International Classification of Diseases and Related Health Problems (ICD). The SMBR has been validated, modified and extended over time and since 1992 the register has continuously included information about maternal height and weight in early pregnancy.^{173, 174} PPH and meconium aspiration have been registered in the SMBR since 1997. CS was subdivided in elective and emergency CS from 1999. Until June 2008, stillbirth was included after 28 weeks of gestation and from July 2008 it was included after 22 weeks of gestation.

ICD

Since 1948, the WHO has been responsible for the ICD. The National Board of Health and Welfare in Sweden is responsible for the Swedish versions of ICD. The classification system has been revised approximately every tenth year and the ICD version 9 (Swedish version KS87) was used between 1987 and 1996 and ICD version 10 (Swedish version ICD-10-SE) has been used since 1997. Some of the diagnoses used in studies I and II were either registered in the SMBR according to the ICD-9 and/or ICD-10 and/or as diagnoses marked in prewritten boxes in the standardized medical records.

Medical records

In studies III and IV, the Obstetrics® Cerner was used for collecting data. Obstetrics® Cerner is an electronic medical record system used by midwives, obstetricians and pediatricians working in the prenatal, delivery and perinatal care. The records include prospectively registered information from early pregnancy until after delivery. The data include both documentation in free text and documentation using standardized prewritten checkboxes to fill in. The checkboxes include e.g. some diagnoses, smoking, start of labor and mode of delivery. Data can also be registered in the partogram (e.g. degree of cervical dilation, oxytocin infusion rate), which is part of the electronic medical record.

STUDY DESIGN, POPULATION AND OUTCOMES

Obstetric and neonatal outcomes in adolescents according to BMI (Studies I and II)

Design and Population

Studies I and II are nationwide population-based retrospective cohort studies using data from the SMBR. Data on all 2,199,139 primiparous women with singleton pregnancy who had given birth between 1992 and 2013 were retrieved from the register. Out of these, 37,492 were younger than 20 years of age. Furthermore, 31,386 (84%) of the adolescents had registered weight and height in early pregnancy, which enabled the calculation of maternal BMI. This group constituted the study group. The study group was subdivided according to BMI into four BMI groups and three obesity classes according to the WHO classification (Figure 7).

In addition, data on a group of normal weight, non-smoking, primiparous women, aged 25-29 years with singleton pregnancies and no known comorbidity (hypertension, DM, asthma, systemic lupus erythematosus, epilepsy and/or chronic renal disease) who had given birth during the same study period was selected from the SMBR. In all, 178,844 women fulfilled these criteria. This group constituted “the standard women” and was defined as an obstetric low-risk group of adult women (Figure 8).

Figure 7. Study population and standard women in studies I and II

* Normal weight, non-smoking, primiparous women, 25-29 years old with singleton pregnancy and no known comorbidity. SMBR, Swedish Medical Birth Register; BMI, body mass index

Figure 8. The standard woman

Outcomes

Pregnancy (Study I)

The pregnancy outcomes were PE, spontaneous onset of labor, induction of labor, gestational age (GA) at delivery (categorized as <28 , <37 , and ≥ 42 weeks), abruptio placentae, placenta previa, and still birth.

Labor (delivery and postpartum) (Study I)

The delivery outcomes were normal VD (defined as neither instrumental VD nor CS), instrumental VD (including forceps and vacuum extractions), CS (all, and subdivided in elective and emergency), and shoulder dystocia. The postpartum outcomes included OASI and PPH >1000 ml (subdivided into CS and VD).

Neonatal (Study II)

The neonatal outcomes were Apgar score <7 and <4 at 5 minutes, birth weight <2500 g, macrosomia (defined as birth weight either >4000 g or >4500 g), SGA/LGA (defined as birth weight more than 2 standard deviations (SDs) below/above the mean birth weight adjusted for GA, sex, and parity according to a reference curve), fetal distress and meconium aspiration.

Oxytocin infusion in labor and BMI (Studies III and IV)

Cumulative oxytocin dose and maximum oxytocin infusion rate (Study III)

Design and Population

Study III was a prospective multicenter cohort study conducted during 2017-2019. Seven maternity wards in the south-east health region of Sweden participated in the study: Norrköping, Linköping, Jönköping, Värnamo, Eksjö, Västervik and Kalmar. All participating maternity wards were instructed how to handle the infusion pump, and how to read off the cumulative oxytocin dose and register the amount in the medical record (Figure 9).

Figure 9: The cumulative oxytocin dose recorded at the infusion pump

The cumulative oxytocin dose was calculated from the start of the oxytocin infusion until the neonate was born. The specific keywords “Cumulative oxytocin dose” were added in the electronic medical record where the attending midwife registered the cumulative oxytocin dose in mL. The maximum oxytocin infusion rate during the first stage of labor was read off the partogram (Figure 4). Maternal, obstetric and neonatal characteristics were registered in the electronic medical record. All maternity wards applied the criteria obtained from the Swedish National guidelines to start oxytocin for augmentation of labor (Table 3).⁸⁵

A total of 1,097 nulliparous women in term labor with singleton, cephalic presentation pregnancy and spontaneous start of labor with cumulative oxytocin dose registered in the medical record were included in the study. The exposure was admission BMI.

Outcomes

The primary outcome was cumulative oxytocin dose measured from the start of the oxytocin infusion until the neonate was born. The secondary outcome was the maximum rate of oxytocin infusion during the first stage of active labor.

The Oxytocin in Labor In Vivo (OLIV) trial (Study IV)

Design and Population

The OLIV trial was a prospective observational study conducted at the labor ward at the University Hospital in Linköping. The study was performed during the period 2019-2020. The OLIV trial was a pilot project. The recruitment of the patients and the plasma sampling were carried out around the clock by a research team including midwives and obstetricians working at the labor ward. Before the study started, the research team was trained in handling the plasma sampling and a flow chart of the sampling and aliquotation was constructed (Figure 10). The indications for treatment with oxytocin infusion at the labor ward followed the Swedish medical guidelines.⁸⁵

Women eligible for the study were at least 18 years old, had mastered the Swedish language, had a singleton term pregnancy (≥ 37 gestational weeks), cephalic fetal presentation, known BMI on admission to the labor ward and had indications for initiating treatment with oxytocin infusion during the first stage of labor, either for induction or augmentation of labor. Women who fulfilled the criteria at the labor ward were informed about the study, orally and in writing. Before the women were included they signed an informed consent document.

A total of 40 women were included in the study, 28 women were obese (BMI ≥ 30 kg/m²) and 12 women were non-obese (<30 kg/m²). The women had an extra peripheral venous catheter inserted into the contralateral arm to where the oxytocin was planned to be infused. From this peripheral venous catheter, blood samples were taken before the start of the infusion and 20 minutes after each increase of the infusion. If the infusion was stopped, decreased or paused, the serial sampling ended. The exposure was admission BMI.

Outcome

The primary outcome was levels of oxytocin in plasma during oxytocin infusion in first stage of labor.

Figure 10. Flowchart used for sampling and aliquotation in the OLIV trial

Blood sample collection and plasma preparation

The blood sample was collected in an ethylenediaminetetra-acetic acid (EDTA)-treated tube and directly placed in ice cold water. Thereafter, the sample was centrifuged for 10 minutes at 2,000 x g for plasma separation. After centrifugation, the plasma was aliquoted into 0.5 mL plastic tubes (5 tubes) with 0.3 mL plasma in each tube. Lastly 0.5-1.0 mL blood cells were aliquoted to a 2 mL tube (Figure 11). The tubes were placed on an ice pack during the handling of the samples to keep them chilled during the procedure. The samples were directly placed in boxes and stored in a -70 degree Celsius freezer until transportation to the laboratory in Uppsala for analysis.

Figure 11. Plasma sample and labelled tubes in the OLIV trial

Ultra performance liquid chromatography (UPLC)-Orbitrap-tandem mass spectrometry (MS) method

The levels of oxytocin in plasma were analyzed at the Department of Chemistry Biomedical Centre, Uppsala University. The analysis method was based on a combination of high resolution liquid chromatography and high resolution tandem mass spectrometry (UPLC-Orbitrap-tandem MS). Here follows a brief overview of the method.

The plasma sample is first prepared for further analysis, by the addition of a stable isotope labeled internal standard of known absolute quantity and precipitation of proteins by the addition of organic solvent. After centrifugation the supernatant is transferred to a clean vial and evaporated under a nitrogen gas flow. The sample is re-dissolved in running buffer and injected onto the UPLC chromatographic system where peptides are separated

based on their hydrophobicity in a gradient system over a reversed-phase column. The separated molecules are ionized in gas phase by electrospray ionization and transferred into the mass spectrometer for detection. The Orbitrap MS consists of two outer electrodes and one inner central electrode, which allows it to act as both analyzer and detector. By analysis of the oscillation frequencies induced by the ions on the outer electrodes, the mass spectra of the specific ions are acquired as mass/charge signals using image current detection. The trapped ions are detected and converted to a mass spectrum using the Fourier transform of the frequency signal. From the mass spectra we get the exact molecular weight detected with high precision and the quantity of the targeted molecule can be calculated in relation to the internal standard. (Figure 12)

Figure 12. Sample analysis using ultra performance liquid chromatography (UPLC) - Orbitrap tandem mass spectrometry (MS)

Figure presented by kind permission from Jonas Bergquist and Mark Dennis Retrato

STATISTICS

Sample size estimation

For study III, a sample size estimation was performed before the study was started. We assumed that the minimal clinically important difference in cumulative oxytocin dose between the BMI groups was 1200 mU and that the standard deviation of the cumulative oxytocin dose was 3000 mU. To detect a significant difference at a 5% level with 80% power, the sample size was estimated to be approximately 100 women in each BMI group.

In study IV there were two conditions to consider regarding the sample size calculation. First, the sample size had to be restricted due to high laboratory costs for analyzing oxytocin levels, and secondly, there was no available valid data on the primary outcome, circulating oxytocin levels in maternal plasma during oxytocin augmented labor. Therefore, we decided that the use of effect size would be appropriate. Effect size measures the sizes of differences between group means. Cohen's *d* is an appropriate effect size for the comparison between two means. Cohen suggested that $d=0.2$ is considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. If 20 women in each BMI group (lean and obese) were included, the power to detect an effect size of $d=0.8$ (large) was 80% with 0.05 significance, for a given dose of oxytocin.

Descriptive and comparative statistics

Studies I and II

Continuous data were presented as mean and one SD and categorical data were presented as number and percent (%). Statistical associations were tested for some of the descriptive categorical data (smoking, asthma) using a Chi-squared test.

The outcomes were assessed using logistic regression models. Risk estimates were presented as odds ratios (ORs) with 95% confidence intervals (CIs). When comparison was made with the normal weight adolescents as a reference group, both crude ORs and adjusted ORs were presented. All outcomes in studies I and II were adjusted for smoking in early pregnancy, the calendar year of the delivery, maternal age and maternal comorbidity. In study II all outcomes were also adjusted for PE. In addition, in study I, PE and CS were also adjusted for GA, and GA was also adjusted for PE. In study II, the neonatal outcomes fetal distress, meconium aspiration, Apgar score and birth weight were also adjusted for GA.

In the comparison with the standard women, crude ORs were presented. The GA in relation to BMI group among adolescents was also analyzed by means of ANOVA (Study I), and fetal birth weight in relation to BMI among adolescents was analyzed by means of ANCOVA (Study II). Post hoc tests were assessed using the Tukey honest significant difference (HSD) test.

Study III

The mean and SD were presented for continuous variables and number and percent for categorical data. Comparisons of categorical data were done by using Chi-squared tests, and for continuous data using ANOVA for normally distributed data and Mann-Whitney U-tests and Kruskal-Wallis ANOVA for non-normally distributed data.

Multivariate analyses were made with ANOVA or ANCOVA. Adjustments were made for cervical dilation at the start of oxytocin infusion (categorized in <6 cm, 6-10 cm and fully dilated), fetal birth weight (continuous variable) and the use of epidural analgesia (EDA) (bivariate, yes or no). Post hoc tests were performed using Tukey's HSD test.

Study IV

The data were expressed by means and SD, median and interquartile range (IQR) or number and percent. The continuous variables were analyzed with the student's t-test (normally distributed data) or the Mann-Whitney U-test (not normally distributed data). For categorical variables Pearson's chi-squared test or Fisher's exact test was used.

The dependent variable (plasma oxytocin concentration) was not normally distributed and a Mann-Whitney U-test was used for comparison between the non-obese and obese group of women. The Pearson Correlation coefficient was used to evaluate bivariate correlations between maternal BMI and plasma oxytocin. No adjustments were made.

The level of significance was set at $p < 0.05$ for two-tailed tests.

Software used

STATISTICA 64, version 12 (Statsoft, Inc. 2300 East 14th Street, Tulsa 74104, OK, USA), Study I

STATISTICA version 13.2 (Dell Software), Study II

TIBCO Statistica™, version 13.5 (TIBCO Software Inc, Palo Alto, CA, USA), Study III

IBM SPSS version 26 (IBM inc, Armonk, NY, USA), Study IV

ETHICAL APPROVAL AND CONSIDERATIONS

The studies in this thesis were approved by the Regional Ethical Review board in Linköping, Sweden (Studies I and II: Dnr 2014/369-32, Study III: Dnr 2017/277-31) and by the Swedish Ethical Review Authority (Study IV: Dnr 2019-03007).

Study IV was registered in ClinicalTrials.gov ID NCT04093479.

It is important to employ ethical reflection in all research, but especially when humans are involved. The studies in this thesis have different aspects to consider. In all studies the confidentiality of the research subjects must be carefully protected. Furthermore, the impact on the study subject's privacy must be minimized. Study IV required most reflection regarding the impact on the patient's integrity during the collection of data. It was a clinical study with blood samples taken repeatedly during the active phase of labor. In the planning phase of the study we decided to create a special research team, including midwives and obstetricians that routinely worked at the labor ward. In this way we thought we would get the best set-up to standardize the collection of the blood samples with the least impact on the study person's integrity. The women who fulfilled the inclusion criteria were informed about the study and their right to withdraw their consent at any time without any further explanation and with no impact on further treatment or care. Before the women were included they signed an informed consent document. However, it is impossible to rule out the possibility that a patient who agreed to be included in the study felt obligated to the researchers to participate. The blood samples taken were handled at the maternity ward and the plasma samples were immediately coded for anonymity. The samples were handled according to the Swedish Biobanks in Medical Care Act (SFS 2002:297).

Another ethical aspect to consider before starting a study is the usefulness and the value of the studies made. All four studies were thought to bring new useful knowledge with direct clinical implications (Studies I and II) or were considered pieces of a bigger puzzle expected to have clinical implications in the future (Studies III and IV).

RESULTS

OBSTETRIC AND NEONATAL OUTCOMES IN ADOLESCENTS ACCORDING TO BMI (Studies I and II)

A total of 31,386 primiparous adolescents with singleton births were included in studies I and II. The prevalence of overweight adolescents was 19.5% and obese 7.3%. Subdivided into obesity classes, the prevalence was 5.5% in obesity class I, 1.4% in class II and 0.4% in class III. The majority of the adolescents were normal weight and 19 years of age. Smoking in early pregnancy was common in all BMI groups (around 30%) and the frequency increased with rising BMI. In obesity class III the prevalence of smoking was 40%.

The adjusted multivariate logistic regression analysis showed that the risk for PE, still birth and post-term pregnancy increased in both overweight and obese adolescents and the risk increased with rising BMI (Table 5). Compared with normal weight adolescents, adolescents in obesity class III had 3-fold increased risk for induction (7.9% vs. 25.0%) and more than 2-fold increased risk for CS (7.9% vs. 19.2%) (Figure 13, 14). The risk for PPH increased in both VD and CS with increasing BMI, however, in CS the risk only increased for obese, but not for overweight adolescents (Table 6). Compared with the normal weight adolescents, the overweight adolescents had a lower risk for a neonate with SGA (3.9% vs. 3.0%) and adolescents in obesity class II had an almost fourfold increased risk for a neonate with LGA (1.3% vs 4.8%) (Figure 15).

Table 5. Pregnancy outcomes in adolescents with overweight and obesity class I-III

		Preeclampsia		Still birth		≥42 weeks GA	
N		n (%)	aOR ^a (95% CI)	n (%)	aOR ^a (95% CI)	n (%)	aOR ^a (95% CI)
Overweight	6,109	109 (1.8)	1.83 (1.43-2.33)	23 (0.4)	1.86 (1.12-3.10)	493 (8.1)	1.36 (1.22-1.52)
Class I	1,734	30 (1.7)	2.31 (1.53-3.47)	11 (0.6)	2.78 (1.38-5.60)	153 (8.8)	1.55 (1.29-1.85)
Class II	433	8 (1.8)	2.58 (1.16-5.75)	3 (0.7)	3.36 (1.03-10.98)	45 (10.4)	1.88 (1.37-2.58)
Class III	120	2 (1.7)	1.97 (0.43-8.96)	2 (1.7)	8.20 (1.94-34.63)	8 (6.7)	1.18 (0.58-2.44)

Data are presented with adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Reference group: Normal weight adolescents. GA, gestational age

^aAdjusted for smoking in early pregnancy, calendar year of the delivery, maternal age and maternal comorbidity. Preeclampsia (PE) also adjusted for GA. GA also adjusted for PE.

Figure 13. Onset of labor in adolescents according to body mass index (BMI)

Spontaneous onset (n= 27,075), Induction (n=2,812) Dots indicate adjusted odds ratios (aORs) and bars indicate 95% confidence intervals (CIs). Reference group: adolescents with BMI 18.5-24.9. Adjusted for smoking in early pregnancy, calendar year of the delivery, maternal age and maternal comorbidity.

Figure 14. Instrumental vaginal delivery (VD) and Cesarean section (CS) in adolescents according to body mass index (BMI)

Instrumental VD (n=2,320), CS (n=2,764). Dots indicate adjusted odds ratios (aORs) and bars indicate 95% confidence intervals (CIs). Reference group: adolescents with BMI 18.5-24.9. Adjusted for smoking in early pregnancy, calendar year of the delivery, maternal age and maternal comorbidity. CS also adjusted for gestational age.

Table 6. Postpartum hemorrhage (PPH) in adolescents with overweight and obesity class I-III

	PPH >1000 ml, VD		PPH >1000 ml, CS	
	n (%)	aOR ^a (95% CI)	n (%)	aOR ^a (95% CI)
Overweight	185 (4.5)	1.23 (1.04-1.47)	8 (1.7)	1.47 (0.60-3.59)
Class I	55 (4.6)	1.24 (0.93-1.66)	8 (3.8)	3.47 (1.41-8.54)
Class II	20 (6.7)	1.77 (1.10-2.85)	3 (4.1)	4.25 (1.16-15.6)
Class III	7 (8.2)	2.29 (1.05-5.00)	0 (0.0)	N/A

Figures denote adjusted odds ratios (aORs) and 95% confidence intervals (CIs). Reference group: Normal weight adolescents. PPH registered in the SMBR from 1997. ^aAdjusted for smoking in early pregnancy, calendar year of the delivery, maternal age and maternal comorbidity. VD, vaginal delivery; CS, Cesarean section; BMI, body mass index; N/A, non-applicable

Figure 15. Small for gestational age (SGA) and large for gestational age (LGA) in adolescents according to body mass index (BMI)

SGA (n=1,178) LGA (n=550) Reference group: adolescents with BMI 18.5-24.9. Dots indicate adjusted odds ratios (aORs) and bars indicate 95% confidence intervals (CIs). Adjustments were made for smoking in early pregnancy, calendar year of the delivery, maternal age, maternal comorbidity and preeclampsia.

Compared with the standard women

Compared with the standard women, the obese adolescents had threefold increased risk for stillbirth, 0.2% vs. 0.7% (crude OR 3.27 (95% CI 1.98-5.41)) and adolescents with class III obesity had about a 60% lower chance for a spontaneous onset of labor, 85.3% vs. 68.3% (crude OR 0.36 (95% CI 0.24-0.53)). The overweight adolescents showed a 50% increased chance for a normal VD and both overweight and obese adolescents showed around a 40% lower risk for instrumental VD (Table 7, Figure 16). Both overweight and obese adolescents had >60% lower risk for OASI and the overweight adolescents had a lower risk for PPH in VD (Table 7, Figure 16). Both the overweight and obese adolescents had an increased risk for preterm labor, SGA, LGA and low Apgar score compared with the standard women (Table 7,8).

Table 7. Labor and neonatal characteristics in adolescents according to body mass index (BMI) and in standard women^a

		Adolescents, BMI				Standard women ^a
		<18.5 N=2,271	18.5-24.9 N=20,719	25.0-29.9 N=6,109	≥30.0 N=2,287	N=178,844
Normal VD	n	1,966	17,571	5,021	1,744	134,226
	%	86.6	84.8	82.2	76.3	75.1
Instrumental VD	n	161	1,506	466	187	22,666
	%	7.1	7.3	7.6	8.2	12.7
CS, all	n	144	1642	622	356	21,952
	%	6.3	7.9	10.2	15.6	12.3
OASI ^b	n	17	215	62	25	5,217
	%	0.8	1.1	1.1	1.3	3.3
PPH in VD ^c	n	65	482	185	82	7,046
	%	4.2	3.6	4.5	5.2	5.9
GA at delivery < 37 w	n	175	1275	383	150	9421
	%	7.7	6.2	6.3	6.6	5.3
Apgar score at 5 min <7	n	18	234	104	50	2116
	%	0.8	1.1	1.7	2.2	1.2
SGA	n	118	798	185	77	4654
	%	5.2	3.9	3.0	3.4	2.6
LGA	n	15	267	182	86	2455
	%	0.7	1.3	3.0	3.8	1.4

^aStandard women: Normal weight, non-smoking, primiparous, 25-29 years old with singleton pregnancy and no known comorbidity. ^bOASI only in VD, ^cPPH defined as bleeding > 1000 mL, registered in the Swedish Medical Birth Register since 1997. VD, vaginal delivery; CS, Cesarean section; OASI, obstetric anal sphincter injury; PPH, postpartum hemorrhage; GA, gestational age; SGA, small for gestational age; LGA, large for gestational age

Figure 16. Mode of delivery (a) and postpartum outcomes (b) in adolescents according to BMI compared with standard women

Standard women: Normal weight, non-smoking, primiparous, 25-29 years old with singleton pregnancy and no known comorbidity. Dots indicate crude odds ratios (ORs) and bars indicate 95% confidence intervals (CI). BMI, body mass index; VD, vaginal delivery, CS, Cesarean section; OASI, obstetric anal sphincter injury; PPH, postpartum hemorrhage

Table 8. Neonatal outcomes in overweight and obese adolescents compared with standard women^a

	Overweight crude OR (95% CI)	Obese crude OR (95% CI)
GA at delivery < 37 weeks	1.20 (1.08-1.34)	1.26 (1.07-1.49)
Apgar <7 at 5 min	1.45 (1.19-1.77)	1.88 (1.41-2.49)
Small for GA	1.17 (1.01-1.36)	1.30 (1.04-1.64)
Large for GA	2.21 (1.89-2.57)	2.81 (2.26-3.50)

^aStandard women: Normal weight, non-smoking, primiparous, 25-29 years old with singleton pregnancy and no known comorbidity. OR, odds ratio; CI, confidence interval; GA, gestational age

OXYTOCIN INFUSION IN LABOR AND BMI (Studies III and IV)

Cumulative oxytocin dose and maximum oxytocin infusion rate (Study III)

A total of 1,097 nulliparous women with spontaneous start of labor and oxytocin infusion during labor were included in study III. Table 9 shows maternal weight in the first trimester, weight gain and obstetric characteristics in the study group subdivided into BMI groups according to admission BMI. The degree of cervical dilation at the time of start of oxytocin augmentation was significantly associated with BMI (Pearson chi-squared; df=4, p<0.0001). This was mainly attributed to a higher proportion of women with obesity (28.3%) that started oxytocin augmentation at a cervical dilation less than six cm compared with women with normal BMI (12.1%), and a lower proportion in the obesity group (31.0%) that started oxytocin augmentation when cervix was fully dilated compared with women with normal BMI (62.1%).

Women with obesity had a higher risk for emergency CS compared with normal weight and overweight women (8.4% vs. 2.3% and 3.9%, respectively) (Pearson Chi-squared test; df=2, p<0.01).

Table 9. Maternal and obstetric characteristics according to admission body mass index (BMI) (Study III)

		BMI 18.5-24.9 (n= 132)	BMI 25.0-29.9 (n=456)	BMI ≥30.0 (n=509)
<i>Maternal characteristics</i>				
Maternal weight in first trimester (kg)		56.1 [6.1]	62.4 [6.7]	78.3 [14.4]
Gestational weight gain (kg)		11.1 [3.6]	14.2 [4.4]	16.9 [6.6]
<i>Obstetric characteristics</i>				
Time from active labor until start of oxytocin (h)		8.6 [4.0] (n=105)	9.0 [5.3] (n=385)	8.4 [4.6] (n=422)
Time from start of oxytocin until delivery (h)		3.0 [2.7]	3.8 [3.4]	5.0 [4.1]
Cervical dilatation at start of oxytocin infusion	< 6 cm	16 (12.1)	87 (19.1)	144 (28.3)
	6-10 cm	34 (25.8)	142 (31.1)	207 (40.7)
	Fully dilated	82 (62.1)	227 (49.8)	158 (31.0)
	Normal VD	107 (81.1)	379 (83.1)	405 (79.6)
Mode of delivery	Instrumental VD	22 (16.7)	59 (12.9)	61 (12.0)
	Cesarean section	3 (2.3)	18 (3.9)	43 (8.4)

Figure denote mean and [one standard deviation] or number and (%).
VD, vaginal delivery

In the unadjusted analyses the mean cumulative oxytocin dose differed significantly in the BMI groups, normal weight 2278 [2748] mU, overweight 3108 [3839] mU and obese 4082 [4895] mU ($p<0.0001$). Post hoc analyses showed that the cumulative oxytocin dose was higher in the obese compared with the overweight and normal weight women ($p<0.01$ vs. $p<0.001$) (Figure 17). In the multivariate analyses, adjusting for cervical dilatation stage at the start of oxytocin infusion, fetal birth weight and EDA the statistically significant difference between the groups was no longer seen (Table 10).

Furthermore, in the unadjusted analyses obese women were shown to be treated with a higher maximum oxytocin infusion rate during the first stage of labor compared with overweight women ($p<0.05$) (Figure 18). However, the adjusted analyses showed that the independent predictive factors together, but not individually, influenced the statistically significant difference. (Table 10)

Figure 17. Cumulative oxytocin dose (mU) according to admission body mass index (BMI)

Plots indicate mean and bars indicate 95% confidence interval.

** $p < 0.01$; *** $p < 0.001$

Figure 18. Maximum oxytocin infusion rate in first stage of labor (mU/min) according to admission body mass index (BMI)

Plots indicate mean and bars represent 95% confidence interval. * $p < 0.05$

Table 10. Cumulative oxytocin dose and maximum oxytocin infusion rate during active phase of first stage of labor according to admission body mass index (BMI)

	ANOVA / ANCOVA between BMI groups, p-value					
	BMI 18.5-24.9 (n=132) 2278 [2748]	BMI 25.0-29.5 (n=456) 3108 [3839]	BMI ≥30 (n=509) 4082 [4895]	Crude	Adjusted ¹ Adjusted ²	Adjusted ³ Adjusted ⁴
Cumulative oxytocin dose (mU)						
<i>Independent predictive factors:</i>						
Cervical dilatation				<0.0001	<0.0001	<0.0001
Fetal birth weight					<0.0001	<0.0001
Epidural analgesia					<0.0001	<0.0001
Maximum rate of oxytocin during active phase of first stage of labor (mU/min)						
<i>Independent predictive factor:</i>						
Cervical dilatation				<0.01	<0.05	0.10
Fetal birth weight					<0.01	<0.0001
Epidural analgesia					<0.01	<0.01

Figures denote mean and [SD]

1 Adjusted for cervical dilatation at start of oxytocin infusion

2 Adjusted for fetal birth weight

3 Adjusted for epidural analgesia

4 Adjusted simultaneously for 1, 2, and 3.

The OLIV trial (Study IV)

A total of 40 women were included in study IV, subdivided into non-obese (BMI <30) and obese (BMI ≥30) according to admission BMI. Table 11 shows maternal and obstetric characteristics in the two BMI groups. Except for weight and BMI, no statistically significant difference between the two groups was found according to the characteristic variables.

Table 11. Maternal and obstetric characteristics in non-obese and obese women according to admission body mass index (BMI) (Study IV)

	BMI < 30.0 n= 12	BMI ≥30.0 n=28
MATERNAL CHARACTERISTICS		
Weight in early pregnancy (kg)	59.5 [7.9]	80.7 [16.8]
Weight at delivery (kg)	72.2 [7.6]	97.1 [16.6]
BMI in early pregnancy	21.8 [2.1]	29.7 [5.2]
BMI on admission labor to the labor ward	26.5 [2.1]	35.8 [5.1]
Parity		
Nulliparous	7 (58.3)	15 (53.6)
Multiparous	5 (41.7)	13 (46.4)
OBSTETRIC CHARACTERISTICS		
Spontaneous start of labor	7 (58.3)	16 (57.1)
Induction of labor	5 (41.7)	12 (42.9)
Cervical dilatation at start of oxytocin		
< 6 cm	4 (33.3)	16 (57.1)
≥ 6-10 cm	8 (66.7)	12 (42.9)
Mode of delivery		
Vaginal, non-instrumental	11 (91.7)	21 (75.0)
Instrumental delivery	0 (0.0)	3 (10.7)
Cesarean section	1 (8.3)	4 (14.3)

Figures denote mean and [one standard deviation] or number and (%).

After the start of the oxytocin infusion the median plasma oxytocin concentration levels were higher at the oxytocin rate of 3.3 mU/min in obese compared with non-obese women (median 19.55 ng/mL (IQR 10.61; 29.06 ng/mL) vs. median 6.97 ng/mL (IQR 5.55; 13.70 ng/mL), $p=0.016$). In all four subsequent increased infusion rates the median levels were higher in the obese women; however, no significant difference was seen between the groups (Figure 19). There was also a positive correlation between BMI and oxytocin in plasma at the oxytocin infusion rate of 3.3 mU/min (Pearson correlation coefficient 0.335, $p=0.035$). The study showed high intra and inter-individual variability in plasma levels of oxytocin in both non-obese and obese women.

Figure 19. Median oxytocin levels before and at each increase of the oxytocin infusion rate in obese (n=28) and non-obese (n=12) women according to admission body mass index (BMI)

The plots indicate median and bars indicate 25% and 75% percentiles.

*Statistically significant difference ($p=0.016$) between the groups.

Figure 20. Scatterplot presenting the correlation between maternal admission body mass index and plasma oxytocin at the oxytocin infusion rate of 3.3 mU/min

Pearson correlation coefficient 0.335 ($p=0.035$)

DISCUSSION

MAIN FINDINGS

Obstetric and neonatal outcomes in adolescents according to BMI (Studies I and II)

In two large Swedish nationwide register studies we showed that overall, primiparous overweight and obese adolescents had, compared with their normal weight counterparts, an increased risk for adverse pregnancy, delivery and neonatal outcomes, and the risk increased with rising BMI. Compared with a defined low-risk group of adult women, the overweight and obese adolescents had increased risk for adverse pregnancy and neonatal outcomes. However, in labor, the overweight and obese adolescents had a lower risk for instrumental VD and OASI. The obese women had an increased risk for CS but the same chance for a normal VD and no increased risk for PPH in VD. The overweight adolescents had a lower risk for CS and a better chance for a normal VD and a lower risk for PPH in VD.

Oxytocin infusion in labor and BMI (Studies III and IV)

Cumulative oxytocin dose and maximum oxytocin infusion rate (Study III)

This Swedish observational multicenter study included 1,097 nulliparous women with spontaneous start of labor and oxytocin infusion during labor. We found that women with increasing maternal admission BMI received a higher cumulative oxytocin dose until the neonate was born and they had a higher maximum oxytocin infusion rate during the first stage of labor. When adjusting for cervical dilation at the start of oxytocin infusion, birth weight and EDA, the statistically significant differences were no longer seen.

The OLIV trial (Study IV)

The OLIV trial was an observational study conducted at the maternity ward in the university hospital in Linköping, including 40 women in term labor with oxytocin infusion during the first stage of labor. The study showed that the obese women had increased median levels of oxytocin in plasma at the beginning of the oxytocin infusion (at 3.3 mU/min) compared with the non-obese women. A positive correlation was also found between BMI and plasma oxytocin levels at this rate. When the oxytocin infusion was further increased the median concentration in plasma in the obese women continued at higher levels compared with the non-obese women, however with no statistically significant differences.

CLINICAL INTERPRETATION

Obstetric and neonatal outcomes in adolescents according to BMI (Studies I and II)

Age and BMI are both factors to take into consideration when making risk-assessments in maternal health care. In studies I and II we studied adolescent pregnancies in relation to BMI and compared them with both normal weight adolescents and a group of low-risk adult women, called the standard women. This approach was supposed to give valuable information and knowledge in the clinical setting when making risk-assessments in adolescents based on BMI in pregnancy, labor and neonatal care.

Overweight and obese adolescents had increased risks for PE, still birth and LGA neonates compared with both normal weight adolescents and the standard women. These risks are of major concern since they can lead to long-term consequences for the mother and/or the child.¹⁷⁵⁻¹⁷⁷ Overweight and obesity are increasing in the young population and actions might need to be taken to improve the school health services to prevent increasing BMI in the youths. Furthermore, compared with the standard women, the overweight and obese adolescents had increased risk for preterm labor and SGA neonates. The increased risk for preterm labor is well known in adolescents and the risk is probably related to age more than BMI.^{28, 32} In antenatal care, it is suggested the overweight and obese adolescents should be seen as having high risk pregnancies. Extra surveillance resources are needed due to the increased risks for several adverse pregnancy outcomes.

However, after entering the labor ward, the overweight adolescents had more favorable outcomes compared with the low-risk adult women. Therefore, in labor, it is suggested the overweight adolescents should be considered as low-risk patients. When the resources are limited in the labor ward and the staff resources are allocated, this should be kept in mind. Obese and morbidly obese adolescents had both similar outcomes (VD, PPH in VD), more favorable outcomes (instrumental VD, OASI) and increased risk for adverse outcomes (CS, shoulder dystocia) compared with the standard women. Therefore, it is suggested they should be considered as intermediate risk patients in the labor ward. Thus, the morbidly obese adolescents can probably not be compared with the morbidly obese adult women regarding risk aspects. The morbidly obese adults have shown considerable increased risks in labor and are looked upon as high risk in obstetric care.^{37, 48-50} However, women with morbid obesity, both adolescents and adults, will probably require extra resources due to practical difficulties in the clinical care of these women, including monitoring fetal heart registration and uterine contractions. The

assessment of the fetal station in the birth canal can also be more complicated in morbidly obese women.

Regarding neonatal outcomes such as low Apgar score, SGA, LGA, low birth weight and macrosomia, the overweight and in particular the obese adolescents had increased risks compared with the standard women. Extra attention to ensure fetal well-being at the time of birth is suggested.

Oxytocin infusion in labor and BMI (Studies III and IV)

The crude analyses showed that the obese nulliparous women with spontaneous onset of labor received a higher cumulative oxytocin dose compared with the overweight and normal weight women. As shown by Soni et al., we observed that obese women were diagnosed with labor arrest (time receiving oxytocin), at an earlier cervical dilation stage than the normal weight women.¹⁵⁹ The adjusted analyses showed that the degree of cervical dilatation when oxytocin infusion was started could be one explanatory factor for the result of a higher cumulative oxytocin dose in women with obesity.

Furthermore, we showed in crude analysis that the obese women had a higher mean maximum oxytocin infusion rate in the first stage of labor compared with overweight women. The result was still significant when separately adjusted for fetal birth weight, cervical dilatation stage and EDA. Our findings are in agreement with earlier studies. Soni et al. showed that women with BMI ≥ 35 received significantly more oxytocin during the first three hours of augmentation in successfully treated labor arrest, compared with women in lower BMI groups.¹⁵⁹ Adam et al. showed, in a group of women with induced and spontaneous labors, that oxytocin infusion >20 mU/min was more common in women with obesity class III compared with normal weight women.¹⁶³ The results from our study also showed, in line with several earlier studies, a significant increased risk for emergency CS in obese women, compared with lower BMI groups.^{45, 47}

The present results strengthen the theories about obesity-related pathophysiological mechanisms affecting uterine contractility negatively in the obese women. The obese women seem to develop labor arrest at an earlier cervical dilatation stage and also do not respond adequately to treatment with oxytocin infusion. These observations lead to the hypothesis in study IV, that obese women have lower levels of oxytocin in plasma during treatment with oxytocin infusion. The hypothesis was rejected in the OLIV trial (study IV). We found that the oxytocin levels in plasma in the obese women, compared with the non-obese women, were significantly higher at the beginning of the oxytocin infusion. With a further increase of the infusion rates, the oxytocin

concentration continued at higher levels, but with no statistically significant differences.

There is little knowledge regarding levels of oxytocin in plasma according to BMI in labor, both with and without oxytocin infusion. The higher plasma levels of oxytocin observed in the OLIV trial in the obese women can be speculated about. If the binding of the oxytocin to the oxytocin receptor in the myometrium is affected negatively by alterations in the oxytocin receptor complex, the circulating oxytocin in plasma might be higher during oxytocin infusion in the obese women. Another hypothesis is that obese women have an impaired ability to assimilate the circulating oxytocin, leading to increased levels of oxytocin in plasma. The distribution and clearance of administered oxytocin might also be different in obese women, compared with normal weight women. The higher levels of oxytocin seen in the obese women might be due to lower levels of the degrading enzyme oxytocinase. De Tina et al. showed that the levels of oxytocinase were lower in women with obesity, compared with normal weight women, before the start of the oxytocin infusion treatment for induction of labor.¹⁴⁵

Furthermore, the higher levels of oxytocin in plasma found in the obese women during oxytocin infusion raise questions about potential side effects. Intravenous injection of oxytocin in women who undergo elective CS has shown cardiovascular effects including hypotension and tachycardia.^{165, 166}

Prolonged labor has been shown to cause a reduction in the number of oxytocin receptors.¹⁵² In addition, stimulation of the oxytocin receptors can lead to desensitization and internalization.¹⁵¹ Obese women might have fewer oxytocin receptors, or desensitization of the receptors might last longer in obese women, compared with normal weight women, leading to an impaired response to oxytocin.

With an increased risk for induction of labor and labor arrest, obese women also have a higher risk of being treated with oxytocin infusion during labor. We also know that obese women have an increased risk for CS due to a failed attempt to treat labor arrest.^{47, 91, 159} Oxytocin infusion is a tool we need to try to refine in an attempt to give obese women a higher chance for a normal VD. The actual guidelines for oxytocin infusion are based on outcomes regarding the frequency of contractions, fetal well-being and labor progress. The treatment does not consider knowledge about the function in the oxytocin-oxytocin receptor complex, the pharmacokinetics or pharmacodynamics of oxytocin, which may vary according to BMI.

In the light of the oxytocin studies included in this thesis, several questions arise. Maybe the treatment with oxytocin infusion should be handled differently in accordance with the woman's BMI. The oxytocin infusion in

obese women might have to start at lower doses and be increased slower at the beginning of the infusion and later may require more frequent and/or increased doses. The oxytocin receptors might also be desensitized to a higher degree in obese women and the oxytocin infusion therefore might need to be paused in active labor to achieve increased sensitivity of the oxytocin receptors.

There is a need to further investigate the oxytocin-oxytocin receptor complex specifically in obese women in labor. Future clinical trials investigating how to refine the dosage of oxytocin according to BMI are also needed. In addition, studies are required regarding potential negative consequences of the higher concentrations of oxytocin in plasma shown in the obese women.

METHODOLOGICAL CONSIDERATIONS

Use of BMI

There is no specific pregnancy BMI to use. In studies I and II we used early pregnancy BMI to classify the adolescents into BMI groups. By using early pregnancy BMI the adolescents could be better categorized for risk assessment during both pregnancy and in labor. However, the weight at the first trimester was either measured or self-reported and the height was self-reported. Self-reported height and weight in high school students have to some extent been shown to underestimate the prevalence of overweight in the adolescent populations.¹⁷⁸ This could lead to misclassification in some of the BMI groups. Furthermore, we chose to use BMI cut-offs according to the adult population and not cut-offs available to be used specifically for children and adolescents (e.g. the WHO or the International Obesity Task Force (IOTF) systems). We made this choice to be able to subdivide the obese group into obesity classes. The differences in numbers in the overweight and obese groups of adolescents using the adult BMI cut offs compared with the IOTF cut-offs were approximately 1%.

In studies III and IV we decided to use BMI on admission to the labor ward to better reflect the actual body composition at the time of the study. However, we were aware that gestational weight gain, apart from increased body fat, also includes the extravascular fluid, blood, maternal tissue from the breast and uterus and the weight of the fetus, placenta and amniotic fluid. Furthermore, it could be a shortcoming that we did not subdivide the BMI groups into obesity classes since the effect of BMI might be stronger/more obvious in a higher obesity class.

BMI correlates with body fatness, but it is an indirect measure and does not reflect the amount or distribution of the fat in the body. However, BMI is easy to measure and it is used by most clinical studies and is therefore useful in

comparison of data. There are other methods that might have been more accurate to use as measures for increased body fat (e.g. skinfold thickness, underwater weighing, waist circumference, bioelectrical impedance analysis (BIA)). These methods are difficult to standardize and/or did not seem suitable or possible to use for practical reasons. As a predictor for cardiovascular disease the use of BMI has been shown to be similar or even better than the use of skinfold thickness or hydrostatic weighing.¹⁷⁹ BMI has also been shown to be as good as BIA as a predictor for adiposity.¹⁸⁰

Sample size

Random errors can be reduced by increasing the sample size. If the sample size is too low there is a risk for type II error, meaning that there is a risk that a statistical test will fail to detect a significant difference even if there is a true difference. In study IV, the number of plasma samples taken decreased with increasing oxytocin infusion rates, resulting in low absolute numbers at higher rates of infusion. Thus, there was a risk for type II error. On the other hand, large sample sizes can show statistically significant differences with no clinical relevance. This is shown in study I, where we found a statistically significant difference according to GA between the BMI groups, and the difference was less than four days.

Systemic errors

Studies I and II were retrospective register studies while studies III and IV were prospective observational studies. In both retrospective and observational studies there are risks for systemic errors, bias. **Information bias** (misclassification or measurement bias), occurs if the data collected in the study is inaccurate and does not reflect the truth. It is also affected by the degree of missing data in the study population. The large data set in studies I and II made it possible to study rare outcomes like still birth, OASI, shoulder dystocia, meconium aspiration and fetal distress. However, misclassification and under/over-reporting of data from SMBR has to be considered, especially for diagnosis codes where there is no available information about missing data. For example, meconium aspiration and fetal distress are reported in the SMBR in very low absolute numbers and missing data is likely. However, the outcomes probably did not vary over the BMI-groups.

Selection bias can occur when the study population does not represent the population potentially eligible for the study. In study III, we only included nulliparous women with spontaneous onset of labor minimizing the effect of selection bias caused by differences related to parity or onset of labor. However, there might still have been a risk for selection bias since cumulative oxytocin dose was not registered for all women during the study period and therefore were excluded from the study. Women were also excluded because

of missing admission BMI and/or participation in another clinical trial at the labor ward. Out of 2,303 women who were eligible for the study, 1,097 (48%) fulfilled the inclusion criteria. Due to the large number of missing data, a statistical analysis was made to compare the included and excluded groups of women regarding potential selection bias. The analysis showed that the proportions of CS and PPH differed significantly and were higher in the excluded group. The reason for the missed registration of cumulative oxytocin dose may have been associated with time pressure or forgetfulness among the staff in situations where large bleeding or emergency CS occurred. No other differences were seen between the groups, and this speaks against selection bias in the study.

Confounding bias occurs when a variable, associated with both the exposure and the outcome, incorrectly implies a causation. A confounder should not be confused with an intermediate or a collider, variables that should not be adjusted for. Adjustments according to these variables can lead to “over-adjustments”, a sort of selection bias, with risk of reducing a true association or inducing an incorrect association. The intermediate variable affects the outcome but not the exposure. The collider is affected by both the exposure and the outcome (in an opposite direction to the confounder) (Figure 21).¹⁸¹⁻¹⁸³

Figure 21: The principles how confounders, intermediates and colliders affect or are affected by the exposure and the outcome.

To what extent adjustments should be made and which variables you should adjust for is not always clear. Confounders to adjust for can be chosen according to statistically significant differences in the study groups, or chosen according to clinical knowledge (e.g. fetal birth weight and labor progress) or based on earlier studies. In some contexts it is also of clinical interest to not adjust for all potential confounding factors. In studies I and II, in the comparison with the standard women, we decided not to perform adjusted statistical analyses. Our purpose was to compare defined and clinically relevant groups, not to imply causality between the exposure and the outcome. If the purpose had been to come as close as possible to proving causality

between BMI and the outcomes it would have been more appropriate to control for all potential confounding variables.

In study III we chose to adjust the cumulative oxytocin dose and the maximum oxytocin infusion rate for fetal birth weight, EDA and cervical dilatation at the point when oxytocin infusion was started. EDA and cervical dilation are variables that could have been considered as intermediates.

Plasma collection and laboratory analysis (Study IV)

It is probably impossible to reach full standardization in the procedure of collecting serial blood samples from women in active labor and this might have affected the levels of oxytocin measured in the plasma in the end. Furthermore, we did not acidify the plasma with hydrochloric acid to inhibit oxytocinase activity, as was done in some earlier studies.¹³⁶ On the other hand, we prepared the plasma immediately after collection, froze the samples, transported and stored them at -70 °C until analysis to prevent degradation by oxytocinase.

The specific MS method (UPLC-Orbitrap-tandem MS) used in study IV has, as far as we know, not been used before in this setting. The linearity of the oxytocin was evaluated over a range of concentrations (0.1-10000 ng/mL) and the correlation coefficient (r^2) was 0.9993. The limit of quantification of oxytocin was 0.05 ng/mL and the coefficient of variation (CV) (the ratio of the SD to the mean, the lower the CV the more precise the estimate) was less than 15%. The intra-assay CV was less than 10% and the inter-assay CV was less than 15%. The tests showed that the method had high validity and accuracy.

However, as with all types of analysis, the tandem MS method also has some limitations to consider. It is only the intact oxytocin molecule that will be selected in the MS1 scan. Single samples could exist that present with matrix effects that cause ion suppression, affecting the results. Furthermore, if another molecule is present in the sample with the exact same retention time in the UPLC, with the exact same weight and a similar structure this could give the same fragmentation pattern in the MS2 and another molecule could then be mixed up with oxytocin.

Generalizability

Studies I and II were conducted nationwide and the results of the studies are largely applicable to other countries with similar standards of maternal health care and socioeconomic status. However, only 5-8% of the adolescents in the BMI groups were 16 years and younger and the results should therefore be used in the context of older adolescents. The results from study III can probably only be applicable to maternity units with similar oxytocin infusion

guidelines and with similar rates of obstetric interventions and outcomes. However, the results may well be used in comparison of data with other studies with a similar study design. The results from study IV provide novel knowledge that has not been presented before. The study gives valuable data to compare with in future research using the same laboratory techniques, measuring oxytocin in plasma in different kinds of clinical settings. With similar characteristics of the study population and with the same guidelines for the oxytocin infusion, it can be applicable to other maternity wards.

CLINICAL IMPLICATIONS

Based on the studies in this thesis, the following clinical implications may be drawn:

- In prenatal care, extra surveillance can be considered (e.g. extra control of blood pressure and ultrasonography) in overweight and obese adolescents since adverse outcomes (PE, stillbirth, preterm labor, SGA) are increased compared with normal weight adolescents and/or low-risk adults.
- Overweight adolescents have better labor outcomes compared with low-risk adult women and can be assessed as “low-risk” in labor.
- The obese and morbidly obese adolescents have increased risks for adverse outcomes in labor. However, they have in some respects similar or more favorable labor outcomes than low-risk adult women. This knowledge can be taken into account when making risk-assessments at the labor ward to allocate the resources where most needed.
- Overweight, and to a greater extent obesity, are associated with adverse neonatal outcomes in adolescents. Extra neonatal attention can be considered at the time of birth and immediately afterwards.
- The obese women seemed to require a higher cumulative oxytocin dose in labor and developed labor arrest at an earlier cervical dilation stage. Obese women also received a higher maximum oxytocin infusion rate in the first stage of labor. There is a need, in future research, to try to refine the administration of oxytocin infusion in labor with the intention of giving women with obesity a higher chance for a normal vaginal delivery.
- The plasma concentration of oxytocin in obese women, compared with non-obese, showed higher levels at the beginning of the oxytocin infusion during the first stage of labor. This is a new finding that has to be confirmed in future studies and should be further investigated to determine potential negative consequences.

CONCLUSIONS

Based on the studies in this thesis, the following conclusions may be drawn:

- With rising BMI, the adolescents had an increased risk for adverse obstetric and neonatal outcomes compared with their normal weight counterparts. (Studies I and II)
- The overweight and obese adolescents had an increased risk for adverse pregnancy and neonatal outcomes compared with a group of low-risk adult women. (Studies I and II)
- Overall, the overweight adolescents had more favorable labor outcomes and the obese adolescents had to some extent more favorable labor outcomes compared with a low-risk group of adult women. (Study I)
- Obese women with spontaneous start of labor received a higher cumulative oxytocin dose compared with overweight and normal weight women and they had a higher maximum oxytocin infusion rate during the first stage of labor compared with overweight women. In the bivariate analyses, EDA and fetal birth weight did not affect the statistically significant associations. In the multivariate analyses, also including adjustments for cervical dilation at the start of oxytocin infusion, the statistically significant differences were no longer seen. (Study III)
- Obese women at term labor had higher plasma oxytocin levels at the beginning of the oxytocin infusion compared with non-obese women. (Study IV)
- Tandem mass spectrometry seemed to be a reliable methodology with high validity for analyzing oxytocin in plasma in women in labor. (Study IV)

FUTURE PERSPECTIVES

- To study obstetric outcomes in morbidly obese adolescents and compare these with morbidly obese adults.
- To evaluate neonatal outcomes such as birth injuries, infections, convulsions, birth asphyxia, hypoxic ischemic encephalopathy and long-term child outcomes in relation to BMI in adolescents.
- To examine different methods for refining the dosage and management of oxytocin according to BMI.
- To investigate cumulative oxytocin dose and its relation to obstetric outcomes.
- To confirm the results of study IV concerning higher levels of oxytocin in plasma at the beginning of the oxytocin infusion in obese women and to further investigate potential negative consequences linked to these findings.
- To investigate the possible association between the concentration of oxytocin in plasma and uterine contractions, including fetal well-being (measured with CTG), during oxytocin infusion.
- To investigate the oxytocin receptor (amount, function) according to BMI and age, in women after active labor and with vaginal deliveries.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Övervikt och fetma – betydelsen för tonårsgraviditeten och för oxytocin under förlossningen

I Sverige, liksom i stora delar av övriga världen, ökar andelen gravida kvinnor med övervikt och fetma. Under år 2018 hade 27 % av kvinnorna vid inskrivningen till mödravården i Sverige övervikt och 15 % hade fetma. Övervikt och fetma kan klassificeras genom uträkning av body mass index (BMI, kg/m²). BMI 25,0-29,9 innebär övervikt och BMI ≥ 30 innebär fetma. Hos vuxna är det välkänt att övervikt, och ännu mer tydligt fetma, är relaterat till ökade risker för både mamma och barn under graviditet och förlossning. Hos tonåringar är betydelsen av BMI på graviditet/förlossning inte lika väl studerad. Studier som undersökt ålderns påverkan på graviditet och förlossning har i vissa avseenden visat mindre risk för komplikationer (t.ex. färre kejsarsnitt och stora bristningar) hos tonåringar jämfört med hos vuxna.

Kvinnor med fetma har ökad risk för värksvaghet, det vill säga att förlossningen inte fortskrider på ett normalt sätt. Orsaken till att värksvaghet är vanligare hos kvinnor med fetma är okänd, men en stark teori är att muskulaturen i livmodern fungerar annorlunda hos kvinnor med fetma än hos normalviktiga kvinnor. Värksvaghet ökar riskerna för bland annat akut kejsarsnitt, instrumentell förlossning (sugklocka eller tång), infektion och stor blödning efter förlossningen.

Oxytocin är ett hormon som utsöndras från hypofysen och som bland annat stimulerar till sammandragningar i livmodern (värkar). Oxytocin kan ges som värkförstärkande behandling under förlossningen om värksvaghet uppstår, eller som behandling om förlossningen behöver sättas igång på medicinsk väg. Oxytocin ges som infusion (dropp) i blodet och doseras enligt riktlinjer som styrs av antal värkar, förlossningsprogress och fostrets mående. Riktlinjerna tar inte hänsyn till den gravida kvinnans vikt eller BMI. Tidigare genomförda internationella studier pekar mot att kvinnor med fetma är i behov av en ökad total mängd och en starkare dosering av oxytocin under förlossningen jämfört med kvinnor med lägre BMI. Ingen tidigare studie i Sverige har undersökt detta.

Det övergripande syftet med den här avhandlingen var att undersöka om BMI påverkar graviditet, förlossning och det nyfödda barnet hos tonåringar. Syftet var även att undersöka om BMI hos den gravida kvinnan påverkar total mängd givet oxytocin och koncentrationsnivåer av oxytocin i blodet vid behandling med oxytocininfusion under förlossningen.

Övervikt och fetma hos tonåringar och betydelsen för graviditet, förlossning och det nyfödda barnet

Studie I och II var registerstudier där det svenska medicinska födelserregistret (SMFR) användes. Syftet var att undersöka graviditets-, förlossnings- och barnutfall hos tonåringar med övervikt och fetma i jämförelse med både normalviktiga tonåringar och med en lågriskgrupp av vuxna kvinnor. Data samlades in från SMFR på alla kvinnor som fött sitt första barn mellan 1992-2013. I materialet fanns drygt 31 000 tonåringar med registrerad vikt och längd i början av graviditeten, vilket möjliggjorde uträkning av BMI. Ur registret hämtades även data ut på alla kvinnor i åldrarna 25-29 år, som fått sitt första barn och var normalviktiga, inte rökte och inte hade några andra sjukdomar (diabetes, högt blodtryck, njursjukdom, SLE, epilepsi och astma). Gruppen omfattade ca 180 000 kvinnor och benämndes *standardkvinnor*. Standardkvinnorna representerade en lågriskgrupp av vuxna kvinnor under graviditet och förlossning. Tonårsgruppen delades in i fyra BMI-grupper (undervikt, normalvikt, övervikt och fetma) och i tre fetmaklasser. Resultaten visade att tonåringar med övervikt och fetma hade en ökad risk för komplikationer relaterat till graviditet, förlossning och det nyfödda barnet jämfört med normalviktiga tonåringar. Riskerna sågs till stor del öka med stigande BMI. Bland annat sågs en ökad risk för havandeskapsförgiftning, dödfött barn, kejsarsnitt, stor blödning efter förlossningen, barn med låg Apgar-poäng och stort barn. I jämförelse med standardkvinnorna hade tonåringarna med övervikt och fetma ökade risker under graviditet och ökade risker relaterat till det nyfödda barnet. Vid förlossningen hade däremot de överviktiga tonåringarna mindre risk för instrumentell förlossning, kejsarsnitt, stor bristning och stor blödning efter förlossningen. Tonåringarna med fetma hade ökad risk för kejsarsnitt, men mindre risk för instrumentell förlossning och en lika stor chans till en normal förlossning som standardkvinnorna.

Slutsats: I jämförelse med normalviktiga tonåringar hade tonåringar med övervikt och fetma ökade risker för komplikationer under graviditet, förlossning och relaterat till det nyfödda barnet. Riskerna ökade till stor del med stigande BMI. I jämförelse med en lågriskgrupp vuxna kvinnor hade tonåringar med övervikt och fetma ökade risker för komplikationer under graviditet och relaterat till det nyfödda barnet, men i samband med förlossningen hade de överviktiga tonåringarna mindre risk för komplikationer.

Fetma och oxytocin vid värkförstärkande behandling under förlossningen

Studie III var en klinisk observationsstudie där syftet var att undersöka om den totala mängden givet oxytocin samt infusionshastigheten av oxytocin under förlossningen skiljde sig åt mellan olika BMI-grupper. Studien omfattade sju förlossningsenheter i den sydöstra sjukvårdsregionen och pågick från 2017-2019. Totalt inkluderades 1097 kvinnor som väntade sitt första barn, hade en spontan start av förlossningen i fullgången graviditet och fick värkförstärkande behandling med oxytocin under förlossningen. Resultatet visade att kvinnor med fetma fick högre total oxytocinmängd jämfört med överviktiga och normalviktiga kvinnor. Maximal dosering på infusionen var också högre i fetmagruppen. Fördjupade statistiska analyser visade att skillnaderna kunde förklaras av att kvinnorna i fetmagruppen fick behandlingen med oxytocin i ett tidigare skede av förlossningen (livmodertappen var mindre öppen). Även barnets vikt samt epiduralbedövning (ryggbedövning) påverkade skillnaden, dock inte i lika hög grad.

Studie IV var en klinisk observationsstudie som utfördes på förlossningen i Linköping under 2019-2020. Hypotesen var att kvinnor med fetma, som har ökad risk för värksvaghet, svarar sämre på värkstimulerande behandling på grund av lägre nivåer av oxytocin i blodet vid behandling med oxytocininfusion. Totalt ingick 40 kvinnor i studien och kvinnorna delades in i två grupper, utan fetma (BMI <30) och med fetma (BMI ≥30). Blodprover togs innan start av behandling med oxytocin och 20 minuter efter varje dosökning som gjordes. Proverna analyserades med tandem-masspektrometri på biomedicinskt centrum i Uppsala. Resultaten visade att kvinnorna med fetma hade högre nivåer av oxytocin i blodet i början av behandlingen med oxytocininfusionen jämfört med kvinnorna som inte hade fetma, således tvärtemot hypotesen. Vid fortsatt dosökning låg nivåerna av oxytocin i blodet fortsatt högre hos kvinnorna med fetma, men någon statistiskt säkerställd skillnad kunde inte visas mellan grupperna.

Slutsats: Kvinnor med fetma med spontan start av förlossningen fick högre total mängd oxytocin och uppnådde högre dosering av oxytocininfusionen jämfört med kvinnor med lägre BMI. En förklaring till skillnaden visade sig vara att kvinnorna med fetma fick sin behandling med oxytocin i ett tidigare skede av förlossningen. Kvinnor med fetma hade under förlossningen högre nivåer av oxytocin i blodet i början av behandlingen med oxytocininfusion jämfört med kvinnor som inte hade fetma.

Vilken kunskap och nytta bidrar avhandlingen med?

Avhandlingens två första studier ger kunskap om övervikt och fetma hos tonåringar och betydelsen för graviditet, förlossning och det nyfödda barnet. Studieresultaten kan bidra till ett förbättrat omhändertagande av dessa kvinnor i mödra- och förlossningsvård. Resultaten kan också leda till förändrade riskbedömningar inom vården vilket möjliggör att prioriteringar optimeras och resurser inom vården används på bästa sätt.

De två sista studierna som ingår i avhandlingen ger ny kunskap om oxytocin under förlossning med värkstimulerande behandling hos kvinnor med fetma. Resultaten kan användas i framtida forskning för att öka förståelsen kring värksvaghet och oxytocin i relation till kvinnans BMI. Förhoppningsvis kan resultaten leda till en förbättrad behandling av värksvaghet hos kvinnor med fetma och med det öka förutsättningarna för en normal förlossning för dessa kvinnor.

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PAPERS I-IV

Papers

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