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Maternal obesity, duration of labor and the role of leptin

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To my family

ABSTRACT

Background: The prevalence of obesity substantially increases in pregnant women. Maternal obesity is associated with adverse maternal and neonatal outcomes. The increased risk for cesarean section present in obese women has been related to potential impaired uterine contractility. The mechanism that underlies this theory is not clear. *In vitro* studies have shown that leptin, produced by adipose tissue and the placenta, exerts an inhibitory effect on myometrial contractility. The aim of this thesis was to evaluate the labor process in relation to maternal body mass index (BMI) and the clinical role of leptin in this process.

Material and Methods: Studies I-IV are cohort studies. The first two studies analyze the association between labor duration and maternal BMI based on data from the Perinatal Revision South register and the Swedish Pregnancy Register. Study I included 63,829 nulliparous women with a spontaneous onset of labor between 1995 and 2009. Study II included 15,259 nulliparous women with induced labor between 2014 and 2017. In study III, the maternal leptin levels during and after pregnancy were analyzed in 343 obese women with respect to their obesity class (I-III) and degree of gestational weight gain (GWG). In study IV, the association between the maternal leptin levels measured in active labor and duration of the active phase of labor was analyzed in 914 women.

Results: The duration of spontaneous labor significantly increased with an increasing maternal BMI; however, the duration of the pushing phase was inversely related to BMI. Time in induced labor increased with maternal BMI; however, the differences between the BMI categories were more pronounced in the latent phase than the active phase. Leptin levels were higher in women with obesity class III than women with class I during and after pregnancy. The degree of GWG in obese women was not associated with maternal leptin. No significant association between maternal leptin and the duration of the active phase of labor was identified in the adjusted analyses.

Conclusions: Nulliparous obese women have a higher risk for a prolonged duration of spontaneous and induced labor. This is important to consider prior to diagnosing labor arrest that results in a cesarean delivery. As maternal leptin levels are increased with the degree of obesity during pregnancy, future research on the association of high maternal leptin levels and the duration of labor is warranted.

LIST OF SCIENTIFIC PAPERS

- I Maternal body mass index and duration of labor**
Sara Carlhäll, Karin Källén and Marie Blomberg
Eur J Obstet Gynecol Reprod Biol. 2013;171:49-53

- II The effect of maternal body mass index on duration of induced labor**
Sara Carlhäll, Karin Källén and Marie Blomberg
Manuscript submitted

- III Maternal obesity (class I-III), gestational weight gain and maternal leptin levels during and after pregnancy: a prospective cohort study**
Sara Carlhäll, Marie Bladh, Jan Brynhildsen, Ing-Marie Claesson, Ann Josefsson, Gunilla Sydsjö, Annika Thorsell and Marie Blomberg
BMC Obesity 2016 20;3:28

- IV Maternal plasma leptin levels in relation to duration of the active phase of labor**
Sara Carlhäll, Karin Källén, Annika Thorsell and Marie Blomberg
Manuscript resubmitted after review

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ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
ANC	antenatal clinic
ANCOVA	analyses of covariance
ANOVA	analyses of variance
BMI	body mass index
CAPs	contraction associated proteins
COX	cyklooxygenase
CRH	corticotropin-releasing hormone
CS	cesarean section
ELISA	Enzyme-Linked ImmunoSorbent Assay
EMR	electronical medical records
GDM	gestational diabetes mellitus
GWG	gestational weight gain
IOL	induction of labor
IOM	Institute of Medicine
LGA	large for gestational age
PE	pre-eclampsia
PRS	Perinatal Revision South
SD	standard deviation
SFOG	Swedish Society of Obstetrics and Gynecology
SGA	small for gestational age
WHO	World Health Organization

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INTRODUCTION

Obesity in pregnant women has substantially increased over the previous several decades and has reached pandemic proportions. This trend is alarming because maternal obesity is accompanied by numerous adverse outcomes for both the mother and the child. Many of these maternal complications, including the well-documented increased risk for cesarean section (CS) have been related to a potential impaired uterine contractility in obese women. There are indications of a dysfunctional progression of labor in obese women. However, most previous studies on labor progression in relation to maternal body mass index (BMI) have included mixed parities and used different definitions of obesity. The reason for this ineffective uterine contractility has not been clarified. It has been demonstrated *in vitro* that myometrial fibers from obese women contract with less force and frequency than normal weight women. Other *in vitro* studies have shown that leptin, an adipokine produced by the adiposity tissue and the placenta, has an inhibitory effect on myometrial contractility.

The general aim of this thesis was to evaluate the labor process in relation to maternal BMI and the clinical role of leptin in this process.

BACKGROUND

MATERNAL OBESITY

Definition

Obesity is defined as abnormal or excessive fat accumulation that may impair health. BMI is commonly used to classify overweight and obesity in adults (Table 1) (1). It is defined as an individual's weight in kilograms divided by the square of their height in meters (kg/m^2). BMI correlates well with the proportion of body fat and is easy to measure; therefore, it is employed in clinical studies as a marker of health problems related to an increased amount of body fat.

Maternal obesity in pregnancy is typically defined as a BMI $\geq 30 \text{ kg/m}^2$ at the first antenatal consultation in early pregnancy (2).

Table 1. WHO classification of BMI

BMI (kg/m^2)	Classification
<18.5	Underweight
18.5-24.9	Normal weight
25-29.9	Overweight
30-34.9	Obesity class I
35-39.9	Obesity class II
≥ 40	Obesity class III (morbid obesity)

Prevalence

Obesity has become a worldwide epidemic, and the prevalence of obesity in pregnant women or women of reproductive age has substantially increased in recent decades. The worldwide prevalence of obesity in women has doubled since 1975, and the global increase has not slowed down (3). In the USA, 34% of women of reproductive age are obese, (4) and one of the highest rates in Europe is found in the United Kingdom, in which 26% of women are obese (5). In Sweden, 40% of pregnant women are overweight or obese and the prevalence of obesity increased from 7% in 1992 to 14% in 2016 (6) (Figure 1).

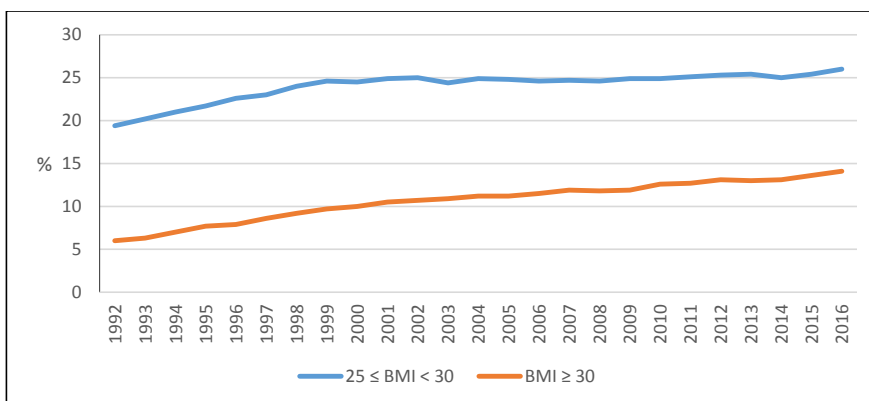


Figure 1. Proportion of pregnant women with overweight (BMI 25.0–29.9) and obesity (BMI ≥ 30.0) at registration for antenatal care in Sweden, 1992–2016

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

Maternal complications associated with obesity.

Obese women have a higher risk of developing hypertension before and during pregnancy (gestational hypertension). Both conditions are associated with serious complications such as pre-eclampsia (PE), placental abruption, gestational diabetes mellitus (GDM), premature delivery and small for gestational age (SGA) (7). The risk of developing gestational hypertension is six times higher in obese pregnant women than in normal weight women (7). Maternal obesity is also associated with PE a potential life-threatening hypertensive disorder of pregnancy. Obese women have a three to eight-fold higher risk of developing PE than normal weight women (7-9). Women who enter pregnancy obese are up to six times more likely to develop GDM than normal weight women (7). GDM implies a substantial risk to develop subsequent diabetes later in life, in addition to associated pregnancy complications such as PE, premature delivery, large for gestational age (LGA) and shoulder dystocia (7, 9, 10). The risk for both PE and GDM is proportional to increasing maternal BMI (8, 10).

Obese women are more likely to experience complications during labor. Post-dated pregnancies, induction of labor (IOL) and abnormal labor progression are more common in obese women. The rates of both elective and emergency CS successively increase with maternal BMI (11-13). Post-operative complications, including postpartum hemorrhage, anesthesiology complications, infections and thromboembolic complications, are also more common in obese women (9, 14).

GESTATIONAL WEIGHT GAIN

The total amount of weight gain during pregnancy varies among women and is a combination of fetal and uterus weight, amniotic fluid, the placenta, an increased maternal blood volume and maternal fat. A pronounced gestational weight gain (GWG) influences pregnancy outcome, however to a lesser extent than maternal obesity (9, 15).

In general, obese women gain less weight during pregnancy than normal weight women (16). The risk for a majority of the obesity related adverse outcomes during pregnancy may be amplified by excessive GWG (17, 18). Further, excessive GWG is associated with postpartum weight retention, which is an important indicator of obesity in midlife (19). Maternal weight retention between the first and second pregnancies is also associated with adverse pregnancy outcomes in the following pregnancy, even in normal weight women (20). Inadequate GWG is associated with small for gestational age and preterm birth (21).

In 2009, the American Institute of Medicine (IOM) published new guidelines on recommended weight gain during pregnancy according to pre-pregnancy BMI class (22) (Table 2). There are no specific recommendations within the different obesity classes. However, more recent studies indicate that women in higher obesity classes would benefit from lower GWG than recommended by the IOM. A GWG below the recommendations in morbidly obese women decreases the risk for LGA, gestational hypertension, PE and CS; however the risk increases for preterm birth and SGA (18, 23, 24).

Table 2. The IOM recommendations for total weight gain during pregnancy

Pre-pregnancy BMI (kg/m²)	Recommended GWG (kg)
< 18.5 (underweight)	12.5-18
18.5-24.9 (normal weight)	11.5-16
25-29.9 (overweight)	7-11.5
≥ 30 (obese)	5-9

THE PROCESS OF PARTURITION

The multifactorial process that regulates parturition and labor has been described in four phases. The phases correspond to the physiological changes in the myometrium and cervix during pregnancy as a result of hormonal and mechanical changes (14, 25-27) (Figure 2).

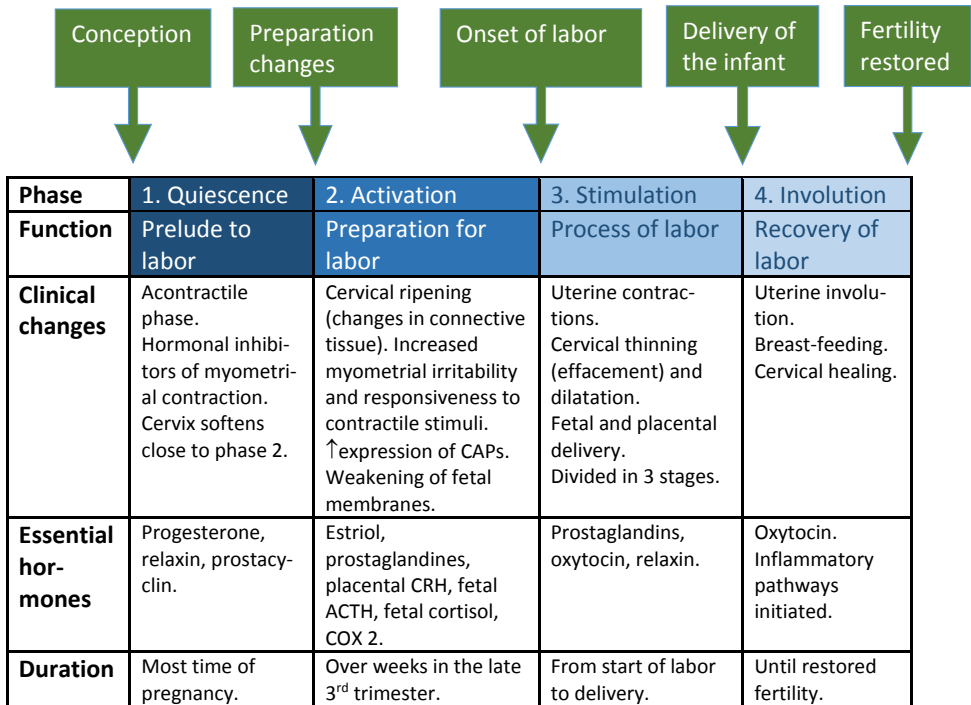


Figure 2. The different phases of parturition.

THE PROCESS OF LABOR

The onset of labor in humans is a complex multifactorial process that is not completely understood. The process involves mechanical and hormonal interactions between the mother, the fetus and the placenta. These interactions include fetal and maternal hypothalamic-pituitary-adrenal axis activation, myometrial stretch and inflammation. The combination of the stimulatory factors triggers the onset of labor and transforms the myometrium from a quiescent to a contractile state (25). As in other smooth muscle cells, myometrial contractions are mediated through adenosine triphosphate-dependent binding of myosin to actin, which is triggered by increased intracellular calcium ions (Ca^{2+}). Agents that stimulate myometrial contractions, such as prostaglandins and oxytocin, act on myometrial cells to increase the intracellular Ca^{2+} release from the sarcoplasmic reticulum or allow an influx of extracellular Ca^{2+} through ligand- or voltage-regulated calcium channels (14, 28). The process of labor is divided into three stages of labor (Figure 3).

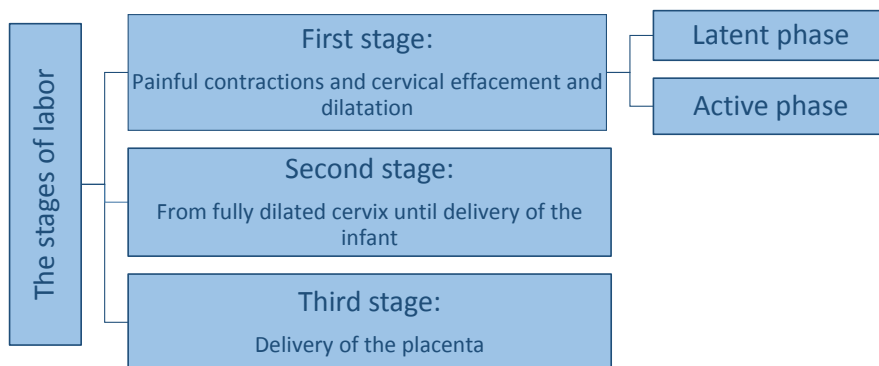


Figure 3. The stages and phases of the process of labor.

Research conducted by Friedman in the 1950s on the labor progress in 500 nulliparous women was presented as a sigmoid curve that illustrated the first stage of labor and has defined the normal course of labor world-wide for decades (29) (Figure 4). As the evaluation of the labor progression was based a small homogenous cohort that gave birth more than half a decade ago, it has been questioned whether this curve can be applied to current obstetrical care. Currently, the laboring women are older, have higher BMI and deliver by CS to a larger extent. Furthermore, the different obstetrical interventions that are more commonly used (inductions, epidural anesthesia and oxytocin use) may affect the labor process. Recent studies suggest that labor progression in contemporary labor cohorts differs from Friedman's results (30-33). A longer duration of the active phase and a later transition from the latent to the active phase than previously described have been reported (30-32). In a study on 62,415 nulli- and multiparous women with a term singleton pregnancy, spontaneous onset of labor and vaginal delivery, Zhang et al determined that labor progressed more slowly between 4-6 cm than previously described by Friedman and that the acceleration phase started at a cervical dilatation of 6 cm (30) (Figure 5). Oladapo et al studied labor patterns of 5,606 nulli-and multiparous women in a sub-Saharan African population and found, similar to Zhang et al, greater individual variability in labor progression than generally appreciated and that the acceleration phase may not start until 5 cm cervical dilatation (33).

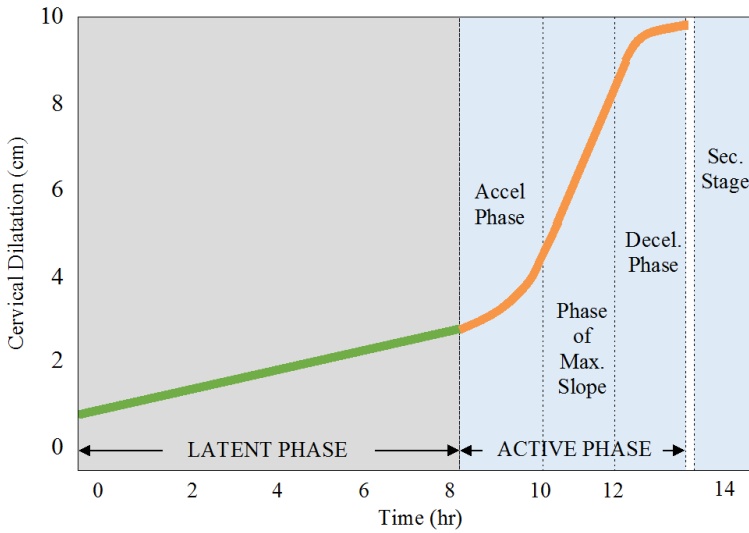


Figure 4: Friedman's labor curve. Friedman. Primigravid Labor, A graphicostatistical analysis. Obstet and Gynecol 1955.

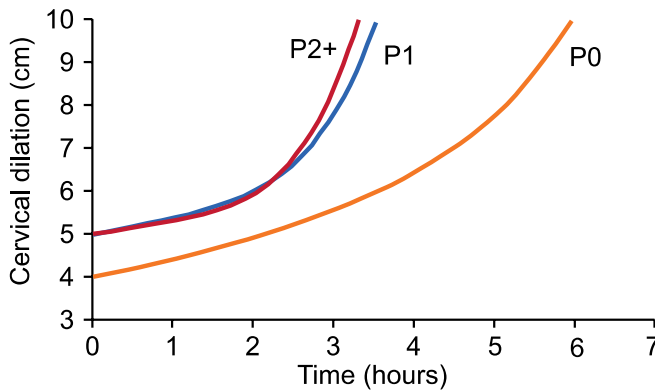


Figure 5: Zhang's labor curves. Average labor curves by parity in singleton, term pregnancies with spontaneous onset of labor, vaginal delivery and normal neonatal outcomes. P0: nulliparous; P1: women of parity one; P2+: women of parity two or higher. Zhang, Obstet and Gynecol 2010.

Definitions of the latent and active phases of the first stage of labor

The latent phase has been described to start with (irregular) painful uterine contractions, changes in cervical effacement and initial dilatation (34). It ends when the active phase starts. However, partly as a result of the lack of an international consensus regarding what time the active phase commences, the latent phase is commonly ill defined (35). According to the Swedish Society of Obstetrics and Gynecology's (SFOG) definition of the International Classification of Diseases, 10th revision (ICD-10), a prolonged latent phase is defined as more than 18 hours. A long duration of the latent phase of labor has been associated with an increased risk of CS, oxytocin augmentation and admission to the neonatal intensive care unit (36).

The active phase of the first stage of labor (referred to as the active phase) is commonly defined to start at a cervical dilatation of 3-4 cm together with painful uterine contractions, and it ends when the cervix is fully dilated. The threshold of 3-4 cm of cervical dilatation for defining the start of the active phase is based on the Friedman curve and is used in the definitions by the NICE (National Institute for Health and Care Excellence) guidelines (34) and have been used by the World Health Organization (WHO) (37) until recently. In February 2018 the WHO published new recommendations on intrapartum care presenting a cervical dilatation of 5 cm as a threshold for entering the active phase of labor (38, 39). The Swedish guidelines by the National Board of Health and Welfare from 2001 recommend that two of the following three criteria should be fulfilled for start of the active phase: cervical dilatation of 3-4 cm, three or more regular contractions/10 minutes and rupture of the amniotic membranes (40). A revised recommendation was proposed by the Swedish Association of Midwives and SFOG in 2015, which indicated that two of three criteria should be fulfilled for the start of the active phase: dilatation of the cervix of 4 cm or complete effacement of the cervix and dilatation >1 cm, 2-3 regular spontaneous painful contractions or spontaneous rupture of membranes and in addition to a progression of labor within the following two hours (41). However, the extent to which this revised recommendation is used remains unclear. The guidelines from the American College of Obstetricians and Gynecologists in 2014 recommends that a cervical dilation of 6 cm should be considered the threshold for the active phase of most women in labor (42).

Prolonged duration of labor

Different terms for a prolonged duration of the active phase include labor dystocia, failure to progress and obstructed labor. Traditionally, it has been defined as no dilatation in two hours or a dilatation rate less than 1.2

cm/hour. In a large American cohort, nulliparous women with prolonged active labor had higher odds for cesarean delivery and chorioamnionitis but not an adverse neonatal outcome (43). In another large American cohort of women who all reached 10 cm dilatation, Harper et al demonstrated that a prolonged labor increased the risk of maternal fever, a prolonged second stage, shoulder dystocia, and adverse neonatal outcomes (44).

There appears to be a normal physiological variation in the duration of labor, particularly in early labor, which may not be linear from 3-4 cm of cervical dilatation according to recent studies on contemporary cohorts of women in labor (30, 31, 33). The effectiveness of uterine contractions and the duration of labor may be influenced by numerous factors such as parity, fetal position and size and pelvic size and shape, maternal psychological state and maternal obesity (25, 45).

ONSET AND PROGRESSION OF LABOR IN OBESE WOMEN

Maternal obesity is associated with a longer gestation and an increased risk of post term pregnancy. It has been demonstrated that as maternal BMI increases, the chance of a spontaneous start of labor decreases (46, 47). The risk for post-term pregnancies, defined as a gestational length of more than 42 completed weeks from the last menstrual period, also increases with maternal BMI (48).

During labor, the process of cervical dilation is slower in obese women than normal weight women (25, 49, 50) and the duration of active labor increases with maternal BMI (45). It appears as if the prolonged duration of labor in obese women is restricted to the active phase of labor, particularly before 6-7 cm of cervical dilatation (45, 49-51). This is supported by studies that indicate the duration of the second stage of labor in nulliparous women is similar irrespective of maternal BMI (45, 52) and that the pushing ability is not related to maternal BMI (53).

The dose-dependent relationship between an increasing maternal BMI and a higher risk for cesarean delivery remains even after adjusting for obesity-associated co-morbidities (11, 54). The risk appears to be confined to the active phase of labor (54) and is mainly a result of a failure to progress /dysfunctional labor (55-57). When labor dystocia or failure to progress is diagnosed, augmentation with oxytocin is recommended. Oxytocin is administered according to a standard regimen regardless of BMI. However,

there are studies indicating that obese women have higher oxytocin requirements during the induction of labor (58, 59).

The exact mechanism of dysfunctional labor in obese women is not completely understood and is presumably multifactorial. Obesity is a chronic inflammatory state characterized by hyperinsulinemia and dyslipidemia. Adipose tissue has neuroendocrine functions that produce adipokines and cytokines, which may influence the onset and progression of labor. However, given the multiple labor abnormalities that are more common in obese women, including an increased risk for post-term pregnancies, slow progress and prolonged duration of labor, oxytocin for augmentation, postpartum hemorrhages and CS, the leading theory is that obesity may be associated with impaired myometrial contractility (25, 56, 57). This theory is supported by Zhang et al who demonstrated in an *in vitro* study that myometrium obtained from obese women undergoing an elective CS at term contracted spontaneously with less force and frequency than myometrial fibers from normal weight women (55). The difference in contractility ability was explained by demonstrated alterations in intracellular Ca^{2+} as myometrial fibers from obese women had less Ca^{2+} flux. (55). However, in a similar *in vitro* study, no correlation was identified between maternal BMI and spontaneous myometrial activity; this study included fewer myometrial biopsies from obese women compared the study by Zhang et al (60). Muir et al identified asynchronous myometrial contractility in obese laboring rats compared to synchronous contractions in lean animals. They also identified adverse alterations in uterine contractile protein expression and progesterone production in obese animals compared to lean animals (61).

INDUCTION OF LABOR IN OBESE WOMEN

Induction of labor (IOL) has become a common intervention in contemporary obstetrical practice. In Sweden, the proportion of induced singleton deliveries at full-term pregnancy (≥ 37 full gestational weeks) increased from 7.4% in 1991 to 17.8% in 2016 (6). Nulliparous women with IOL are three to four times more likely to have a cesarean delivery compared to nulliparous women with a spontaneous onset of labor (62, 63). Among women with induced labor the risk of a cesarean delivery increases further with maternal obesity (64-67). Unfortunately, obese women are more likely to undergo IOL compared to normal weight women (64-66). This is explained, in part, by the positive association between maternal obesity and post-term pregnancy (46-48). The increased rates of obesity associated comorbidities such as PE, GDM and hypertension, also contributes to the greater need of IOL (59, 63).

Considering the increasing prevalence of obesity and the associated risk for a cesarean delivery, obese nulliparous women with IOL represent a challenging risk group in contemporary obstetrical care. It has been demonstrated that the duration of the total time in induced labor increases with a higher maternal weight at the time of delivery (45, 59, 67, 68) and failure to progress is a more common indication for cesarean delivery in obese women with IOL than normal weight women (69, 70). Limited studies have assessed the effect of maternal early pregnancy BMI on the duration of induced labor, with contradictory results (58, 64, 71).

Studies that have compared labor lengths of spontaneous and induced labor, without relation to maternal BMI, also show contradictory results (72, 73). If induced labor is longer perhaps some CSs in women with IOL as a result of no progress are performed prematurely? This question is raised by Harper et al who determined that nulliparous women with IOL spent a longer time in labor than women with a spontaneous onset of labor (73).

LEPTIN

In the search for biological linkages between maternal obesity and adverse outcomes during pregnancy, the adipokine leptin is of substantial interest. Adipose tissue is now recognized not only as the main site for energy storage but also as an endocrine organ that secretes bioactive substances. These substances are referred to as adipokines, cell-signaling proteins, that are involved in energy homeostasis and have pro- or anti-inflammatory activities (74). Leptin is one adipokine. It is mainly produced by white adipose tissue, is principally associated with the regulation of energy metabolism and acts as a central satiety-signaling hormone. Obesity is associated with increasing serum leptin levels, proportional to the BMI and percentage of body fat in humans (75, 76). This paradoxical effect of increased levels of leptin in obese humans may be explained, in part, by a loss of signaling capacity to central satiety centers that may occur as a result of leptin resistance, which results in high leptin levels without the expected anorectic response (74).

Leptin is thought to have pro-inflammatory effects and promotes the production of pro-inflammatory cytokines (77). Leptin's actions are mediated by acting on leptin receptors in different target tissues. There are five known isoforms of leptin receptors. Four isoforms are membrane bound, and the full-length receptor Ob-Rb is primarily responsible for leptin-

signaling. Ob-Rb is expressed in the endometrium, myometrium, placenta and umbilical cord (77).

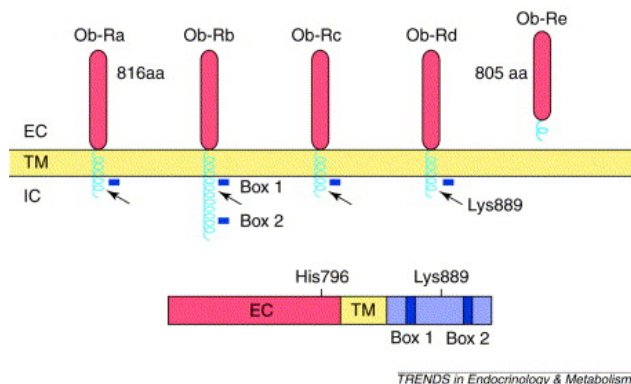


Figure 6. The isoforms of the leptin receptor. Caprio. Leptin in reproduction. Trends Endocrinol Metab. 2001

Other factors, in addition to the amount of adipose tissue that influence the leptin levels include gender, age, puberty, fasting, feeding and prolonged strenuous exercise (78). Leptin has also shown a diurnal pattern, with peak values during the night and lower values during the afternoon. However, it has been indicated that this pattern relates to food intake rather than the circadian clock (78). It has also been shown that plasma leptin levels measured in the fasting state are stable and reproducible in lean and obese men and women (79).

Leptin and pregnancy

During pregnancy, the placenta also produces leptin. Irrespective of maternal BMI, leptin levels substantially increase during a normal pregnancy, peak in the late second or early third trimester and return to pre-pregnancy levels after delivery, which indicates an important role for normal fetal development and growth (80-82). In normal pregnancies, there appears to be a central leptin resistance, which is beneficial for adequate energy supply to the fetus (80). An important placental function is to prevent embryo rejection by the maternal immune system. Leptin appears to have an important role as an immune-modulator in the placenta (77).

Leptin levels are higher in obese pregnant women than normal weight women during the whole pregnancy (82-84). It has also been shown that although leptin concentrations in overweight and obese women are higher, they increase at a lower rate across gestation compared to normal weight women (85, 86).

Although leptin appears to be of importance during a normal pregnancy, increased levels of leptin have been associated with adverse maternal pregnancy outcomes. The pro-inflammatory actions of leptin may be of importance in the pathogenesis of obesity associated pregnancy disorders, such as PE and GDM characterized by hyperleptinemia, leading to increased levels of pro-inflammatory mediators present in these diseases (77, 87-89). It may also contribute to the placental inflammation present in obese pregnant women which may result in placental damage and altered function (80).

Leptin and myometrial contractility

There are no published studies on the effect of leptin on human myometrial contractility *in vivo*. However, several authors have analyzed the effect of leptin on myometrial muscle cells *in vitro* and have suggested that leptin may play a role in the regulation of myometrial activity and obesity related parturition complications (90-94).

Moynihan et al. analyzed myometrial biopsies from pregnant non-laboring women who underwent elective CS at term. They determined that leptin had a cumulative inhibitory effect on both spontaneous and oxytocin-induced contractions in all myometrial strips *in vitro* (92). In a similar study, this *in vitro* cumulative inhibitory effect of leptin on contractions in pregnant human myometrial biopsies was confirmed (94). Wendremaire et al proposed that elevated leptin levels may play a role in obesity related delivery disorders, by demonstrating that leptin prevented remodeling of myometrial extracellular matrix, which is necessary for effective uterine contractions during labor (91), and leptin inhibits myometrial apoptosis, which is of importance for uterine smooth muscle to change from a proliferative to contractile status (90). Barrichon et al showed *in vitro* that leptin induced human myometrial proliferation. This proliferative effect on the myometrial cells lead to the maintenance of uterine quiescence and thereby opposed the mechanisms that trigger labor and myometrial contractions (93). These findings have led to speculations regarding whether leptin could be used as a tocolytic agent (93, 95).

The mechanism by which leptin mediates this inhibitory effect on myometrial contractility is unknown. It has been speculated that if leptin has the same function in the uterine smooth muscle cells as in vascular smooth muscle and reduces intracellular calcium $[Ca^{2+}]$ release, it may impair the contractility ability of the myometrium (96). This thought was supported by Zhang et al, who demonstrated that myometrium from obese women contracted with reduced frequency and amplitude *in vitro*. Simultaneous measurements of intracellular $[Ca^{2+}]$ showed less $[Ca^{2+}]$ flux in the myometrium of obese women than normal weight women (55).

Based on clinical experience, and the results from the aforementioned clinical studies and *in vitro* studies, we hypothesized that duration of both spontaneous and induced labor would be longer in obese women than in normal weight women. As leptin has been associated with hypertensive disorders during pregnancy and GDM, that are more common in obese pregnant women, and had an *in vitro* relaxing effect on myometrial contractility we hypothesized that leptin would be higher with increasing maternal obesity class. Further we hypothesized that leptin would have a relaxing effect on myometrial contractility *in vivo*, resulting in a prolonged duration of labor, regardless of maternal BMI.

AIMS

General aim

The general aim of this thesis was to evaluate the labor process in relation to maternal BMI and the clinical role of leptin in this process.

Specific aims

Study I

To evaluate whether duration of the active labor is associated with maternal pre-pregnancy BMI in nulliparous women with a spontaneous onset of labor and to evaluate the duration of the second stage of labor in relation to maternal BMI separately.

Study II

To evaluate whether the durations of the latent and active phases of labor are associated with early pregnancy maternal BMI in nulliparous women with induced labor.

Study III

To estimate whether maternal plasma leptin levels during and after pregnancy are associated with different degrees of maternal obesity and different levels of GWG.

Study IV

To analyze the relationship between the duration of the active phase of labor and maternal plasma leptin levels measured at the time of delivery.

MATERIAL AND METHODS

A brief overview of the subjects and methods of the four studies is presented in table 3 below.

Table 3. Overview of the studies included in the thesis

PAPER	I	II	III	IV
Design	Cohort study	Population based cohort study	Cohort study	Cohort study
Years	1995 - 2009	Jan 2014 - Aug 2017	Nov 2003 - Dec 2005	April 2014 - Dec 2015
Data sources	Perinatal Revision South register	Swedish Pregnancy Register	Electronic medical records and biobank	Electronic medical records and biobank
Subjects	63,829 nulliparous with spontaneous onset of labor	15,259 term nulliparous with induced labor	343 obese pregnant women	914 term nulli and multiparous women
Exposures	Maternal BMI	Maternal BMI	Maternal obesity class and degree of GWG	Maternal plasma leptin levels in active labor
Outcome measures	Duration of labor with a spontaneous onset	Duration of the latent and active induced labor	Maternal leptin levels during pregnancy and postpartum	Duration of the active phase of labor
Covariates	Maternal age, birth weight, year of delivery	Maternal age, birth weight, GWG (smoking and vaginal delivery in active labor analyses)		Parity, use of EDA or oxytocin, birth weight, induction. (Parity, gestational age, EDA and oxytocin in spontaneous labor analyses)
Statistics	Descriptive statistics, Kruskal-Wallis, ANOVA, ANCOVA, multiple logistic regression analyses and Kaplan-Meier analysis	Descriptive statistics, one-way ANOVA, ANCOVA and cox regression analyses	Descriptive statistics and two-way ANOVA model (Bonferroni adjusted)	Descriptive statistics, univariate and multiple linear regression analyses and Kaplan-Meier analysis

DATA SOURCES

Registers

Data from two different registers were used in **studies I and II**. The perinatal Revision South (PRS) register, which was used in **study I**, is a regional perinatal database in southern Sweden, instituted in 1995 and based on approximately 17,600 annual births at nine obstetric units in the region. The database closed in 2015 (97).

The population-based cohort (**study II**) was based on data from the Swedish Pregnancy Register (www.graviditetsregistret.se) (98). The register was established in 2013 by merging the Maternal Health Care register and the National Quality Register for Prenatal Diagnosis and collecting information from deliveries in electronic medical records (EMRs). The register currently contains information on maternal characteristics, pregnancy complications, labor and birth data from 90 % of all deliveries in Sweden. The majority of the variables included in the register are continuously transferred electronically from the medical antenatal, labor and delivery records. A few variables are manually registered by midwives at the antenatal care (ANC) clinics. These data include information on country of birth, level of education and diagnosis of GDM (98).

Electronic medical records

For **studies III and IV**, pregnancy and delivery data were collected from the electronic medical record (EMR) system Obstetrix[®]. Information on all pregnant women in the Region Östergötland who attend the maternal ANC clinics is recorded in Obstetrix[®] (Cerner). This EMR system contains detailed, prospectively registered information for each pregnancy from the first visit until the mother and infant are discharged from the delivery hospital. These data include maternal reproductive, demographic and health data, prenatal maternal medical diagnoses and pregnancy outcome for the mother and infant.

Biobank and maternal blood samples

For leptin analyses in **study III**, we used saved maternal blood samples from a previous intervention study on weight gain during pregnancy (99). The women were recruited from the ANC clinic in Linköping and two other nearby ANC clinics (Norrköping and Värnamo). For leptin analyses in **study IV**, we used maternal blood samples from women included in “GRABB”, a local pregnancy biobank. The maternal blood samples in both **studies III and IV** were handled similarly and stored in a common biobank

with register number 185 at the Department of Obstetrics and Gynecology, Östergötland County Council.

“GRABB” is a research project in which all women at the ANC clinic in Linköping are asked to participate with the aim to collect blood samples from pregnant women to build a biobank for future research. It was initiated in 2011, and the aim is to collect samples from 8000 individuals. Blood samples are collected at the same time as routine blood tests are performed, including twice during pregnancy, as well as at the time of delivery from 2014. To date, approximately 55 % of all women who have been registered for antenatal care during this time period have agreed to participate in “GRABB”.

STUDY POPULATIONS AND STUDY DESIGNS

Studies I and II

Study populations

Studies I and II are large cohort studies that include nulliparous women with a singleton pregnancy. **Study I** included 63,829 women with a spontaneous onset of labor from 1995 until 2009. Of these women, 57,500 women also had information on time in the second stage of labor. **Study II** is population based and included 15,259 women with IOL from January 2014 until August 2017. Women with non-available information on the start of active labor and the time of birth and missing maternal BMI were excluded from **studies I and II**. Additional exclusion criteria in **study II** included stillbirth and no information on maternal age. Women with a CS during the active phase of labor were included in both studies; however, women with a cesarean delivery in the second stage in **study I** or the latent phase in **study II** were not included.

Exposure

The exposure in **studies I and II** was pre-pregnancy or early pregnancy maternal BMI. BMI was calculated based on self-reported pre-pregnancy weight or measured weight and height in the first trimester in **study I**. In **study II**, BMI was calculated based on the maternal weight and height measurements provided at the first antenatal visit between gestational weeks 8 and 10 in a majority of the study patients. The study population was categorized in six classes of BMI according to the WHO definition (Table 1).

Outcomes

Time in labor was the main outcome in **studies I and II**. The time estimates on labor that are available in the PRS register and in the Swedish Pregnancy Register include the start of the active phase of labor, start of pushing efforts and time of birth. In **study I**, the labor outcomes included the duration of active labor, defined as from the start of the active phase of labor until the time of birth, and the second stage of labor. As there was no information in the PRS register on the time when the cervix was fully dilated, we defined the second stage as from the start of the pushing efforts until the time of birth. In **study II**, the main outcomes included the duration of the latent and active labor. The active labor was defined as in **study I**. Information on the start of induction is not available in the Swedish Pregnancy Register; however, the time of arrival to the delivery ward for the IOL is available. In Sweden, most patients admitted for IOL start induction shortly after arrival to the delivery ward; therefore, we used the time of arrival as a proxy for the start of IOL. Thus, latent labor was defined from the time of the arrival to the delivery ward for IOL until the start of the active phase of labor. Another outcome in **study II** was the rate of emergency CS in the active labor and other modes of delivery. As the inclusion criteria in **study II** comprised information on the time of the start of the active phase of labor, all women who did not reach the active phase were not included. Therefore, women who had a CS in the latent phase were not included in the study population.

Studies III and IV

Study populations

In **studies III and IV**, we used cohorts from the south-eastern health care region of Sweden. In **study III**, we analyzed 343 obese pregnant women with a singleton pregnancy from three ANC clinics included in a previous intervention study on weight gain during pregnancy (99). The exclusion criteria in the original study were a pre-pregnant diagnosis of diabetes mellitus, thyroid dysfunction or psychiatric disease treated with neuroleptic drugs. In **study IV**, we included 914 nulli- and multiparous women who were included in the local biobank GRABB at the first antenatal visit at the ANC clinic in Linköping and who delivered at the Linköping University Hospital. Women with multiple pregnancies, diabetes mellitus, intrauterine fetal death, premature labor (gestational week < 37+0), elective CS, a missing leptin value or incomplete information on the time estimates of the active phase of labor were excluded. Thus, all women who had undergone an emergency CS during the active phase of labor (before pushing efforts started) were excluded. In **study IV**, 766 women, out of the 914 women

included in the study, had a spontaneous onset of labor and were also analyzed separately. Further in **study IV**, 660 women had information on GWG and were categorized in three classes of GWG according to the recommended weight gain based on their early pregnancy BMI and the IOM's guidelines (Table 2).

Exposures

The exposures in **study III** included the degree of early pregnancy maternal obesity and degree of GWG. The study population was categorized in three obesity classes according to the WHO definition on obesity classes I-III (Table 1 and Figure 14) and was divided into three groups of GWG based on the IOM guidelines advising optimal weight gain during pregnancy (Table 2 and Figure 14).

The exposure in **study IV** included the maternal plasma leptin value measured in active labor. Maternal plasma was collected shortly after the women had arrived to the delivery ward as soon as she was assessed to be in active labor.

Outcomes

The outcome in **study III** included maternal leptin levels during pregnancy and postpartum. Maternal plasma leptin levels were measured in gestational weeks 15 and 29 and 10 weeks postpartum. The women fasted prior to sampling of the maternal blood, which was performed in the morning in all patients. The blood samples were handled as in **study IV** and were stored in the same biobank. The outcome in **study IV** time included the duration of the active phase of labor. The duration of the active phase of labor was defined as from the start of active labor until the start of pushing efforts.

LEPTIN SAMPLING AND ANALYSES

For leptin analyses in **studies III and IV** maternal blood was collected in a test tube with a clot activator and gel for plasma separation. Within one hour after sampling, the blood was centrifuged and aliquoted and the plasma was stored at -70 degrees Celsius in the local biobank (register number 185, at the department of Obstetrics and Gynecology, Östergötland County Council) until further analyses.

The plasma leptin concentration was obtained using a direct sandwich-based ELISA (Enzyme-Linked ImmunoSorbent Assay) in **studies III and IV**. This method measures the antigen concentration in an unknown sample. The antigen of interest is quantified between two layers of antibodies: the capture and the detection antibody. These antibodies must bind to non-overlapping epitopes on the antigen. An enzyme is used to convert a sub-

strate to a product that may be detected, typically with quantitative colorimetric methods (Figure 7). This ELISA method for the detection and measurement of leptin levels in human plasma is now routine with available assays commercially available (78).

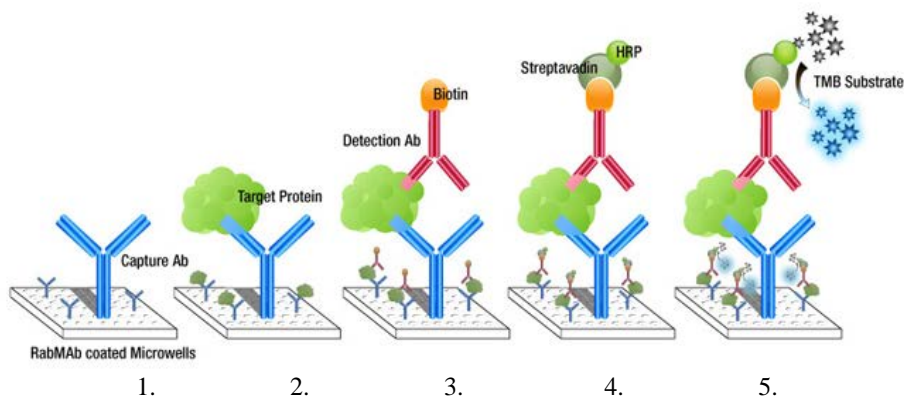


Figure 7. Direct sandwich based-ELISA method

Teuscher, N. (2014, July 7). Ligand Binding Assays [Sandwich assay]. Retrieved April 3, 2018, from <https://www.certara.com/2014/07/22/ligand-binding-assays/>

1. Microwell plate is coated with a capture antibody.
2. Maternal plasma is added to the plate and the human leptin in the plasma-sample binds to the capture antibody.
3. A detection antibody (monoclonal biotinylated antibody) is added to the plate and binds to the captured human leptin.
4. Streptavidin-horseradish peroxidase is subsequently added and binds to the immobilized biotinylated antibodies.
5. TMB (tetramethylbenzidine) substrate is added in the final step and converted to a detectable colored form.

The enzyme activity was spectrophotometrically measured after the acidification of the sample products terminated the enzymatic reaction.

In between each step, the wells were washed three to five times to eliminate unbound material. As increased absorbance is directly proportional to the amount of captured human leptin in unknown samples, quantification of human leptin may be derived from a generated reference curve with reference calibrators of known concentrations of human leptin.

STATISTICS

Descriptive statistics

In **studies I-III**, the mean and standard deviation (SD) were presented for continuous variables and numbers and percentages were presented for categorical variables. Chi-square tests were performed to analyze descriptive frequency data, whereas one-way analyses of variance (ANOVA) were conducted to compare descriptive, continuous, normally distributed data over the BMI-classes.

In **study IV**, the leptin levels were not normally distributed and were therefore presented as medians and percentiles.

Analyses of outcomes

Studies I, II and IV

The outcome duration of active labor in **study I** was normally distributed. All other outcome parameters (durations of different phases of labor) were not normally distributed; however the logarithmic values were normally distributed.

To compare the differences in the mean labor duration between the BMI classes in **studies I and II**, one-way ANOVAs were employed. When the outcome parameters were not normally distributed, the logarithmic values were used or the Kruskal-Wallis non-parametric tests were performed to compare distributions between BMI groups. Analyses of covariance (ANCOVAs) were used to control for possible confounders.

To evaluate the relationships among the outcome, duration of labor, and BMI and/or leptin, survival analyses were employed. The reason for using these methods was to be able to include the duration of labors ending in CSs in the analyses. Survival analyses are often used to investigate the time to an event. In our studies, the event was defined as the end of each phase or stage of labor that was analyzed (i.e., birth or end of the active phase of labor). We used the Kaplan-Meier method and the Cox regression method in the analyses in **studies I, II and IV**. The Kaplan-Meier method is a descriptive method of the “survival process” that may also be used to compare the time to an event between several groups. However, it is not possible to analyze the effect of different covariates on the time to an event with the Kaplan-Meier method. The cox regression method is the most common survival analysis method to compare the time to an event between groups, as well as investigate how different covariates influence the survival-time. Censoring was performed in our survival analyses, for the women who had a cesarean delivery during the active phase.

In **study IV**, the associations between the outcome (duration of the active phase of labor) and maternal leptin levels were also investigated with univariate and multiple linear regression analyses. Multiple linear regression analysis is used to analyze several variables to determine whether one or more variables are predictive of a certain outcome. Multiple imputations were used to address missing information on GWG in the statistical analyses, which included GWG as a potential confounding factor. This is a common method to handle missing values. As the amount of missing data was substantial we included 20 imputed data sets.

Potential confounders were included in the adjusted analyses in **studies I, II and IV**. In **study I**, maternal age and birth weight and year of delivery were included as confounders. In **study II**, ANCOVA was used to identify and control for confounders when evaluating differences in mean labor duration over BMI-groups. Only factors with a p-value < 0.2 were included in the final analyses (maternal age, GWG, birth weight and vaginal delivery). Moreover in **study II**, when analyzing the relationship between the duration of labor and BMI, the confounders were identified with cox regression analyses as single independent factors that influenced the time in labor with a p-value < 0.2 . Maternal age, birth weight, smoking and GWG were included as confounding factors in the analyses on active labor. Birth weight and GWG were included as confounding factors in the analyses on latent labor. In **study IV**, univariate and multiple linear regression analyses were used to identify and control for confounders when analyzing the association between the duration of labor and leptin. The first multivariable model included leptin levels and variables considered possible confounding factors with $p < 0.2$ in the univariate analyses and the final restricted multivariable model included leptin levels and variables with $p < 0.2$ in the first full multivariable model. Parity, gestational age, induction, epidural anesthesia, oxytocin, birth-weight and leptin were included in the final multivariable model.

Study III

The outcome parameters, maternal leptin levels, were normally distributed. A two-way ANOVA model was used to analyze the mean value and confidence interval of maternal plasma-leptin in women with obesity class (I-III) and the different GWG groups (Bonferroni adjusted for multiple comparisons within each gestational week). Only BMI and GWG were included in the final model. No significant interaction effect between maternal BMI and GWG was identified (tested with a two-way ANOVA model). Therefore the analyses on leptin and GWG group were not adjusted for BMI and vice versa. No significant confounder was identified using general linear models to assess the possible confounding effects of smoking, GDM and PE, in addition to the main effect model of BMI and GWG.

For **study I**, the statistical software Gauss (Gauss™, Aptech Systems Inc., Maple Valley, WA, USA) (<http://www.aptech.com>) was used. The statistical software IBM SPSS version 23 (IBM, Inc., Armonk, NY, USA) was used for statistical analyses in **studies II-IV**. A p-value <0.05 was considered statistically significant.

ETHICAL APPROVAL AND CONSIDERATIONS

The studies in this thesis were approved by the Regional Ethical Review board in Linköping (Study I; Dnr M44-09, study II; Dnr 2017/274-31, study III; Dnr 2010/296-31 and Dnr 2013/378-32 and study IV; Dnr 03-231).

Studies I and II were performed without the participants' informed consent. In research on personal health with data maintained in large registers informed consent is typically not required. The Personal Data Act (1998) aims to prevent the violation of personal integrity in the processing of personal data. Before treatment of sensitive personal data, such as health data, can be conducted, permission by a regional ethical review board is required. The ethical board can decide whether data from large registers may be accessed for research without informed consent. Inclusion of data in the Swedish Pregnancy Register does not require consent from the patients and participation in the register is voluntary. After ethical approval and application to register holders of the Swedish Pregnancy Register and PRS register, data were retrieved unidentified.

Written informed consent was obtained from all study subjects included in **studies III and IV**. The patients had the right to withdraw their consent at any time. The maternal blood samples used in **studies III and IV** were handled according to the Swedish Act Biobanks in Medical Care (SFS 2002:297). The samples were coded, and the key code to the personal identity number is securely maintained at Region Östergötland. All leptin analyses were performed on coded plasma samples. The key code was used to identify the patients in the EMR.

RESULTS

DURATION OF LABOR AND BODY MASS INDEX (studies I and II)

Main findings of study I

In the study population of 63,829 nulliparous women with a spontaneous start of labor, the duration of active labor significantly increased with increasing maternal pre-pregnancy BMI, illustrated with survival curves from the Kaplan-Meier analysis ($p=0.038$) (Figure 8). The mean duration of the active labor increased with a higher BMI class from 8.8 hours in normal weight women to 9.8 hours in women with a BMI ≥ 40 . In 57,500 of the women, the median time in the pushing phase decreased with an increasing maternal pre-pregnancy BMI from 0.55 hours in normal weight women to 0.45 hours in morbidly obese women. The active labor durations were normally distributed. The second stage durations were not normally distributed; however the logarithmic values were normally distributed. The differences between the BMI categories in both mean active and log second stage durations remained significant when adjusting for maternal age and birth weight ($p<0.001$).

Main findings of study II

In nulliparous women with IOL, we determined that the durations of both the latent and active labor increased with maternal early pregnancy BMI; however the differences between the BMI categories were more pronounced in latent labor, illustrated with survival curves from the cox regression analyses (Figures 9 and 10).

Overweight women and women in obesity classes I-II who reached the active phase of labor had similar durations of active labor as normal weight women and a similar chance for a normal vaginal delivery.

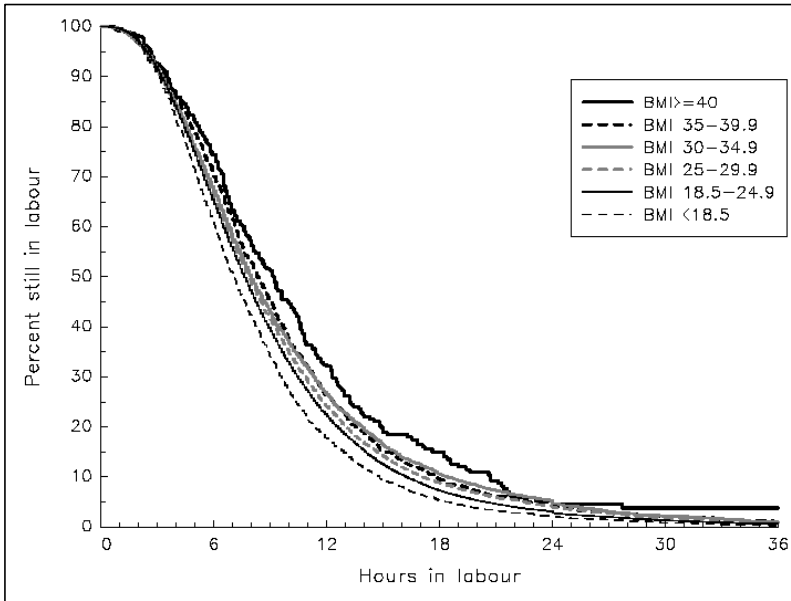


Figure 8. Duration of labor (hours) in nulliparous women with a spontaneous onset of labor in relation to their BMI. Women were censored at the time of emergency caesarean section. P for difference between groups = 0.038.

Median labor duration in studies I and II

The median duration of latent labor and active spontaneous labor successively increased with maternal BMI. Underweight women had a shorter median duration of active labor (both spontaneous and induced labor) than women in other BMI classes (Table 4). The durations of the latent and active induced labor were not normally distributed; however the logarithmic values were normally distributed and were used to explore differences between the BMI categories. The differences were significant when adjusted for confounding factors.

Table 4. Median duration of labor in nulliparous women with a spontaneous onset of labor or induction of labor.

Maternal Body Mass Index (kg/m ²)	Time in latent induced labor (hours). N=15,073		Time in active induced labor (hours). N=15,259		Time in active spontaneous labor (hours). N=63,829	
	N (%)	Median	N (%)	Median	N (%)	Median
<18.5	322 (2.1)	12.9	325 (2.1)	6.1	2,024 (3.2)	7.05
18.5-24.9	8,434 (56.0)	14.5	8,509 (55.8)	7.4	43,052 (67.4)	7.53
25-29.9	3,993 (26.5)	16.3	4,044 (26.5)	7.6	13,823 (21.7)	7.70
30-34.9	1,568 (10.4)	18.2	1,605 (10.5)	7.6	3,641 (5.7)	7.75
35-39.9	549 (3.6)	21.0	562 (3.7)	7.0	988 (1.5)	8.08
≥40	207 (1.4)	22.6	214 (1.4)	7.4	301 (0.5)	8.45

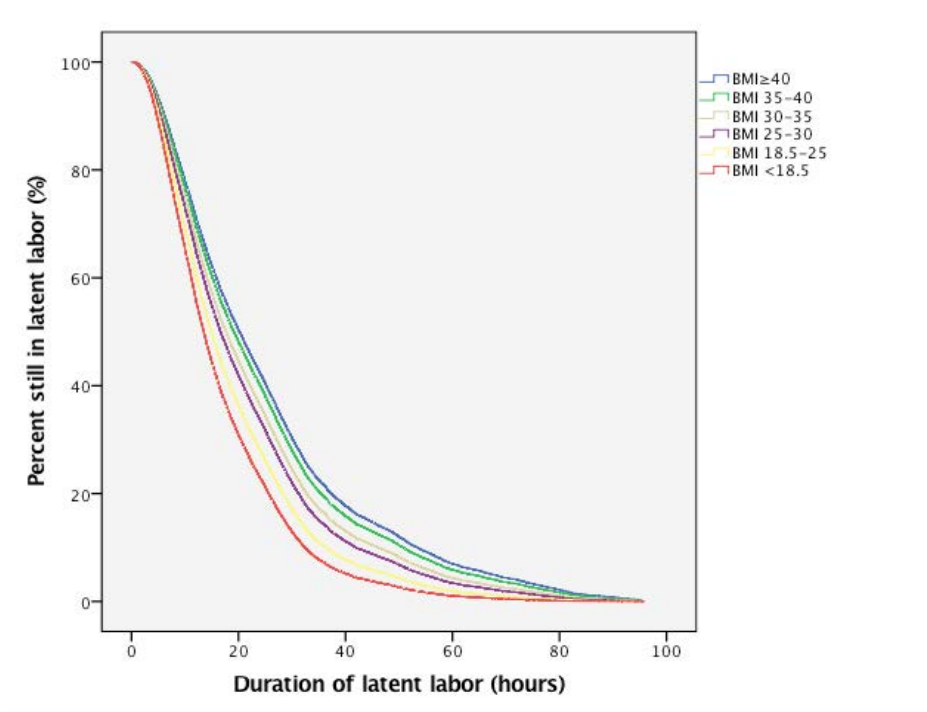


Figure 9. Survival curves illustrating time in latent labor in nulliparous women with IOL in relation to maternal early pregnancy BMI. Latent labor was defined as the time from admission for IOL until the start of active labor. Event was defined as entering active labor. Adjustments were made for birth weight and GWG. P for difference between BMI-groups <0.001.

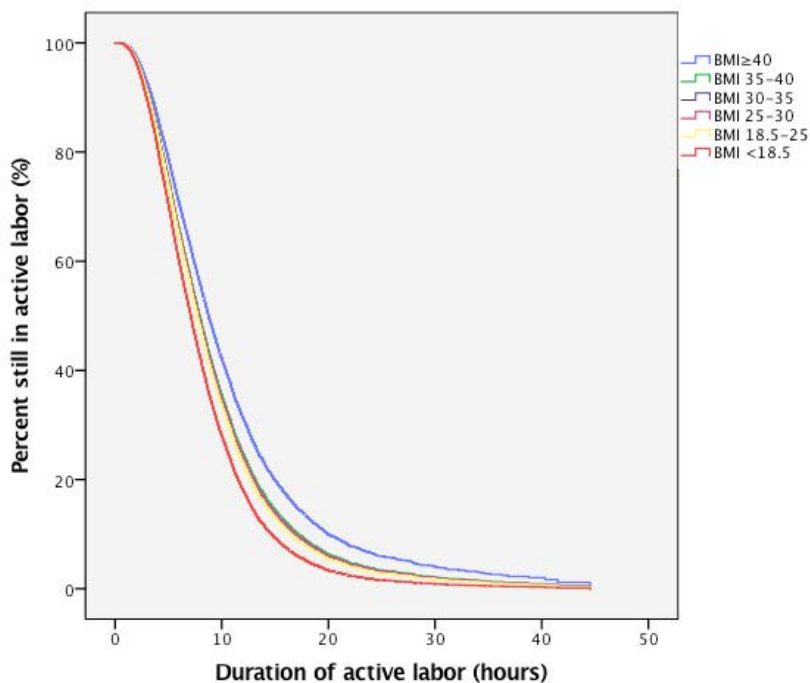


Figure 10. Survival curves illustrating time in active labor in nulliparous women with IOL in relation to maternal early pregnancy BMI. Active labor was defined from the onset of regular painful contractions and cervical dilatation ≥ 3 cm until the time of delivery. Event was defined as delivery. Women were censored at the time of CS. Adjustments were made for maternal age, birth weight, GWG and smoking in early pregnancy. P for difference between BMI-groups < 0.001 .

MATERNAL AND LABOR CHARACTERISTICS, MODE OF DELIVERY AND BODY MASS INDEX (studies I and II)

The prevalence of obesity in the study population in **studies I and II** differed. In the study population in **study I**, conducted between 1995 and 2009, the prevalence of overweight was 21.7% and 7.7 % were obese, compared to 26.5% with overweight and 15.6 % with obesity in **study II**, conducted between 2014 and 2017. The mothers were older in **study II**; 15.9% of women were older than 35 years compared to 7.9% in **study I**. Birth weight increased with BMI in both studies. The rate of infants with a birth weight ≥ 4500 g was higher in **study II** (4.2%) than in **study I** (2.2%).

In **study I**, oxytocin for augmentation was administered to 45.0% of normal weight women and 55.1% of women in obesity class III ($p < 0.001$). The reported rate of oxytocin usage in induced labor in **study II** was similar in normal weight and obese women (Figure 11).

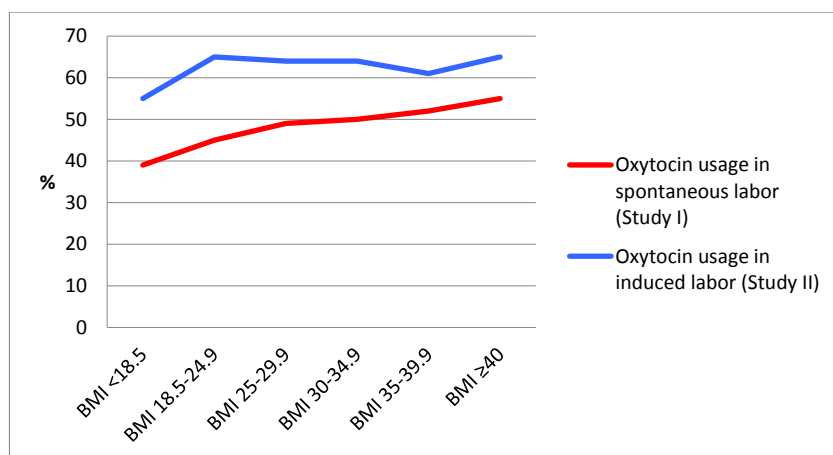


Figure 11. The reported rates of oxytocin usage in the different BMI categories in study I and study II.

The prevalence of CS in the population of women with a spontaneous onset of labor was 6.0% (**study I**) compared with 15.5% in the population of women with IOL (**study II**). The CS rates during the active phase of labor successively increased with BMI in nulliparous women with a spontaneous onset of labor (**study I**) and women with induced labor (**study II**) and, in general, were higher in women with induced labors. In **study I**, the CS rate was 5.1% in normal weight women compared to 15.6% in women in obesi-

ty class III ($p < 0.001$). In **study II**, the CS rate significantly increased from 7.4 % in underweight women (13.5% in normal weight women) to 22.0 % in women in obesity class III ($p < 0.001$). In **study II**, the rate of operative vaginal delivery was lower in all obesity classes compared to normal weight women with IOL (p for homogeneity < 0.001). This trend was not identified in women with spontaneous labor (**study I**). Figures 12 and 13 illustrate the mode of delivery in the different populations in **studies I and II**.

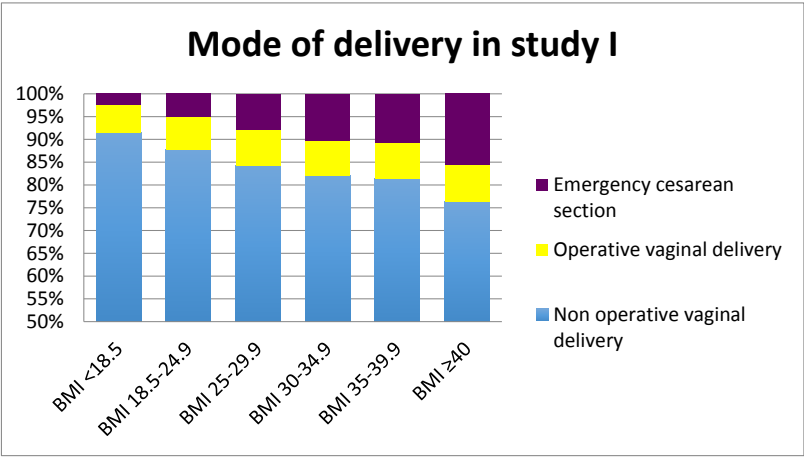


Figure 12. Mode of delivery in women with spontaneous onset of labor.

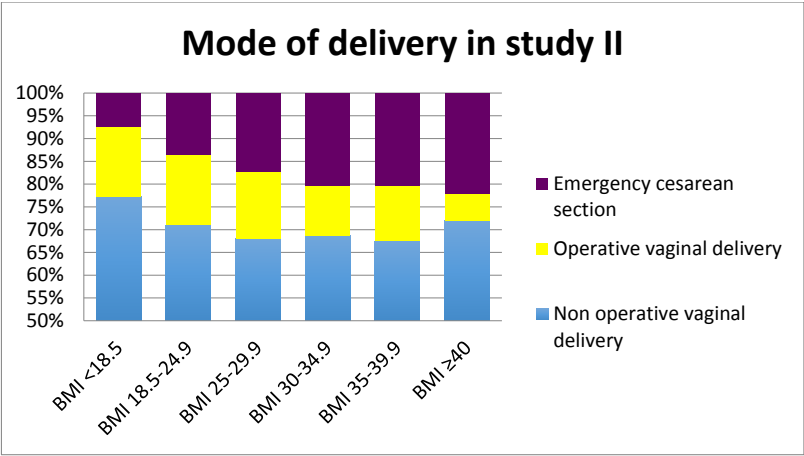


Figure 13. Mode of delivery in women with induced labor.

MATERNAL LEPTIN LEVELS IN OBESE WOMEN (study III)

Main findings

The mean maternal plasma leptin concentrations during and after pregnancy appear to be associated with the degree of maternal obesity but not with the degree of GWG. In the study population of 343 women with early pregnancy obesity, the mean maternal leptin levels were significantly higher during and after pregnancy in women with obesity class III than women with obesity class I. No major differences in the maternal leptin levels were identified during or after pregnancy between the obese women when they were classified into groups according to the degree of GWG based on the recommendations from the IOM (Table 2).

Maternal characteristics and classification

The study population was classified according to the degree of obesity classes I-III (n=343), and the degree of GWG during pregnancy based on the recommendations of the American IOM for obese pregnant women i.e., below, recommended or above recommendations (n=304) (Figure 14). The mean GWG was significantly lower in women with obesity class III (7.7 kg) than classes I (10.6 kg) and II (9.6 kg). The prevalence of PE increased with a higher obesity class, with 5.4% in obesity class I compared to 18.6 % in obesity class III. The rate of GDM did not differ between obesity classes I-III.

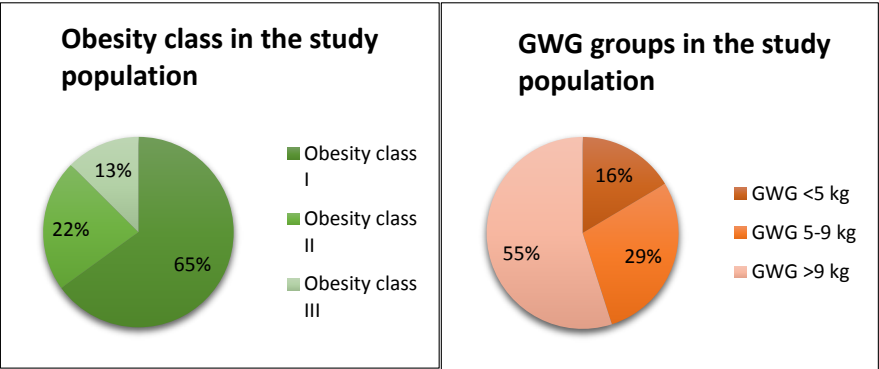


Figure 14. Classification of the study population in study III

Leptin levels

Maternal plasma leptin was measured in gestational week 15 (n=340), gestational week 29 (n=331) and 10 weeks postpartum (n=295). There was no significant correlation between the gestational week when the maternal plasma sampling was performed and the value of leptin within each time-period of leptin measurement. No significant interaction between maternal BMI and GWG was identified. Figure 15 demonstrates the mean plasma leptin values in the different obesity classes. The differences in the mean value were significant between all categories with the exception of women with obesity classes I and II in gestational week 29 and classes II and III postpartum. Figure 16 demonstrates the mean plasma leptin values in the different GWG classes. The degree of GWG in obese women did not have a significant effect on the mean plasma leptin values with the exception of gestational week 29 when obese women with a weight gain above recommendations (>9 kg) had significantly higher values than women with the recommended GWG (5-9 kg).

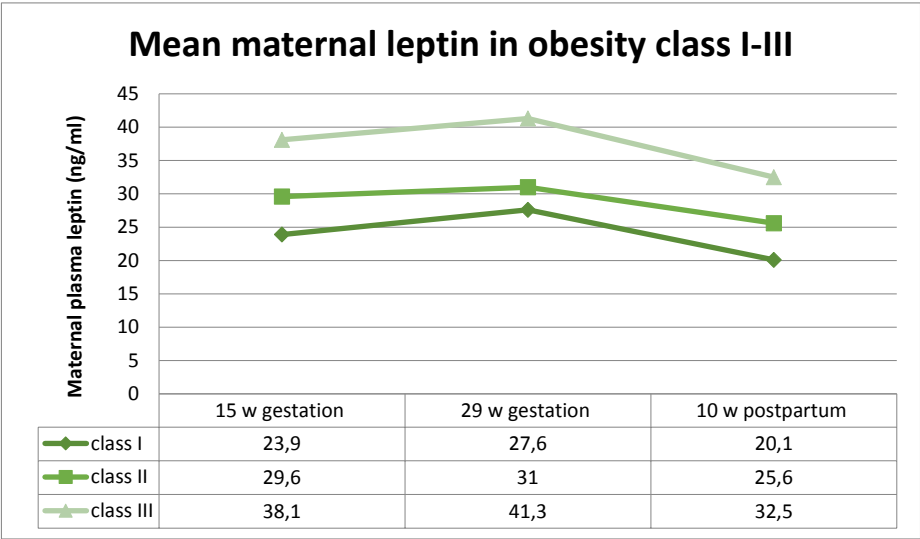


Figure 15. Mean maternal plasma leptin (ng/ml) during and after pregnancy in obesity classes I-III. (w = weeks)

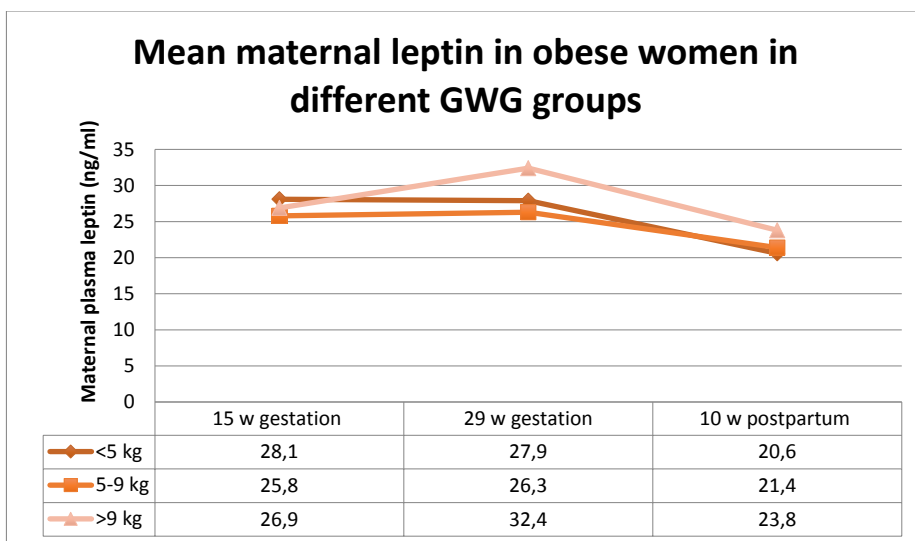


Figure 16. Mean maternal plasma leptin (ng/ml) during and after pregnancy in obese women classified according to degree of GWG. (w = weeks)

MATERNAL LEPTIN AND DURATION OF LABOR (study IV)

Main findings

In this study of 914 women, we did not identify a statistically significant association between the maternal plasma leptin levels measured in active labor and the duration of the active phase of labor. Positive associations between increasing maternal leptin levels and a longer time in the active phase of labor in the total study population and women with a spontaneous onset of labor (n=766) were identified in the unadjusted analyses. In the unadjusted analyses, a one ng/ml increase in maternal plasma leptin was associated with a 0.015 hour increase in the duration of the active phase of labor ($p < 0.007$) in the total study population. In women with a BMI ≥ 35 , the median leptin value was 50 mg/ml, which would indicate that the time in the active phase of labor increased with 0.75 hours. This association was not statistically significant when adjusted for confounding factors or when nulliparous and multiparous women were analyzed separately.

Maternal characteristics and leptin levels

The prevalence of obesity was low in the study population; 6.7% of women were obesity class I, and 2.1% of women had an early pregnancy BMI ≥ 35 . Moreover 2.1 % of women were diagnosed with PE, and 1.3% of women were diagnosed with GDM. As all women with an unknown start of active labor and start of the pushing phase were excluded (67 women), women with CS during the active phase of labor were thus excluded. Moreover, 72% of women had information on GWG and these women were categorized in three classes of GWG, i.e., below recommended, recommended or excessive weight gain, based on the IOM guidelines on weight gain during pregnancy, in relation to pre-pregnancy BMI (Table 2).

The median leptin values were higher with increasing BMI class (20.2 ng/ml in normal weight compared to 50.0 ng/ml in women with a BMI ≥ 35). The median leptin value was also higher with an increasing degree of GWG. Women with a GWG below the recommendation had a mean leptin of 16.4 ng/ml compared to 33.0 ng/ml in women with a GWG above the recommendations. Women with PE or GDM had a higher leptin value than their counterparts.

Maternal leptin, duration of labor and maternal BMI

The association among maternal leptin, time in labor and maternal BMI was analyzed with a Kaplan-Meier analysis. The study population was categorized in four groups based on the maternal BMI and mean leptin levels. Two groups included normal weight and underweight women with mean leptin levels above (≥ 37 ng/ml) or below (< 37 ng/ml) the third quartile and two groups included overweight and obese women with mean leptin levels above (≥ 37 ng/ml) or below (< 37 ng/ml) the third quartile. The relationship between the groups and the time in labor is presented in Figure 17. This Kaplan-Meier graph, illustrates the cumulative chance to end the active phase of labor at a certain time point by the maternal BMI category and leptin value in active labor. There was no overall statistically significant difference between the groups ($p=0.296$). However, the figure indicates a difference between the groups after a 10 hours duration of labor when normal weight/underweight women with lower leptin levels (below the third quartile/ <37 ng/ml) had a greater chance to end the active phase of labor at a given time point than overweight/obese women with high leptin levels (≥ 37 ng/ml).

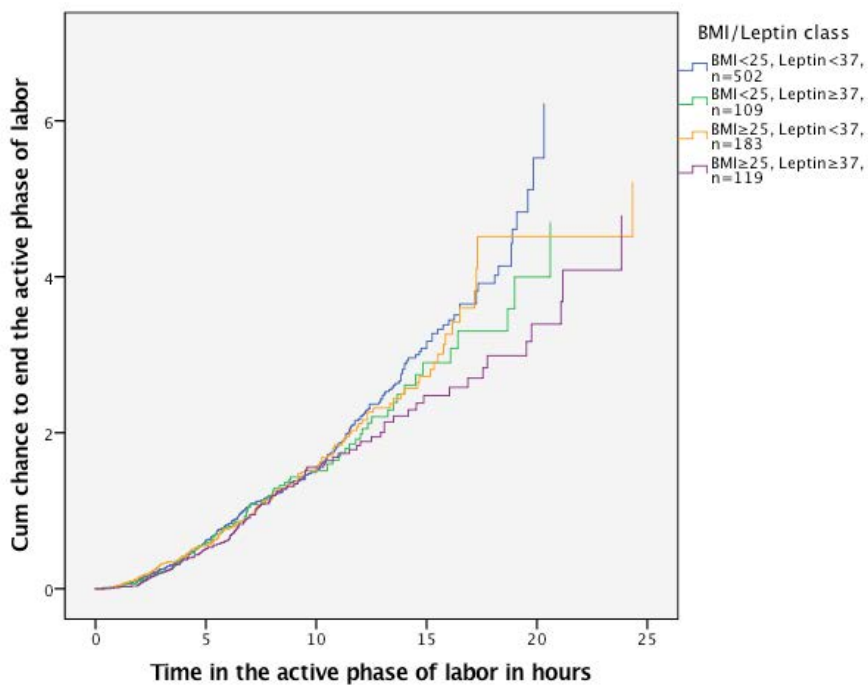


Figure 17. Kaplan Meier graph illustrating the association between leptin levels, maternal BMI and duration of labor (P for difference between groups = 0.296).

DISCUSSION

METHODOLOGICAL DISCUSSION

All four studies included in this thesis are designed as observational cohort studies. This type of **study design** evaluates the association between an exposure and specific outcomes. The use of previously collected data accessible in registers in observational studies may be an alternative to reduce the risk of associated disadvantages with this study design, such as a long study duration and substantial costs. All data obtained in the studies included in this thesis are prospectively collected in the PRS register, Swedish Pregnancy Register or in EMR/Obstetrix®. The large sizes of the study cohorts in **study I** and **study II** enabled us to restrict our analyses to nulliparous women and to evaluate the time in labor according to six maternal BMI classes, including three obesity classes. A major disadvantage when using previously collected data in registers is that the information on exposures and outcomes is limited to the information that is available in the registers. In **studies I, II** and **IV** we defined the different phases of labor according to the available time estimates on labor in the PRS register, Swedish Pregnancy Register and EMR/Obstetrix®. We initially aimed to analyze the active phase of labor in **study II**, defined as in **study IV**. However, during the analyses, we discovered that the variable “start of pushing contractions” was incorrect and was not usable in the Swedish Pregnancy Register. This issue may be a result of an error in the data extraction programme to this new register.

In observational cohort studies, the **internal validity**, i.e., the degree to which the results of a study are correct for the specific study patients included, is affected by **systematic errors** (bias) and random errors (chance). Large study populations reduce the risk of random errors; however systematic errors (bias) are not affected by sample size. There are three types of bias that are always present to some degree in observational studies: selection bias, information bias and confounding bias (100).

Selection bias occurs when comparisons are performed between groups that differ in other ways than the outcome of the study, if these factors also affect the outcome. In **studies I, II** and **IV**, when labor duration was the main outcome, we attempted to reduce the risk of selection bias by restricting the inclusion criteria to nulliparous women, because the active phase of

labor is shorter in multiparous women (30). Furthermore, we chose to independently investigate labor that started spontaneously and inductions in **studies I and II**, because it has been demonstrated that duration and progress differ between spontaneous and induced labors (72, 73). We decided to include women with emergency CS in **studies I and II** but not in **study IV**. This decision was related to the exposure. As the exposure was maternal BMI in **studies I and II** and it is well established that the CS rate increases with an increasing BMI, the exclusion of CS deliveries could have resulted in a selection bias if many of the CSs were performed after a long trial of labor. In **study IV**, the time in labor was not related to maternal BMI and was considered a clinical proxy for myometrial contractility. If emergency CSs were included and most CSs were performed as a result of fetal distress this could have introduced a selection bias. Moreover, if most CSs were performed due to dystocia/no progress, their exclusion may have also caused a selection bias. There was no information on the indication for CS; thus, we chose to include only those who had information on and reached the second stage. Furthermore, in **study IV**, the study population was restricted to women who agreed to participate in GRABB and may not be representative of the total population. The fact that few obese women were included may be a source of selection bias, if the exposure (the maternal leptin-value) causes a dose-response related effect on the time in labor because the obese women had high mean leptin values.

Information/Misclassification bias occurs when information used in a study is measured or recorded inaccurately. The data obtained from the registers or medical records were prospectively recorded, thus diminishing the risk of recall bias. In large registers there is always a risk of underreporting variables. One example is the registration of oxytocin for induction/augmentation in the Swedish Pregnancy Register (**study II**). The use of oxytocin is either automatically transferred from the partogram or manually registered. There is no reason to suspect that the degree of underreporting varies over the BMI classes. Information bias may result from misreporting by study participants. In **study I**, we used self-reported pre-pregnancy or measured early pregnancy BMI. Although previous studies have shown that self-reported BMI is reliable, (101, 102) it may be a potential source of bias. The self-reported pre-pregnancy BMI or early pregnancy BMI employed in **studies I-IV** is preferred to maternal BMI based on weight at delivery. The use of maternal BMI at delivery may cause a misclassification bias as most obesity related risks are related to pre-/early pregnancy BMI. Later in pregnancy, not only the maternal fat mass but also the amount of GWG, birth weight, placental weight and amniotic fluid will contribute to affect maternal BMI. In **studies I, II and IV**, the estimations of the parameters that underlie how the labor phases are defined are based

on subjective measurements and are therefore not uniform across the study population. However, in large study populations, the variation of the estimation is not likely related to the outcome and the risk of a differential misclassification between the BMI-groups or that the variation should be related to the maternal leptin value is likely low. The use of time at admission for IOL as a proxy for the actual start of induction in **study II** is a limitation that may have led to a differential misclassification of the start of latent labor according to maternal BMI. The time difference from admission to the start of induction is not likely related to maternal BMI for most women. However, some women may have been admitted because of a pregnancy complication and observed for a period of time before IOL started. As obese women are at a higher risk for pregnancy complications, such as PE and GDM, which may lead to IOL, there is a risk that this possible misclassification was related to maternal BMI. In an attempt to reduce this risk, women with time estimates that were considered to be incorrect (time from admission until the start of active labor < 30 minutes or > 96 hours) were excluded. Information bias may also occur in objective measurements, such as the leptin analyses. To reduce this risk in **studies III** and **IV**, one trained individual performed the analyses with standardized methods in the same laboratory.

Confounding bias occurs when there is a failure to adjust for common causes of both the exposure and the outcome. A confounder is not on the causal pathway between the exposure and the outcome; thus in this case it is an intermediate variable, which should not be adjusted for in analyses. Adjusting for factors that are not confounders may introduce bias instead of removing it (103). True and known confounders should be controlled for in analyses. In **studies I** and **II**, the study population was restricted to nulliparous women to rule out the effect of parity. Maternal age and birth weight were regarded as confounders in these two studies. In **study I** we did not adjust for other factors, as they were regarded as intermediate variables. In **study II**, we analyzed each possible confounder, and only the variables that had some association with the outcome were included in the final multivariable regression analyses and cox regression analyses. In **study III**, possible confounders were analyzed with regression analyses; however, no significant interactions were found and no factors were included as confounders in the final analyses. In **study IV**, the study population was stratified into subgroups to eliminate the potential confounding effect of parity and induction. In this study, it was more difficult to determine which variables were true confounders because there was no previous study to compare with and the knowledge on labor and birth related factors in relation to maternal leptin is limited. The final multivariable regression model included

only the factors that had an association with the duration of labor in the univariate and full multivariable model.

External validity is the degree to which the results may be applied to other individuals and settings, i.e., the generalizability of the study. As **study I** and **study II** are large cohorts, the results from these studies are generalizable to the Swedish population or similar populations and settings. The results are not generalizable to other populations and countries that have different definitions for the start of the active phase of labor and where the clinical management of laboring women to promote a spontaneous vaginal delivery may differ. Furthermore, when specifically analyzing the effect of maternal BMI, the substantial variations in the prevalence of obesity worldwide must be taken into account as this may limit the possibility to generalize the results of different studies to different populations. The low prevalence of obese women in the study population in **study IV** may explain why BMI was not associated with the duration of labor as in **studies I and II** and may have caused a biased sample that influenced the internal and external validity. The results of **study III** describe leptin levels in a demarcated group. This knowledge may provide information when investigating obese pregnant women in other settings.

Random errors are caused by variations in the data as a result of chance. Statistics may be used to estimate the extent to which chance accounts for the results in a study, i.e., significance testing. The role of random error may be presented as a p-value. In **studies I-IV**, a p-value of 0.05 was set as the significance level. This indicates the probability that the null hypothesis is true. If the p-value is low (<0.05), the null hypothesis may be rejected. However, a low p-value does not indicate that the difference is of clinical importance. In large cohorts, such as in **studies I and II**, even small differences may be statistically significant but without clinical importance. The risk of random errors in cohort studies are reduced with large study cohorts and with dose-response associations between the exposure and the outcome, such as in **studies I and II**.

DISCUSSION OF FINDINGS IN STUDIES I-IV AND CLINICAL IMPLICATIONS

Spontaneous onset of labor

The study population in **study I** is one of the largest cohorts of nulliparous women with a spontaneous onset of labor in which the duration of labor has

been analyzed. It is of substantial importance to understand the course of labor in this defined group because they constitute a substantial part of all laboring women. If a CS may be avoided among these women, the chances are great that their following deliveries will be normal and uncomplicated. The results of previous studies that demonstrated the time in labor increases with maternal BMI are difficult to compare because of the different definitions of maternal obesity and active labor employed and the inclusion of mixed parities with both spontaneous and induced labor onset (45, 49-51, 104). However, the results from our study support previous findings that the time in active labor significantly increases with maternal BMI. We determined that the duration of the pushing phase significantly decreased with an increasing maternal BMI. Although the difference in the duration of the pushing phase between obese and normal weight women was not of clinical importance, (6 minutes difference in the median value), it indicates that the prolongation of labor progression in obese women was restricted to the active phase of labor. The question of whether the statistically significant difference in the mean duration of active labor between the BMI groups is clinically meaningful may also be considered. The largest difference in the mean values was identified between underweight (8.2 h) and morbidly obese women (9.8 h), whereas the differences in the mean duration between other BMI classes were less. However, there were substantial variations within each BMI category. A similar time difference of mean duration between BMI classes was identified in a large American multicenter study (45). The main conclusion from **study I** is that obese women, particularly morbidly obese women, have a statistically and clinically significant increased risk for a longer duration of active labor compared to normal weight women. The general recommendations for diagnosing labor arrest are not defined according to BMI class. If obese women are allowed to be in active spontaneous labor for a longer time than the general recommendations, it may increase their chance to avoid a CS, which causes a major impact on future pregnancy outcomes.

Induced labor

Among previous research that addressed the specific impact of maternal BMI on labor progression, limited studies have been restricted to induced labors in nulliparous women and most studies are based on maternal BMI at labor admission (45, 59, 67, 68). We identified only one study that compared the latent and active phases of induced labor in relation to maternal early pregnancy BMI (71). The results from **study II** contribute knowledge regarding the duration of induced labor, both latent and active labor, in nulliparous women with respect to their early pregnancy BMI. As most women are risk-classified according to their early pregnancy BMI, this study provides important information from a national cohort where few women

had an unknown BMI in early pregnancy (4.6% of all nulliparous term women with IOL). The duration of induced labor increases with a higher maternal early pregnancy BMI. However, the survival curves that illustrated the duration of active labor were not visually different between normal weight, overweight and obesity classes I and II, in contrast to the survival curves from latent labor when the duration successively increased with BMI class. This finding is in contrast to the previous mentioned study that analyzed latent labor, in which no association was identified with maternal BMI; however, different definitions of the labor phases were employed (71). Our results on latent labor must be considered in light of the factors that may have biased the results. The use of the time at admission instead of the actual time when the induction started may have falsely prolonged the latent phase for some women who may have been observed after admission and before the initiation of the induction method. Furthermore, we were not able to adjust for cervical ripeness and we excluded women with CSs during the latent phase. As obese women, to a larger extent, have pregnancy complications that may lead to observation before IOL, more often have an unfavorable bishop score at induction and may be at a higher risk for a CS during the latent phase (7, 105), it is possible that the assessment of latent labor duration in obese women was biased. When interpreting the results and considering the limitations, there are two groups that stand out from the rest. The results on these groups constitute one of the most important messages from this study. First, women with morbid obesity (class III) constitute a risk group with longer durations of both the latent phase and active labor, with the highest rate of oxytocin and EDA usage and the highest risk for a cesarean delivery during active labor. Second, underweight women have substantially less risks than other BMI classes. They had shorter labor durations (latent and active labor), the lowest rate of EDA and oxytocin usage, the lowest rate of CS and the highest rate of normal vaginal delivery. This information is important to take into account when the pros and cons are considered in the clinical decision of whether a labor should be induced or not.

Mode of delivery related to BMI

The mode of delivery in relation to maternal BMI differs in the large cohorts analyzed in **studies I and II**. This finding is partially a result of the different nature of the study populations, i.e., spontaneous labor onset vs. IOL. It is shown that women with IOL have a greater risk for a cesarean delivery than women with a spontaneous onset of labor (OR 2.54-3.06 for CS in induced labor compared to spontaneous onset) (62, 63). This finding explains the different prevalence of CSs between the cohorts (6.0% vs. 15.5%, respectively). However, when considering women with a BMI ≥ 40 with the highest CS rates, the difference between spontaneous and induced

labor may not be as substantial as expected (15.6% vs. 22.0%, respectively). The time difference between when the studies were conducted may explain the lower difference in the CS rate in obese women. During this time span, the general knowledge of obesity related complications in pregnant women had increased. This knowledge may have led to obese women being handled in a better way to reduce the risk of CS in this group. This may also be reflected in the prevalence of normal vaginal delivery in morbidly obese women, which is approximately the same in the different cohorts (76.4% in spontaneous labor vs. 72.0% in induced labors). When comparing the CS prevalence in **study II** with the results from older studies on nulliparous women with IOL, the total CS rate in our study is approximately half the size (48, 64, 70). In **study I**, the CS rate increased proportionally with an increasing BMI, which reflected the same pattern as the labor duration in relation to BMI. This was not identified in **study II**, where the CS rate did not reflect the pattern of active labor duration in relation to BMI, which may indicate that there are other factors than a prolonged labor duration in induced women that contribute to the higher rate of CS in overweight and obese women.

Leptin in obese women

Previous studies indicate that leptin levels in overweight and obese women are elevated during pregnancy compared to normal weight women (81, 84). It has also been shown that the rate at which leptin levels increase across gestation is lower for obese/overweight women (85, 86) than normal weight women. Misra et al determined that these different patterns in leptin increase could not be fully explained by the lower GWG in overweight/obese women because the change in leptin/kg body weight increased in normal weight but decreased in overweight/obese women, which suggests that factors other than GWG could influence leptin levels during pregnancy (85). To our knowledge **study III** is the first investigation to describe leptin levels during and after pregnancy in different obesity classes and contributes new knowledge on leptin profiles in obese pregnant women. Women with obesity class III had significantly higher mean leptin values at each leptin measurements than women with obesity class I. As no significant interaction effect was identified between BMI and GWG, these parameters were not included as confounders in the analyses. When the mean leptin values were analyzed according to the degree of GWG, no significant changes were identified. To evaluate the full effect of GWG, a leptin measurement in late pregnancy would have been valuable. However, in this study it appears that leptin levels in obese women during and after pregnancy are associated with pre-pregnancy BMI but not the degree of GWG.

In the study population, the prevalence of PE significantly increased with the degree of obesity. It has previously been shown that obesity associated pregnancy complications, such as PE and GDM, are associated with increasing maternal leptin levels, as well as an increasing degree of obesity (80, 89). If leptin is involved in the step-wise increased risk for several adverse outcomes, including a prolonged time in labor, with each increase in obesity class the leptin levels should reflect this increased risk. Our results contribute to knowledge regarding this issue by demonstrating significant differences in leptin levels between the maternal obesity classes.

Leptin and duration of labor

The results from **study IV** contribute new knowledge on an issue that has previously only has been analyzed in *in vitro* settings. This investigation is the first study to analyze the association between maternal leptin levels measured in active labor and the duration of the active phase of labor. We hypothesized that high leptin levels would correlate with a longer labor duration based on findings from *in vitro* studies. A reduced frequency and amplitude of contractions in myometrium from obese women compared to myometrium from normal weight women have been demonstrated *in vitro* (55). It has also been shown that leptin has an *in vitro* cumulative inhibitory effect on human myometrial contractions (spontaneous and oxytocin induced) (92, 94). The combination of these *in vitro* findings, the high leptin levels identified in obese pregnant women and the increased risk for a prolonged duration of labor led to our hypothesis. However, in our study-population, we did not identify a statistically significant association in the adjusted analyses between leptin levels and the duration of the active phase of labor. Our initial attempt was to investigate the effect of leptin on labor duration without classifying the study population based on maternal BMI. If leptin *in vivo* exhibits a similar dose-response effect on myometrial contractility as *in vitro*, it may not be possible to demonstrate this putative effect of leptin in a study population that includes a limited number of obese women. The results from this study should be considered a first attempt to investigate the clinical effect of leptin on myometrial contractility and encourage future studies to assess this effect in obese women compared to normal weight women.

CONCLUSIONS

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

- The duration of active labor significantly increases with an increasing maternal pre-pregnancy BMI in nulliparous women with a spontaneous start of labor. The duration of the pushing phase, defined as the second stage, is inversely associated with maternal BMI, which indicates that the prolonged time in active labor in obese women is restricted to the active phase of first stage labor.
- In nulliparous women with IOL, the duration of active labor increases with maternal BMI, and the difference is most pronounced between underweight and morbidly obese (BMI ≥ 40) women. The duration of the latent phase of induced labor successively increases with maternal early pregnancy BMI.
- Maternal plasma leptin levels in obese women are associated with the degree of maternal obesity but not with the degree of GWG based on the IOM's guidelines for obese women. The plasma leptin levels are higher in early and mid pregnancy and postpartum in women with obesity class III than women with obesity class I.
- In a study population that includes a limited number of obese women, maternal leptin levels measured in active labor are not associated with the duration of the active phase of labor when adjusting for possible confounders. If leptin *in vivo* displays a similar dose-response effect on myometrial contractility as demonstrated in *in vitro* studies, a larger proportion of the study population may need to be obese to demonstrate this conceivable effect.

FUTURE PERSPECTIVES

- To evaluate the labor curves that are used for the clinical assessment of labor progression and consider adapting them for maternal BMI.
- To explore the effect of maternal leptin levels on the duration of labor in obese women.
- To explore the role of oxytocin on labor progression in obese and normal weight women.
- To estimate the total dosage of administered oxytocin over the BMI groups.
- To measure the maternal oxytocin serum levels in relation to the total dosage of oxytocin administered during labor in different maternal BMI classes.
- To investigate the *in vitro* effects of leptin and oxytocin on human myometrial biopsies obtained after vaginal delivery.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Andelen gravida kvinnor med fetma ökar i Sverige liksom i resten av världen. I dag har ca 40 % av alla gravida i Sverige övervikt eller fetma. Fetma innebär att man har ett body mass index (BMI kg/m^2) ≥ 30 och brukar klassificeras i tre svårighetsgrader efter ökande BMI (klass I = BMI 30-35, klass II = BMI 35-40 och klass III = BMI > 40). Att ha fetma och vara gravid innebär högre risker för både mamman och barnet. I de flesta fall ökar riskerna med stigande fetma grad. Riskerna för mamman inkluderar sjukdomar under graviditet, t ex havandeskapsförgiftning och graviditetsdiabetes. Flera av de förlossningsrelaterade riskerna verkar orsakade av en försämrad förmåga i livmodermuskulaturen att dra ihop sig. Kvinnor med fetma har till exempel en ökad risk att bli överburna d.v.s. att värkarbetet inte startar av sig själv och behöver få medicinsk hjälp med att sätta igång förlossningen. Detta kallas induktion av förlossning och har blivit en mycket vanlig åtgärd i dagens förlossningsvård. Kvinnor med högt BMI har en ökad risk att bli igångsatta men också en ökad risk att igångsättningen misslyckas och leder till ett akut kejsarsnitt. Tidigare studier har även visat att kvinnor med fetma verkar ha ett försämrat värkarbete och att de kräver värkstimulerande medicin i högre utsträckning än normalviktiga kvinnor. Detta bidrar också till den högre frekvensen av kejsarsnitt i denna grupp. Risken att förlösas med kejsarsnitt ökar med stigande BMI och innebär dels risker relaterade till operationen men framförallt för kommande graviditeter och förlossningar. Dagens riktlinjer för vad som är normal tid i förlossningsarbete är samma oavsett om man är normalviktig eller har fetma. Det är viktigt att veta om kvinnor med fetma har en ökad förlossningstid för att omhändertagandet på förlossningsavdelningarna ska bli bra och för att de inte ska utsättas för kejsarsnitt i onödan.

Mekanismen bakom teorin att livmodermuskulaturen fungerar sämre hos kvinnor med fetma är inte klarlagd. Studier på laboratoriet har visat att muskelfibrer från livmodern hos kvinnor med fetma drar ihop sig sämre. I laboratoriemiljö har man även studerat ett hormon, leptin, och visat att det minskar styrka och frekvens av sammandragningarna i muskelfibrer från livmodern. Detta hormon bildas av fettvävnaden och finns i ökad mängd i blodet hos personer med fetma. Under graviditet bildar även moderkakan detta hormon. Gravida kvinnor med fetma har dock högre halter än normalviktiga gravida kvinnor. Höga halter av leptin är förknippat med fetma

relaterade sjukdomar under graviditet som havandeskapsförgiftning och graviditetsdiabetes.

Det övergripande syftet med denna avhandling var att utvärdera förlossningstiden i relation till mammans BMI och undersöka den kliniska betydelsen av mammans leptinhalt under förlossningen.

I avhandlingens första delarbete undersökte vi om förlossningstiden skiljer sig mellan normalviktiga förstföderskor och de med högt BMI som har spontan start av förlossningen. Vi använde data från graviditetsdatabasen Perinatal Revision Syd och fann bland 63,829 förstföderskor en signifikant längre förlossningstid hos kvinnor med högt BMI jämfört med normalviktiga kvinnor (BMI 18.5-25). Vi undersökte då också hur länge man krystade och fann att krystningstiden är kortare hos kvinnor med fetma än hos normalviktiga.

I den andra delstudien undersökte vi om förlossningstiden hos förstföderskor med igångsatt förlossning skiljer sig mellan normalviktiga kvinnor och kvinnor med fetma. Vi använde i detta arbete data från det nationella svenska graviditesregistret och fann bland 15,259 igångsatta förstföderskor att förlossningstiden är signifikant längre hos kvinnor med sjuklig fetma (klass III, BMI ≥ 40) jämfört med normalviktiga. Vi studerade två olika faser av förlossningen, dels den första förberedande latensfasen och dels den aktiva fasen. Det visade sig att mammans BMI verkar ha större effekt på tiden i latensfas som ökade med stigande BMI klass. Skillnaderna mellan BMI grupperna var inte lika tydliga i den aktiva fasen.

I avhandlingens tredje delarbete studerade vi 343 kvinnor med fetma. Vi ville undersöka om det var någon skillnad i kvinnans leptinhalt i blodet under graviditet och efter förlossningen mellan de tre fetmaklasserna. I denna studie använde vi oss av sparade blodprover från en tidigare studie på gravida kvinnor med fetma. Mammans leptinhalt var signifikant högre i fetmaklass III jämfört med fetmaklass I vid alla mättillfällena. Vi fann dock inget samband mellan leptinhalt och viktuppgång under graviditeten hos dessa kvinnor.

I den fjärde delstudien mätte vi mammans leptinhalt i blodet vid starten av förlossningsarbetet på 914 kvinnor. Därefter undersökte vi om det fanns ett samband mellan mammans leptinhalt och tiden i förlossningsarbete. De första analyserna visade att förlossningstiden ökade med mammans leptinhalt, men sambandet var inte längre signifikant när vi justerade för ett antal störfaktorer. Möjligen krävs det en större andel kvinnor med högt BMI (som har höga leptinhalter) än vad vi hade i vår studie för att visa om högre halter av leptin hämmar livmodermuskulaturens sammandragningar ännu mer.

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PAPER I



Maternal body mass index and duration of labor



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ABSTRACT

Objective: To evaluate whether the duration of the active phase of labor is associated with maternal body mass index (BMI), in nulliparous women with spontaneous onset of labor.

Study design: Historical prospective cohort study including 63,829 nulliparous women with a singleton pregnancy and a spontaneous onset of labor, who delivered between January 1, 1995 and December 31, 2009. Data were collected from the Perinatal Revision South registry, a regional perinatal database in Southern Sweden. Women were categorized into six classes of BMI. Overweight and obese women were compared to normal weight women regarding duration of active labor. Adjustments were made for year of delivery, maternal age and infant birth weight.

Results: The median duration of labor was significantly longer in obese women (class I obesity (BMI 30–34.9) = 9.1 h, class II obesity (BMI 35–39.9) = 9.2 h and class III obesity (BMI > 40) = 9.8 h) compared to normal-weight women (BMI 18.5–24.9) = 8.8 h ($p < 0.001$). The risk of labor lasting more than 12 h increased with increasing maternal BMI: OR 1.04 (1.01–1.06) (OR per 5-units BMI-increase). The risk of labor lasting more than 12 h or emergency cesarean section within 12 h, compared to vaginal deliveries within 12 h, increased with increasing maternal BMI. Duration of the second stage of labor was significantly shorter in obese women: in class III obesity the median value was 0.45 h compared to normal weight women, 0.55 h ($p < 0.001$).

Conclusion: In nulliparous women with a spontaneous onset of labor, duration of the active phase of labor increased significantly with increasing maternal BMI. Once obese women reach the second stage they deliver more quickly than normal weight women, which implies that the risk of prolonged labor is restricted to the first stage of labor. It is clinically important to consider the prolonged first stage of labor in obese women, for example when diagnosing first stage labor arrest, in order to optimize management of this rapidly growing at-risk group of women. Thus, it might be reasonable to adapt the considered upper limit for duration of labor, according to maternal BMI.

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1. Introduction

Obesity in pregnant women has increased dramatically during the last few decades, accompanied by a number of maternal, perinatal and neonatal complications [1,2]. In Sweden in 2009, 25% of the pregnant women in the first trimester were overweight (body mass index (BMI) 25–29.9) and 12% were obese (BMI ≥ 30) [3].

Several studies have demonstrated an increased risk of cesarean section (CS), both elective and non-elective, with increasing maternal BMI [4–7]. The reason for this increased CS rate remains

incompletely characterized. One possible explanation is dysfunctional labor in obese women due to cephalopelvic disproportion because of fetal macrosomia and increasing maternal pelvic soft tissue [8–10]. A prolonged duration of labor because of ineffective uterine contractility in obese women has also been proposed [11–13]. Both theories are based on the concept that obese women have a dysfunctional labor resulting in a prolonged duration of labor.

There are some studies investigating duration of labor in overweight and obese women [2,14–20]. Although the majority suggest that labor progression in these women is slower compared to normal weight women, some results are difficult to interpret because of small sample sizes, different definitions of maternal obesity and labor duration, and absence of a definition of accurate onset of active labor.

Accordingly, the primary aim of this study was to evaluate whether duration of the active phase of labor is associated with BMI in nulliparous women with a spontaneous onset of labor, and

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secondly to evaluate the length of the second stage of labor separately.

2. Materials and methods

Data in this historical prospective cohort study were obtained from Perinatal Revision South registry. This is a regional perinatal database in Southern Sweden instituted in 1995, based on approximately 17,600 annual births at nine obstetric units in the region. The register contains information on numerous facts regarding maternal characteristics, pregnancy, delivery and birth data, such as maternal BMI, induction of labor or spontaneous onset of labor, time of beginning of regular contractions, time of beginning of pushing efforts, time of birth, mode of delivery, birth weight, oxytocin for augmentation, etc. [21,22].

A total number of 100,096 women, whom all delivered between January 1, 1995 and December 31, 2009, were included in the study. Inclusion criteria were nulliparous singletons with spontaneous onset of labor. Exclusion criteria were non-available BMI and no information on time of start of active labor, leaving 63,829 women for analysis of duration of active stage of labor, risk of ≥ 12 h in labor and risk of labor ≥ 12 h or emergency CS within 12 h. Emergency CS is defined as CS performed after spontaneous onset of labor. Out of 63,829 women, 57,768 had additional information on time of beginning of pushing efforts. Out of these 57,768 women, 268 had emergency CS done in the second stage. The remaining 57,500 were analyzed regarding duration of the second stage of labor. The aim of this study was to evaluate time in labor overall, therefore no exclusions due to maternal medical disorders were performed.

The study-population was categorized into six classes of BMI (kg/m^2), based on the WHO definition; underweight <18.5 , normal weight 18.5–24.9, overweight 25–29.9, class I obesity 30–34.9, class II obesity 35–39.9 and class III obesity ≥ 40 [23]. In Sweden, 90% of pregnant women attend the antenatal clinic during the first trimester of their pregnancy. The pregnant women reported their pre-pregnancy weight and height at the first antenatal visit at the maternal health care center. The actual weight and height were measured, if they were unknown.

Onset of active labor was defined as regular painful uterine contractions, three to four in a 10 min period, and a cervical dilation of 3 cm or more, according to the Swedish standard practised at all obstetric units included. The degree of cervical effacement or rupture of membrane is not part of this definition. The midwife at the delivery ward recorded the time when the regular contractions started, and performed cervical examinations at least once every second hour during the first stage of labor. If regular contractions had started at home, the pregnant woman reported the time. For the purpose of this study, the second stage is defined as from the time when cervix is fully dilated and the pushing efforts start, to time of delivery. The midwife at the delivery ward registered the time when the pushing efforts started and time of delivery.

Regarding oxytocin requirement for augmentation, the midwife may decide to initiate this treatment if certain criteria are fulfilled, including normal cardiotocography (CTG), unchanged cervical dilatation 1 h after amniotomy or arrest in cervical dilatation for 2 h with ruptured membranes. The midwife may increase the infusion dosage until a defined maximum value. Further increase of oxytocin infusion could only be prescribed by the obstetrician. In Sweden, oxytocin infusion is administered similarly to all women, with a maximum dosage, regardless of weight.

Overweight and obese women were compared to normal weight women regarding time of active labor. Primary outcome was duration of the active phase of labor, risk of labor ≥ 12 h and risk of labor ≥ 12 h or emergency CS. Secondary outcome was

duration of the second stage of labor. Year of delivery, maternal age, and infant birth weight were regarded as confounding factors and were included as covariates in the adjusted analyses (all entered as continuous, linear variables). Shapiro–Wilk tests were performed to check for Gaussian distribution of the outcome parameters (duration of the active phase of labor, and duration of the second stage of labor, respectively). The overall differences in duration (both outcomes) between the BMI categories were evaluated using the Kruskal–Wallis non-parametric test. Analyses of covariance were used to compare mean second stage duration, logarithmic scale, over BMI strata adjusting for maternal age and birth weight (entered as linear, continuous variables). Multiple logistic regression analyses were used to study the association between BMI and binary outcomes (time in labor ≥ 12 h, and the composite outcome: either CS or labor ≥ 12 h, respectively). A Kaplan–Meier analysis was performed, and a graph was produced in order to illustrate the association between BMI and time in labor, taking censoring due to CS into account. A p -value <0.05 was considered statistically significant.

The Local Ethics Committee and the Institutional Review Board at the Faculty of Health Sciences, University of Linköping approved the study.

3. Results

In the study population, 21.7% of the women were overweight and 7.7% were obese (5.6% class I, 1.5% class II, 0.5% class III). Emergency CS was performed on 6% of the women and 7.3% had an instrumental delivery. A birth weight of more than 4000 g was registered in 14.2% of the children and 2.2% had a birth weight of more than 4500 g.

Maternal age, mode of delivery, usage of oxytocin and birth weight over the BMI strata are presented in Table 1. Oxytocin for augmentation was administered to 45.0% of normal weight women and to 55.1% of women in obesity class III ($p < 0.001$).

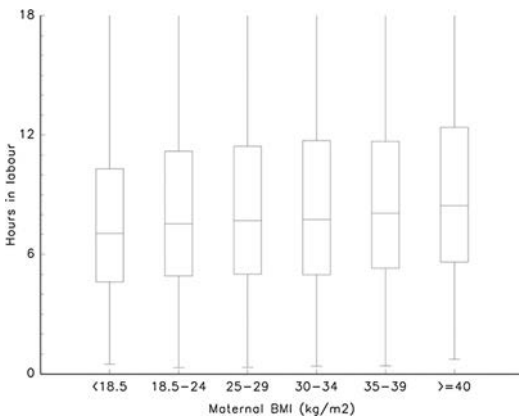
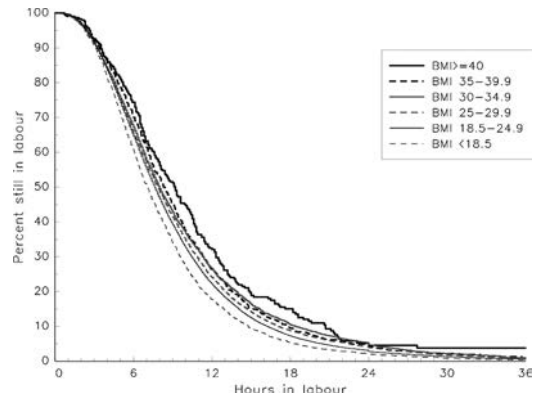
The emergency CS rate increased with increasing BMI: it was 5.1% in normal weight women compared to 15.6% in women in obesity class III ($p < 0.001$). The prevalence of instrumental delivery in normal weight women was 7.1%, in obese women class I 7.7%, class II 8.0% and class III 8.0%. In normal weight women 12.6% had children with birth weight of 4000 g or more. The corresponding rate among women in obesity class III was 25.9% ($p < 0.001$).

The relationship between duration of active labor and maternal BMI is presented in Fig. 1 and Fig. 2. Fig. 1 is a box-plot, showing the median, 25% and 75% quartiles, and the range. From the figure, it is evident that even though a significant association between increasing BMI and increasing time in labor exists, there are huge variations within each BMI category. Fig. 2 shows a Kaplan–Meier graph, illustrating the time in labor by BMI category, taking censoring from CS into account. The overall difference between the curves was statistically significant ($p = 0.038$). The largest difference was seen between the groups BMI < 18.5 and BMI ≥ 40 ($p < 0.001$). For the other BMI categories, the differences were less pronounced but were still statistically significant ($p < 0.001$).

The median duration of labor increased significantly with increasing maternal BMI and was significantly longer in obese women (class I obesity = 9.1 h, class II obesity = 9.2 h and class III obesity = 9.8 h) compared to normal weight women = 8.8 h ($p < 0.001$). The risk of labor lasting ≥ 12 h increased with increasing maternal BMI OR 1.04 (1.01–1.06) (OR per 5-units BMI-increase). The risk remained significantly increased even after excluding women with emergency CS within 12 h ($N = 61,613$) OR 1.06 (1.03–1.08) (OR per 5-units BMI-increase).

Table 1
Maternal age and birth data in relation to maternal body mass index (BMI) (N=63,829).

	BMI < 18.5 N=2024 N (%)	BMI 18.5–24.9 N=43,052 N (%)	BMI 25–29.9 N=13,823 N (%)	BMI 30–34.9 N=3641 N (%)	BMI 35–39.9 N=988 N (%)	BMI ≥ 40 N=301 N (%)	Total N=63,829 (%)
Maternal age (years)							
<20	190 (9.4)	1688 (3.9)	487 (3.5)	143 (3.9)	36 (3.6)	9 (3.0)	2553 (4.0)
20–24.9	773 (38.2)	9584 (22.3)	3212 (23.2)	989 (27.2)	286 (28.9)	72 (23.9)	14,916 (23.4)
25–29.9	657 (32.5)	17,063 (39.6)	5231 (37.8)	1348 (37.0)	362 (36.6)	113 (37.5)	24,774 (38.8)
30–34.9	328 (16.2)	11,481 (26.7)	3589 (26.0)	840 (23.1)	218 (22.1)	73 (24.3)	16,529 (25.9)
35–39.9	71 (3.5)	2886 (6.7)	1151 (8.3)	274 (7.5)	77 (7.8)	33 (11.0)	4492 (7.0)
≥40	5 (0.2)	345 (0.8)	152 (1.1)	47 (1.3)	9 (0.9)	1 (0.3)	559 (0.9)
Not known	0	5	1	0	0	0	6
Oxytocin for augmentation	786 (38.8)	19,382 (45.0)	6741 (48.8)	1827 (50.2)	510 (51.6)	166 (55.1)	29,412 (46.1)
Mode of delivery							
Vaginal	1854 (91.6)	37,805 (87.8)	11,647 (84.3)	2988 (82.1)	804 (81.4)	230 (76.4)	55,335 (86.7)
Cesarean section	50 (2.5)	2190 (5.1)	1078 (7.8)	373 (10.2)	105 (10.6)	47 (15.6)	3844 (6.0)
Instrumental	120 (5.9)	3057 (7.1)	1099 (7.9)	280 (7.7)	79 (8.0)	24 (8.0)	4660 (7.3)
Birthweight (g)							
<2500	102 (5.0)	1034 (2.4)	315 (2.3)	77 (2.1)	20 (2.0)	6 (2.0)	1554 (2.4)
2500–3999	1815 (89.7)	36,635 (85.1)	11,050 (79.9)	2804 (77.0)	735 (74.4)	217 (72.1)	53,256 (83.4)
4000–4499	100 (4.9)	4661 (10.8)	2033 (14.7)	607 (16.7)	179 (18.1)	57 (18.9)	7637 (12.0)
4500–4999	6 (0.3)	667 (1.5)	379 (2.7)	133 (3.7)	47 (4.8)	18 (6.0)	1250 (2.0)
≥5000	1 (0.0)	50 (0.1)	45 (0.3)	20 (0.5)	7 (0.7)	3 (1.0)	126 (0.2)
Not known	0	5	1	0	0	0	6

**Fig. 1.** Median time in active labor (h) in nulliparous women with a spontaneous onset of labor, in relation to their body mass index (BMI). Maximal value (maternal BMI): 47.48 (<18.5); 49.78 (18.5–24.9); 49.47 (25–29.9); 48.98 (30–34.9); 48.35 (35–39.9); 41.88 (>40).**Fig. 2.** Kaplan–Meier graph. Time in active labor (h), in nulliparous women with a spontaneous onset of labor, in relation to their body mass index (BMI). Emergency cesarean section included. Censoring due to cesarean section was performed.**Table 2**
BMI and risk of time in labor ≥12 h or emergency cesarean section within 12 h, compared to vaginal deliveries <12 h. Normal BMI (18.5–24.9) was the reference BMI.

BMI (kg/m ²)	VD < 12 h (N)	≥12 h or CS (N)	≥12 h or CS (%)	OR for time in labor ≥12 h or CS	
				Crude ^a OR (95% CI)	Adjusted ^a OR (95% CI)
<18.5	1644	380	(18.8)	0.73 (0.65–0.82)	0.88 (0.79–0.99)
18.5–24.9	32,681	10,371	(24.1)	1.0 (reference)	1.0 (reference)
25–29.9	10,140	3683	(26.6)	1.14 (1.10–1.20)	1.08 (1.04–1.13)
30–34.9	2559	1082	(29.7)	1.33 (1.24–1.44)	1.26 (1.17–1.36)
35–39.9	695	293	(29.7)	1.33 (1.16–1.52)	1.24 (1.08–1.43)
≥40	192	109	(36.2)	1.79 (1.41–2.26)	1.65 (1.29–2.09)

BMI = body mass index; CS = cesarean section; OR = odds ratio; CI = confidence interval; VD = vaginal delivery.

^a Adjustments were made for year of delivery, maternal age and birth weight (all entered as continuous linear variables).

Table 3
BMI and duration of the second stage (hours), in nulliparous women with a spontaneous onset of labor.

BMI (kg/m ²)	N (57,500)	Duration of the second stage in hours			
		Quartiles			Range
		25%	Median	75%	
<18.5	1890	0.35	0.55	0.85	[0.05–4.87]
18.5–24.9	39,241	0.35	0.55	0.87	[0.05–5.00]
25–29.9	12,192	0.32	0.53	0.83	[0.05–4.98]
30–34.9	3093	0.30	0.48	0.77	[0.05–4.73]
35–39.9	845	0.32	0.48	0.78	[0.05–3.17]
>40	239	0.27	0.45	0.70	[0.05–2.27]

BMI = body mass index.

As presented in Table 2, the risk of labor lasting ≥12 h or emergency CS within 12 h, compared to vaginal deliveries within 12 h, increased with increasing maternal BMI. Underweight women were less likely to be more than 12 h in labor or need CS within 12 h, compared to normal weight women.

On the contrary, duration of the second stage was significantly shorter in obese women compared to normal weight women ($p < 0.001$, Kruskal–Wallis). The Shapiro–Wilk test revealed that the second stage durations were not normally distributed ($p < 0.001$), but the corresponding logarithmic values met the criteria for a Gaussian distribution very well ($p = 0.5$). Table 3 shows the medians, quartiles, and range by BMI category. An analysis of covariance using logarithmic second stage duration values revealed that the difference between the BMI categories remained significant when adjusting for birth weight and maternal age ($p < 0.001$).

4. Comment

This large study of nulliparous women with a spontaneous onset of labor demonstrates a distinct association between maternal obesity and increased duration of labor. Obese women had a shorter second stage compared to normal weight women, emphasizing that the prolongation of labor progression was restricted to the first stage of labor.

There are previous studies indicating that overweight and obese women have a prolonged duration of labor compared to normal weight women [13–20]. Few of these studies, however, have been based on women entirely with spontaneous onset of labor and none has previously separately analyzed duration of the second stage from when the pushing efforts starts.

Vahratian et al. studied 612 nulliparous women and demonstrated a slower labor progression from 4 to 10 cm of cervical dilatation in overweight and obese women compared to normal weight women [16]. An American study on 5204 women demonstrated a prolonged first stage of labor until 6 cm for obese women compared to women with BMI < 30; results were adjusted for parity and labor type [20]. A longer length of labor in patients with BMI > 40 compared to normal weight women was presented in a German retrospective cohort analysis, including 8379 women with a term pregnancy. The results were not stratified for induction or parity [19]. In two American studies on 1273 and 509 women respectively, an association between high maternal weight and increased labor duration were observed. The analyses were restricted to women with induced labor, and based on maternal weight at the time of labor. Contradicting results are presented a British study on 8350 obese versus non-obese nulliparous women. Mean durations of first and second stages of labor were not significantly different between the groups. Inductions were included, and the results were not stratified for birth weight or maternal age [2]. Hilliard et al. demonstrated a longer duration of

first stage of labor among obese women, although women with fewer than 4 cervical examinations were excluded [15].

In this study, the duration of the second stage decreased with increasing BMI. This finding implies that the risk of prolonged labor is restricted to the first stage of labor in nulliparous overweight and obese women, which is supported by previous studies [13,16]. Two multicenter prospective cohort studies, on 2629 and 5341 nulliparous women respectively, demonstrated an increased risk of CS in obese women, restricted to the first stage of labor, suggesting that labor dysfunction in these women is confined to the first stage [24,25].

The reason for a prolongation of the first stage of labor in obese women could only be speculated upon. One explanation could be inadequate uterine contractility. Zhang et al. demonstrated that myometrium from obese women contracted with less force and frequency compared to myometrium from normal weight women [12]. Cedergren showed that the risk of emergency CS due to ineffective uterine contractility increased in obese women [11]. Another reason for prolonged first stage of labor could be cephalopelvic disproportion, due to increased soft tissue in the maternal pelvis [9,26]. Al-Khan et al. found a positive correlation between pre-pregnancy BMI and intra-abdominal pressure in pregnant women at term, which could explain why obese women have a shorter second stage [27]. Buhimschi et al. showed that the uterine contractility and pushing ability in women during the second stage is not dependent on maternal BMI [28].

The advantage of register studies is the large number of participants and the absence of selection bias, which give high statistical power. The large number of individuals made it possible to analyze three subgroups of obesity. This is the first study where the inclusion criteria were restricted to nulliparous singletons with a spontaneous onset of labor. Induction of delivery increases the risk of prolonged duration of labor and obese women have a greater rate of labor induction [14], and induction should therefore be evaluated as a separate group.

The purpose of this study was to evaluate the duration of labor among all women, therefore including cesarean delivery. Another possibility is to study only women with vaginal delivery, thus excluding CS due to labor arrest or fetal distress, but this could bias the result as it is well known that CS rates differ significant between BMI groups.

There are certain limitations of this study. We chose to restrict the exclusion criteria to incomplete information on BMI and time of start of active labor, as the purpose of this study was to evaluate time in labor overall. Women with gestational diabetes, preeclampsia and prematurity were not excluded. It is possible that these conditions may have an effect on the results, but we considered these variables as intermediaries, which do not affect the exposure, only the outcome. Neither oxytocin usage nor epidural anesthesia was included as a confounder in this analysis as they also were looked upon as intermediaries. Further, the measurement of cervical dilatation and defining the start of regular contractions were subjective. Clearly, in this large study population, involving several health care units, the estimation of these parameters may not be uniform across the study population, but the variation is probably not related to maternal BMI. As the population, definition and management of labor differ between countries [29], our findings may not be applied in all countries.

It is clinically important to consider the prolonged first stage of labor in obese women, for example when diagnosing first stage labor arrest, in order to optimize management of this rapidly growing risk-group of women. Thus, it might be reasonable to adapt the considered upper limit for duration of labor according to maternal BMI.

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PAPER

II

The effect of maternal body mass index on duration of induced labor.

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ABSTRACT

Background: Obese nulliparous women with induction of labor (IOL) are at high risk for a cesarean section (CS). There are contradictory results regarding time in induced labor in relation to maternal body mass index (BMI). It is important to characterize the course of induced labor in order to prevent unnecessary CS. We aimed to evaluate whether the time in latent and active labor, respectively, was associated with maternal BMI in nulliparous women with IOL.

Methods: A national cohort study, including 15,259 nulliparous women with a single term pregnancy, admitted for IOL from January 2014 to August 2017. Data were obtained from the Swedish Pregnancy Registry. Cox regression analyses were used to illustrate the association between BMI and time in active and latent labor and adjusting for confounding factors.

Results: Duration of active and latent labor increased with an increasing maternal BMI. The most pronounced difference was between women with BMI ≥ 40 and underweight women. The CS rate increased significantly with an increasing BMI. Obese and normal weight women had similar rates of normal vaginal delivery.

Conclusions: Duration of induced labor increased with maternal BMI. The differences between the BMI categories were more pronounced in latent labor. Overweight women and women in obesity classes I-II, had a similar duration of active labor as normal weight women and a similar chance for a normal vaginal delivery, yet the risk for CS increased. There may be other reasons, than a prolonged active labor, for the higher rate of CS in these women.

BACKGROUND

The increasing prevalence of overweight and obesity in pregnant women is worrying, considering the associated obstetrical interventions and complications (1, 2). Obese women are more likely to undergo induction of labor (IOL) compared to normal weight women (3-5). This is partly explained by the positive association between maternal obesity and post-term pregnancy (6-8). The increased rate of pregnancy complications, such as pre-eclampsia (PE), gestational diabetes mellitus (GDM) and hypertension in obese women also contributes to the greater need for IOL (9, 10). IOL has become a common intervention in contemporary obstetrical practice. In 2016, 17.2% of all nulliparous women in Sweden were induced (11). Studies have reported higher rates of cesarean section (CS) in nulliparous women following IOL, compared to women with a spontaneous onset of labor (10, 12) and the risk of a cesarean delivery increases with maternal weight (3-5, 13). Considering the increasing prevalence of obesity and associated risk for a cesarean delivery, obese nulliparous women with IOL represent a challenging risk group in contemporary obstetrical care. One of the most common reasons for failed IOL in obese women is failure to progress (14, 15). We have previously shown that time in spontaneous labor increases with maternal body mass index (BMI) (16) and various authors have suggested that obese women might need more time in active labor before the arrest of labor can be considered (17).

If a prolonged active induced labor is associated with maternal BMI in the same way as in women with spontaneous labor this may contribute to the higher rates of CS in obese nulliparous women. The results from several studies indicate that total time in induced labor increases with maternal weight (9, 13, 18). However, there are contradictory results regarding time in the active induced labor in relation to maternal BMI (9, 19, 20). It is important to characterize the course of induced labor in order to prevent unnecessary CS due to labor arrest in nulliparous women for whom a cesarean delivery may have a major impact on future pregnancies and deliveries.

Hence, our primary aim was to evaluate whether the time in active labor was associated with BMI in nulliparous women with induced labor. The secondary aim was to analyze the duration of the latent phase of induced labor in relation to maternal BMI.

METHODS

Study design and participants

We performed a prospective national cohort study, including 15,259 nulliparous women with a single term (≥ 37 gestational weeks) pregnancy. The women were admitted to a delivery ward in Sweden for IOL and delivered between January 1, 2014 and August 30, 2017. Data were obtained from the Swedish Pregnancy Register. The register contains information on maternal characteristics, pregnancy complications, labor and birth data from 90 % of all deliveries in Sweden. The majority of the variables included in the register are continuously transferred electronically from the medical antenatal, labor and delivery records. Some variables are registered manually by the midwives at the antenatal care clinics. These data include country of birth, level of education and diagnosis of GDM (21).

Exclusion criteria were stillbirth, non-available information on maternal BMI in the first trimester, no information on maternal age, and missing data concerning time estimates on the start of active labor and the time of birth. Thus, the women who had a cesarean delivery before onset of active labor were excluded, but the women who were delivered by CS in active labor were included in the analyses on labor duration.

The Regional Ethical Review Board in Linköping, Sweden approved this study (Dnr 2017/274-31).

Variables included in study

Maternal BMI was calculated based upon the maternal weight and height measurements provided at the first antenatal visit. A majority had their first visit between gestational weeks 8 and 10. The study population was categorized in six classes of BMI (kg/m^2) according to the World Health Organization (WHO) definition: $<18.5 \text{ kg/m}^2$ (underweight), $18.5\text{--}24.9 \text{ kg/m}^2$ (normal weight), $25.0\text{--}29.9 \text{ kg/m}^2$ (overweight), $30\text{--}34.9 \text{ kg/m}^2$ (class I obesity), $35.0\text{--}39.9 \text{ kg/m}^2$ (class II obesity) and $\geq 40 \text{ kg/m}^2$ (class III obesity/morbidly obese).

After the application to the register holders was approved, data from the Swedish Pregnancy Register was retrieved unidentified. The maternal variables that were assessed were age at delivery, height and weight in the first trimester, weight in late pregnancy, smoking in early

pregnancy, educational level, country of birth, pre-pregnancy diabetes and hypertension, GDM, PE and gestational age at delivery. Labor and neonatal variables that were assessed were type of labor (spontaneous, induction or planned CS), the time at admission for IOL, the time of start of active labor, the time of birth, usage of epidural anesthesia, usage of oxytocin, mode of delivery (normal vaginal delivery, operative vaginal delivery and emergency CS), whether or not the infant was borne alive and birth-weight.

Maternal age was defined as completed years at time of delivery. Gestational weight gain (GWG) was defined as the difference between the maternal weight in early pregnancy and the last weight measured in the third trimester, (on average obtained at 36.3 weeks). Gestational age was based on the measurements from a second trimester ultrasound. Onset of the active phase labor was defined as when the cervix was dilated 3 cm or more in women with painful regular uterine contractions. The midwife at the delivery ward prospectively recorded the time when the active phase of labor started and the time of birth. Cervical examinations were typically performed every second hour during the active phase of labor. Emergency CS was defined as a CS performed after the start of IOL, during active labor.

Duration of labor was defined and analyzed in two different ways. First, as time in active labor, defined as from the start of the active phase of labor until time of birth. Second, as time in latent labor, defined as the time from admission to the delivery ward for IOL until the start of the active phase of labor. The time estimates for latent labor were considered to be incorrect if the time from admission until active labor started was less than 30 minutes or more than four days (96 hours).

Data management and statistical analyses

Chi²- tests were performed to analyze descriptive frequency data, while one-way analyses of variance (ANOVA) were conducted to compare descriptive, continuous, and normally distributed data among BMI groups. The relation between BMI and CS was evaluated by using a linear logistic regression model with BMI as a linear, continuous variable.

One-way ANOVAs were used to compare mean duration of active and latent labor, respectively, among BMI groups. When the outcome variables were not normally distributed, the log values were used instead (provided that they seemed to be reasonably normally distributed). Analyses of covariance (ANCOVA) were used to control for possible

confounders. Only factors with $p < 0.2$ were included in the final analyses. In the final analyses, adjustments were made for maternal age, GWG, and birth weight. The analyses on active labor were also adjusted for vaginal delivery.

Cox regression analyses were performed and graphs were produced to illustrate the association between maternal BMI and time in active and latent labor in women with IOL, taking censoring due to emergency CS into account (when applicable) and adjusting for confounding factors. Cox regression analyses were used to assess the contributions of variables identified as single independent factors influencing time in active and latent labor ($p < 0.2$). Maternal age, infant birth weight, smoking, and GWG were included as confounding factors in the analyses on active labor. Birth weight and GWG were regarded as confounding factors in the analyses on latent labor.

A p -value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 23 (IBM Inc, Armonk, NY).

RESULTS

During the study period between January 1, 2014 and August 30, 2017, 140,452 nulliparous women delivered a singleton term pregnancy, and had their data available in the Swedish Pregnancy Register. The induction rate was 19.9% (27,896 women). 15,259 women with induced labor, information on start of active labor and time of birth were included in the analyses on active labor. Out of these women, 15,073 were included in the analyses on latent labor, after excluding those with incorrect time estimates on latent labor (Figure 1).

The maternal demographics are listed in Table 1. Morbidly obese women were more likely to be of Nordic origin (born in Sweden or Nordic countries), to smoke and to have a lower education level compared to normal weight women (p for homogeneity < 0.001). Underweight women were younger, and were more likely to be from a non-Nordic country, to smoke, and to have a lower educational level compared to normal weight women (p for homogeneity < 0.001). The incidence of GDM or PE was not significantly different over the BMI categories. The higher the BMI class, the less the GWG (p for homogeneity < 0.001).

Labor characteristics are presented in Table 2. Mean birth weight was higher with increasing maternal BMI. A gestational age at delivery of ≥ 42 weeks was more common in normal weight women than among obese women (p for homogeneity <0.001). An operative vaginal delivery was less common with higher maternal BMI: 15.6% in normal weight women compared to 6.1% in morbidly obese women (p for homogeneity <0.001). The rate of emergency CS increased significantly with increasing BMI class, from 7.4% in underweight women to 22.0 % in morbidly obese women (p for linear trend <0.001). Obese women had the same chance for a non-operative vaginal delivery as normal weight women after IOL. The reported rate of oxytocin for induction, alone or as a combination of other methods was less in underweight women compared to women in other BMI categories (p for homogeneity $=0.009$). The reported usage of oxytocin did not differ substantially among the other BMI classes.

The medians, quartiles and range values of time in labor by BMI category are presented in Table 3. Underweight women had 1.8-1.2 hour shorter duration of active labor compared to women in the other BMI categories. The median time in latent labor increased successively with maternal BMI from 12.6 hours in underweight women to 22.6 hours in morbidly obese women.

The values of the durations of active and latent labor, respectively, were not normally distributed ($p<0.001$). Instead, the logarithmic values were used to explore differences between BMI classes using ANOVA and ANCOVA. One-way ANOVAs revealed significant heterogeneity between BMI classes, both for log active and log latent labor durations ($p<0.001$). When ANCOVAs were performed including maternal age, GWG, birth weight and vaginal delivery, significant differences between BMI classes were still found for both outcomes (log duration of active labor, $p=0.02$, and log latent labor duration, $p<0.001$). The relationship between the duration of active and latent labor and maternal BMI is presented as survival curves, from Cox regression analyses, in Figures 2 and 3. Figure 2 illustrates the duration of active labor by BMI category taking censoring from emergency CS into account and adjusting for confounding factors. The figure shows that the number of women who were still in active labor at a certain time point increased with increasing BMI. The largest difference was seen between underweight women (BMI <18.5) and morbidly obese women. The overall difference between the curves was statistically significant when adjusting for maternal age, infant birth weight, smoking and GWG as confounding factors (p

<0.001). The relationship between duration of latent labor and maternal BMI is presented in figure 3. Time in latent labor increased successively with increasing maternal BMI class (figure 3). There was an overall statistically significant difference between the curves when adjusting for birth weight and GWG as confounding factors ($p < 0.001$). Women with cesarean delivery during the latent labor were not included.

COMMENTS

This is one of the largest population-based cohort studies restricted to nulliparous women with induced labor and information on early pregnancy BMI. Survival curves demonstrated that the duration of active labor increased with maternal BMI and the most pronounced difference were between morbidly obese women and underweight women. Our results indicate that maternal BMI seems to have an even greater impact on time in latent labor, which increased successively with increasing maternal BMI, and the differences between the BMI categories were more obvious.

There are several previous studies comparing labor progress by maternal weight but few studies have been restricted to women with IOL and few have analyzed both the latent and active labor separately (9, 13, 18-20). Three American studies, including both spontaneous and induced labor, demonstrated that the time from 4 to 10 cm cervical dilatation increased with maternal BMI in nulliparous women (17, 22, 23). Contradictory results were reported in a Danish study on 1,885 nulliparous women (24). In women with IOL, increasing maternal weight has been associated with longer time from start of induction to delivery. However the results may be less generalizable as they are based on maternal weight at the time of induction (9, 13, 18). One of these studies also demonstrated that time in active labor, from 4 cm cervical dilatation, increased with maternal BMI (9). Hirshberg et al. compared the latent and the active phases in 313 nulliparous women undergoing IOL by BMI category. In contrast to our findings they found no difference in median latent labor (from start of induction until active labor) by BMI category, but a significantly longer median time in active labor from 5 cm cervical dilatation, in overweight women compared to normal weight and obese women (19). In two separate studies on women undergoing IOL, the duration of active labor was similar, regardless of maternal BMI. As they mixed parities in the analyses and defined the start of active labor differently or not at all, our results are difficult to adequately compare (3, 20).

The underlying mechanism for the longer duration of induced labor, which we observed in obese women, could be explained by impaired uterine contractility in obese women based on results from in vitro studies of human myometrium (25).

The current analysis supports previous findings that the cesarean delivery rate increased with rising maternal BMI in nulliparous women undergoing IOL (3, 4, 13). Furthermore, this study showed that overweight and obese women who enter the active stage of labor have the same chance for a non-operative vaginal delivery as normal weight women. In this large study population, 70% had normal vaginal delivery. This finding is different to a British study on 2066 nulliparous women with IOL where 44% had a normal vaginal delivery and fewer obese women had a normal vaginal delivery compared to normal weight women (3).

Although there was less pronounced difference between normal weight, overweight and obese women regarding time in active labor, and that all had the same chance for a normal vaginal delivery, the rate of CS increased noticeably, with increasing BMI. The reason for this can only be speculated upon. Since the risk of an operative vaginal delivery decreases with maternal BMI, it is possible that more obese women are delivered by CS in the active phase of labor (9, 26). It may also reflect the difficulties in assessing the station of the fetal head in the pelvic canal in obese women, resulting in a second stage CS instead of an operative vaginal delivery.

The strengths of this national cohort study are the large number of nulliparous women with IOL and early pregnancy BMI, which gave sufficient power to evaluate time in labor according to six BMI classes, and the diversity of a nationwide cohort covering 90% of all deliveries in Sweden. The detailed data on baseline evaluation of maternal co-morbidity and socioeconomic factors and continuous registration of pregnancy complications enabled us to adjust for possible confounding factors.

General limitations of large register studies are the risk of errors in recorded data and missing values. One example of underreporting variables is the registration of oxytocin for induction/augmentation in the Swedish Pregnancy Register. The use of oxytocin is either automatically transferred from the partogram or manually registered. Although this variable was underreported in the register, there is no reason to suspect that the degree of underreporting varies over the BMI classes.

The Swedish Pregnancy Register contains much maternal pregnancy and labor data, however, we did not have information on all desirable data. Data on Bishop score at admission, indication and method of induction or indication for CS would have been valuable but was not available. Furthermore, we had no information on the time that induction started. Therefore, we used the time of admission as a proxy for start of IOL and defined the start of latent labor as the time of arrival at the delivery ward for IOL. In Sweden, most patients admitted for IOL start induction shortly after arriving at the delivery ward. The time from admission until start of induction was probably not related to maternal BMI. However, a few patients may have been observed after admission due to an obstetrical complication before the induction started. This could have falsely prolonged the latent labor in some women and possibly many could have been obese as they were at higher risk for obstetrical complications. This could have biased the results on latent labor. The fact that we were not able to adjust for the cervical ripeness at admission might also have influenced the results for latent labor, since obese women may have higher risk for unfavorable cervical status and thereby increased risk for longer latent labor (27). Furthermore, women with cesarean delivery during the latent labor were excluded. This could have resulted in a selection bias as they might have had long latent labor before the cesarean delivery. However studies have demonstrated that most women reach active labor in a trial of labor induction (9). Our results on latent labor must be considered in the light of these limitations.

Our definition of start of active labor, i.e. cervix dilated three cm in women with regular contractions, is similar to the recommendation by the WHO (28). In a review article from 2016, Hanley et al. state that there is a lack of international consensus on what degree of cervical dilatation is necessary to indicate that active labor has begun (29). An American study has shown that latent labor may last until six centimeters cervical dilatation has occurred, and that duration of latent labor can vary (30). Hence, our definition of active labor may limit the generalizability of the present study.

In conclusion, this study demonstrated that duration of both latent and active labor in nulliparous women with IOL increased with maternal BMI but the differences between the BMI categories were more noticeable in latent labor. Overweight women and women in obesity class I-II, who reached the active phase of labor had a similar duration of active labor as normal weight women and a similar chance for a normal vaginal delivery, yet the risk for an emergency CS in active labor increased with rising maternal BMI. This may indicate that

there are other reasons, apart from a prolonged time in active labor, for the higher rates of CS in overweight and obese nulliparous women undergoing IOL.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Table 1. Maternal demographics by BMI category, in nulliparous term women undergoing induction of labor. Continuous data are presented as mean and [SD]. Categorical data are presented as number and (%).

Maternal demographics	BMI< 18.5 N= 325 N (%)	BMI 18.5-24.9 N= 8,509 N (%)	BMI 25-29.9 N=4,044 N (%)	BMI 30-34.9 N=1,605 N (%)	BMI 35-39.9 N=562 N (%)	BMI ≥ 40 N=214 N (%)	Total N=15,259 N (%)	P for homo- genity
Age < 20 years	16 (4.9)	132 (1.6)	77 (1.9)	26 (1.6)	12 (2.1)	4 (1.9)	267 (1.7)	< 0.001
Age ≥ 35 years	25 (7.7)	1,378 (16.2)	662 (16.4)	24 (15.0)	83 (14.8)	33 (15.4)	2,436 (15.9)	< 0.001
Maternal age, mean years [SD]	27.8 [5.0]	30.0 [5.1]	29.7 [5.3]	29.3 [5.4]	29.0 [5.5]	28.8 [5.1]	29.7 [5.2]	< 0.001
Height, mean meter [SD]	1.66 [6.4]	1.67 [6.6]	1.66 [6.4]	1.66 [6.8]	1.67 [6.8]	1.65 [9.6]	1.66 [6.7]	0.001
Smoking in first trimester (yes)	27 (8.3)	325 (3.8)	172 (4.3)	120 (7.5)	38 (6.8)	14 (6.5)	696 (4.6)	< 0.001
Country of birth								< 0.001
Nordic	167 (51.4)	5,939 (70.0)	2,831 (70.0)	1,146 (71.4)	432 (76.9)	172 (80.4)	10,687 (70.0)	
Europe	39 (12.0)	633 (7.4)	221 (5.5)	97 (6.0)	24 (4.3)	9 (4.3)	1,023 (6.7)	
Outside Europe	75 (23.0)	1,078 (12.7)	557 (13.8)	198 (12.3)	39 (6.9)	13 (6.1)	1,960 (12.8)	
No information	44 (13.5)	859 (10.1)	435 (10.7)	164 (10.2)	67 (11.9)	20 (9.3)	1,589 (10.4)	
Education level								< 0.001
≤ 9 years	27 (8.3)	397 (4.7)	207 (5.1)	102 (6.4)	38 (6.7)	13 (6.1)	784 (5.1)	
9-12 years	112 (34.5)	2,274 (26.7)	1,400 (34.6)	653 (40.7)	256 (45.6)	111 (51.9)	4,806 (31.5)	
University	105 (32.3)	4,311 (50.7)	1,692 (41.8)	560 (34.9)	159 (28.3)	59 (27.6)	6,886 (45.1)	
No information	81 (24.9)	1,527 (17.9)	745 (18.4)	290 (18.1)	109 (19.4)	31 (14.5)	2,783 (18.2)	
Hypertension before pregnancy (yes)	3 (0.9)	60 (0.7)	18 (0.4)	9 (0.6)	2 (0.4)	1 (0.5)	93 (0.6)	0.501
DM (yes)	4 (1.2)	75 (0.9)	42 (1.0)	5 (0.3)	1 (0.2)	1 (0.5)	128 (0.8)	0.044
GDM (yes)	6 (1.8)	122 (1.4)	46 (1.1)	18 (1.1)	8 (1.4)	0 (0)	200 (1.3)	0.307
PE (yes)	15 (4.6)	410 (4.8)	191 (4.7)	67 (4.2)	28 (5.0)	140 (4.7)	721 (4.7)	0.931
GWG, mean kg [SD]	13.4 [5.5]	14.6 [24.2]	14.4 [23.3]	12.7 [22.3]	10.8 [7.9]	8.6 [10.2]	14.1 [23.0]	< 0.001
Missing GWG (n)	5 (1.5)	113 (1.3)	43 (1.1)	13 (0.8)	1 (0.2)	6 (2.8)	181 (1.2)	

DM= pre-gestational diabetes mellitus, GDM = gestational diabetes mellitus, GWG= gestational weight gain, BMI = maternal body mass index in kg/m²

Table 2. Labor characteristics of nulliparous term women, undergoing induction of labor, by BMI category. Categorical data are presented as number and (%). Continuous data are presented as mean and [SD].

Labor characteristics	BMI< 18.5 N= 325 N (%)	BMI 18.5-24.9 N= 8,509 N (%)	BMI 25-29.9 N=4,044 N (%)	BMI 30-34.9 N=1,605 N (%)	BMI 35-39.9 N=562 N (%)	BMI ≥ 40 N=214 N (%)	Total N=15,259 N (%)	P for homo- geneity
GA								< 0.001
GA 37.0-40.6 weeks	174 (53.5)	4,034 (47.7)	1,958 (48.4)	860 (53.6)	320 (59.6)	123 (57.5)	7,468 (48.9)	
GA 41.0-41.6 weeks	58 (17.8)	1,487 (17.5)	772 (19.1)	298 (18.6)	112 (19.9)	51 (23.8)	2,778 (18.2)	
GA ≥ 42 weeks	93 (28.6)	2,988 (35.1)	1,314 (32.5)	447 (27.9)	139 (23.1)	40 (18.7)	5,012 (32.8)	
BW mean gram [SD]	3,311 [553]	3,540 [518]	3,634 [544]	3,652 [553]	3,668 [549]	3,671 [544]	3,578 [534]	<0.001
BW < 2500g	20 (6.2)	195 (2.3)	74 (1.8)	31 (1.9)	6 (1.1)	2 (0.9)	328 (2.1)	<0.001
BW ≥ 4500g	4 (1.2)	259 (3.1)	226 (5.6)	99 (6.2)	38 (6.7)	18 (8.4)	644 (4.2)	<0.001
EDA yes	177 (54.5)	5,228 (61.4)	2,496 (61.7)	999 (62.2)	336 (59.8)	136 (63.6)	9,372 (61.4)	0.009
Oxytocin yes	179 (55.1)	5,505 (64.7)	2,585 (63.9)	1,022 (63.7)	343 (61.0)	140 (65.4)	9,774 (64.1)	0.009
Mode of delivery								<0.001
Non-operative vaginal delivery	249 (77.1)	6,022 (70.9)	2,743 (68.0)	1,100 (68.7)	377 (67.3)	154 (72.0)	10,645 (69.9)	
Operative vaginal delivery	50 (15.5)	1,321 (15.6)	593 (14.7)	176 (11.0)	69 (12.3)	13 (6.1)	2,222 (14.6)	
Emergency CS	24 (7.4)	1,150 (13.5)	698 (17.3)	326 (20.3)	114 (20.4)	47 (22.0)	2,359 (15.5)	<0.001 *
No information	2	16	10	3	2	0	33	

GA = gestational age

BW = birth weight

EDA = epidural anesthesia

CS = cesarean section

BMI = maternal body mass index in kg/m²

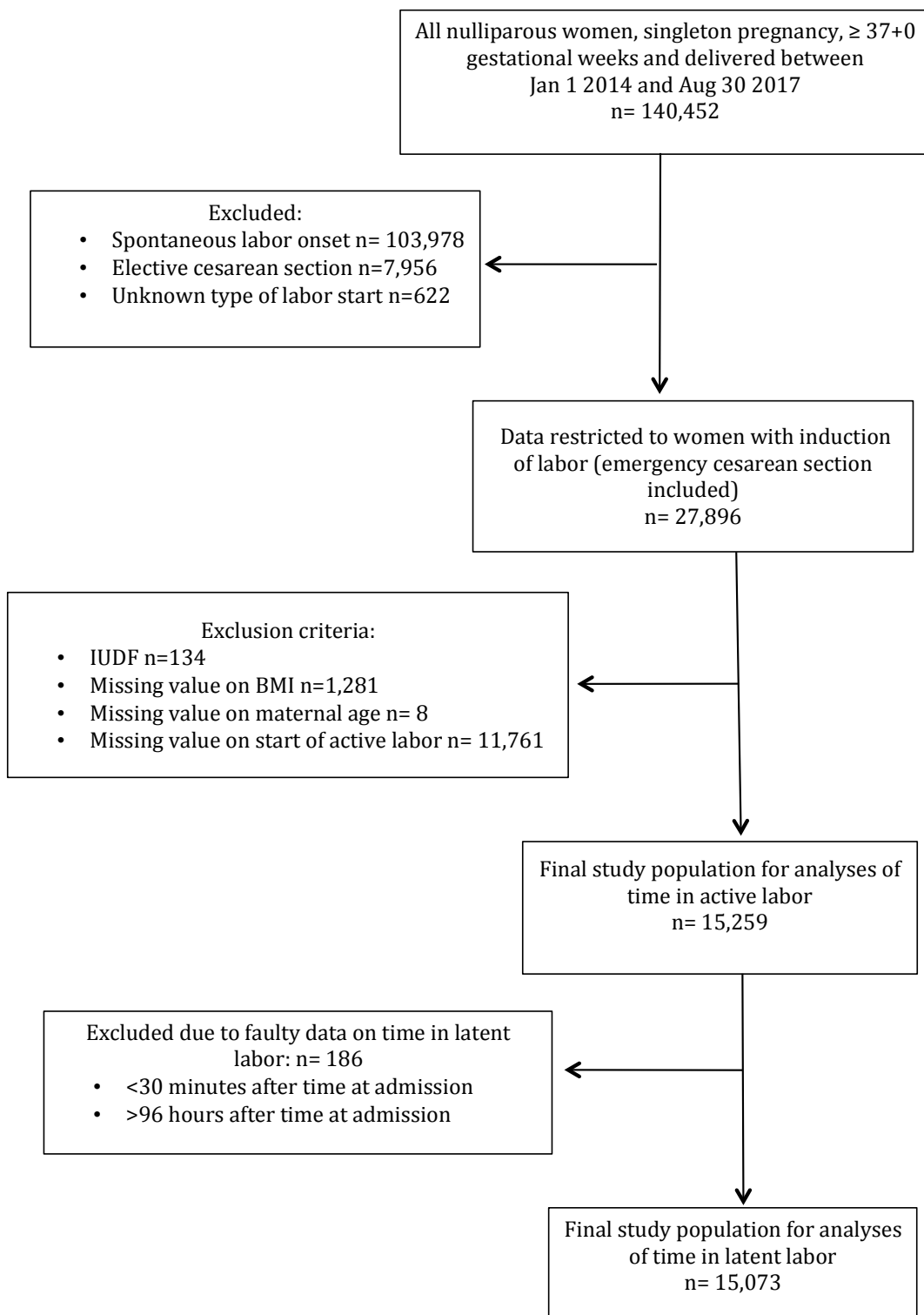
SD = standard deviation

* = p for linear trend

Table 3. Duration of labor, in hours, in nulliparous term women with induction of labor.

Maternal Body Mass Index (kg/m ²)	Time in latent labor in hours (from admission to start of active phase). N=15,073					Time in active labor in hours. N=15,259				
	N	Quartiles			Range [Min-Max]	N	Quartiles			Range [Min-Max]
		25 %	Median	75 %			25 %	Median	75 %	
<18.5	322	7.7	12.9	25.0	[1.5-91.7]	325	4.0	6.1	8.9	[0.5-30.5]
18.5-24.9	8,434	8.4	14.5	25.1	[0.5-95.9]	8,509	4.7	7.4	11.0	[0.5-44.5]
25-29.9	3,993	9.2	16.3	28.2	[0.5-95.6]	4,044	4.8	7.6	11.2	[0.5-40.3]
30-34.9	1,568	9.6	18.2	30.4	[0.7-94.6]	1,605	4.6	7.6	11.1	[0.6-46.5]
35-39.9	549	10.2	21.0	31.7	[0.5-80.0]	562	4.5	7.0	11.3	[0.8-30.9]
≥40	207	11.1	22.6	35.1	[1.0-91.0]	214	4.7	7.4	11.8	[1.3-35.7]

Figure 1. Flow chart of the included and excluded women in the cohort.



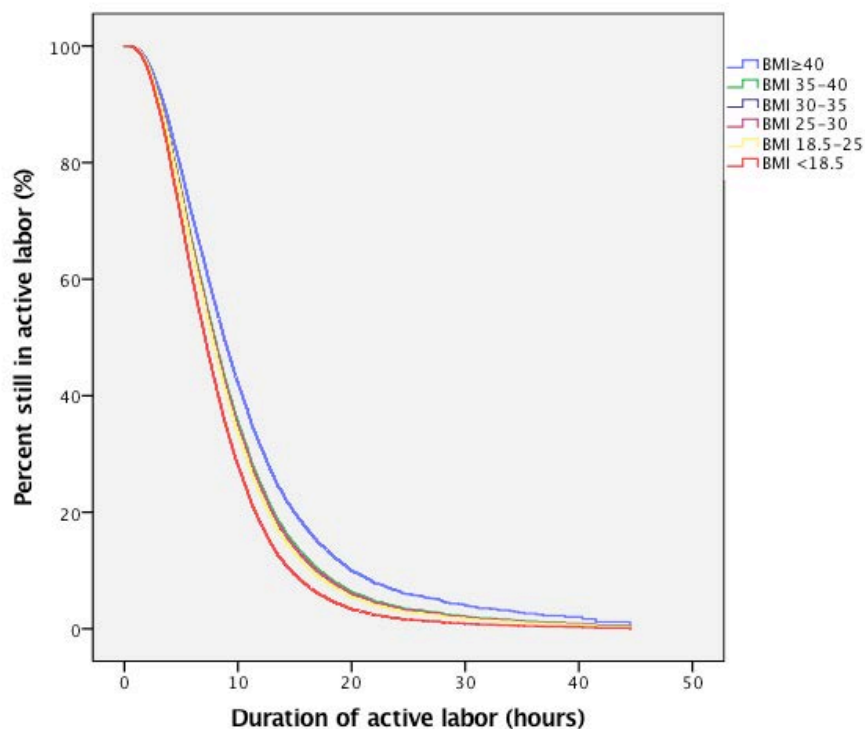


Figure 2

Survival curves illustrating time, in hours, in active labor in nulliparous women with induced labor in relation to maternal early pregnancy body mass index (BMI). Active labor was defined from onset of regular painful contractions and cervical dilatation ≥ 3 cm until time of delivery. Event was defined as delivery. Women were censored at the time of emergency cesarean section. Adjustments were made for maternal age, birth-weight, gestational weight gain and smoking in early pregnancy. P for difference between BMI groups < 0.001 .

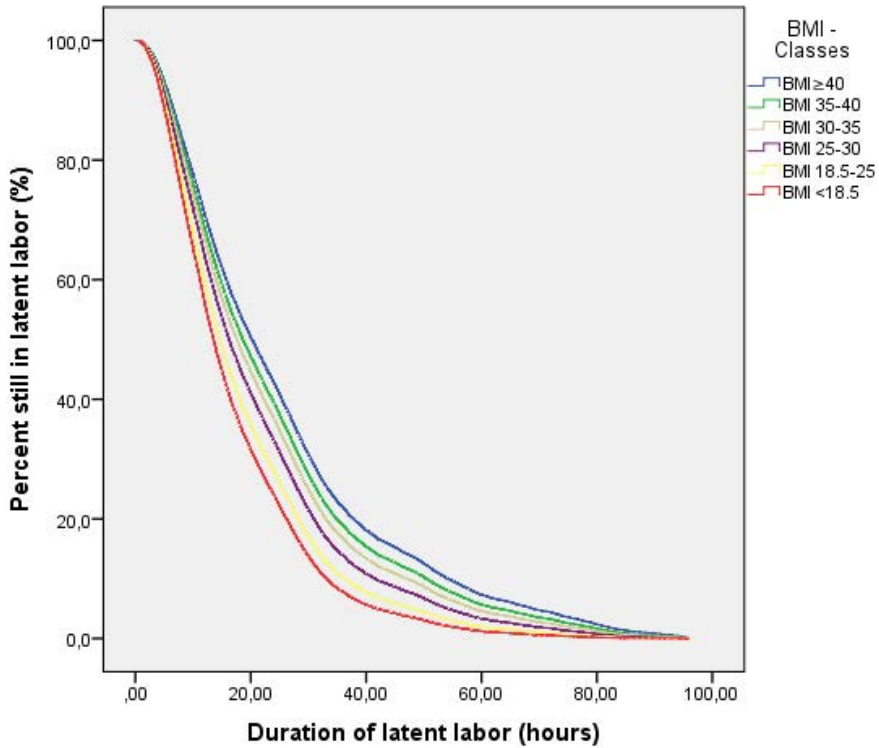


Figure 3.

Survival curves illustrating time, in hours, in latent labor in nulliparous women with induced labor in relation to maternal early pregnancy body mass index (BMI). Latent labor was defined as time from admission for induction of labor until start of active labor. Event was defined as entering active labor. Adjustments were made for birth weight and gestational weight gain. P for difference between BMI groups < 0.001

PAPER III

RESEARCH ARTICLE

Open Access



Maternal obesity (Class I-III), gestational weight gain and maternal leptin levels during and after pregnancy: a prospective cohort study

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Abstract

Background: Maternal obesity is accompanied by maternal and fetal complications during and after pregnancy. The risks seem to increase with degree of obesity. Leptin has been suggested to play a role in the development of obesity related complications. Whether maternal leptin levels differ between obese and morbidly obese women, during and after pregnancy, have to our knowledge not been previously described. Neither has the association between maternal leptin levels and gestational weight gain in obese women. The aim was to evaluate if maternal plasma leptin levels were associated with different degrees of maternal obesity and gestational weight gain.

Methods: Prospective cohort study including women categorized as obesity class I-III ($n = 343$) and divided into three gestational weight gain groups ($n = 304$). Maternal plasma leptin was measured at gestational week 15, 29 and 10 weeks postpartum. Maternal Body Mass Index (BMI) was calculated from early pregnancy weight. Gestational weight gain was calculated using maternal weight in delivery week minus early pregnancy weight. The mean value and confidence interval of plasma-leptin were analysed with a two-way ANOVA model. Interaction effect between BMI and gestational weight gain group was tested with a two-way ANOVA model.

Results: The mean maternal leptin concentrations were significantly higher in women with obesity class III compared to women in obesity class I, at all times when plasma leptin were measured. The mean leptin concentrations were also significantly higher in women with obesity class II compared to women in obesity class I, except in gestational week 29. There was no difference in mean levels of plasma leptin between the gestational weight gain groups. No significant interaction between BMI and gestational weight gain group was found.

Conclusions: Plasma leptin levels during and after pregnancy were associated with obesity class but not with degree of gestational weight gain. These results are in concordance with epidemiological findings where the risk of obstetric complications increases with increased maternal obesity class. The effect on obstetric outcome by degree of gestational weight gain is less pronounced than the adverse effects associated with maternal obesity.

Keywords: Maternal obesity, Leptin, Gestational weight gain, Pregnancy and body mass index

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Background

Maternal obesity is accompanied by several complications for both mother and infant during and after pregnancy [1, 2]. Maternal risks are gestational diabetes mellitus (GDM), pre-eclampsia (PE), hypertension, increased duration of labour, caesarean delivery, postpartum haemorrhage etc. [1, 3–7]. Fetal risks include neural tube and heart defects, macrosomia, stillbirth etc. [1, 3, 8]. The risks for a majority of obesity related complications during pregnancy, for both mother and infant, seem to increase with increasing degree of obesity [1, 3, 8]. A pronounced gestational weight gain (GWG) influences pregnancy outcome as well, but to a lesser extent than maternal obesity [3, 9].

The pathogenetic mechanisms of obesity on obstetric outcome have not yet been clarified. Obesity induces inflammatory processes, associated with some pregnancy outcomes like PE, gestational hypertension and GDM [10, 11]. Leptin, secreted by adipose tissue, is one of several adipokines. It is believed to act as a pro-inflammatory cytokine that might have a role in development of obesity related complications [12–14]. Serum leptin concentrations correlate with body mass index (BMI) and percentage of body fat in humans [15, 16]. During pregnancy, leptin is also produced by the placenta and plays an important role for normal fetal development and growth [12, 13, 17, 18]. High serum leptin levels seem to be associated with adverse pregnancy outcomes, such as PE, GDM and macrosomia [12, 17, 19, 20].

Prior studies have indicated an association between leptin, body fat mass or maternal BMI, during pregnancy [21–23]. Misra et al. demonstrated that leptin concentrations in overweight/obese women were higher but increased at a significantly lower rate across gestation compared to normal-weight women [24]. A similar leptin pattern across gestation, which differed according to pre-pregnancy maternal BMI, was observed in a smaller Brazilian cohort [25]. These studies mainly focused on the longitudinal trends in maternal leptin levels during pregnancy and included few obese and morbidly obese women [22, 24–26]. Hendler et al. demonstrated that maternal leptin levels in the third trimester, increased with pre-pregnancy BMI in 20 obese women [19]. Walsh et al. compared leptin levels in a cohort of women subdivided into those who exceeded the American Institute of Medicine's (IOM) GWG guidelines and those with recommended GWG. They found no difference in leptin levels in early pregnancy but maternal leptin concentration in gestational week 28 were higher in women who exceeded the GWG recommendation [27].

Whether maternal plasma leptin levels differ substantially between obese and morbidly obese women, during and after pregnancy, have to our knowledge not been previously described. There are no available data on the association between maternal leptin levels in obese women,

during and after pregnancy, and recommended GWG, based on the IOM guidelines [28]. Accordingly, the aim of the present study was to estimate whether maternal plasma leptin levels were associated with different degrees of maternal obesity (obesity class I–III) during and after pregnancy and further to evaluate maternal plasma leptin levels during and after pregnancy in obese women with different levels of GWG, based on IOM guidelines.

Methods

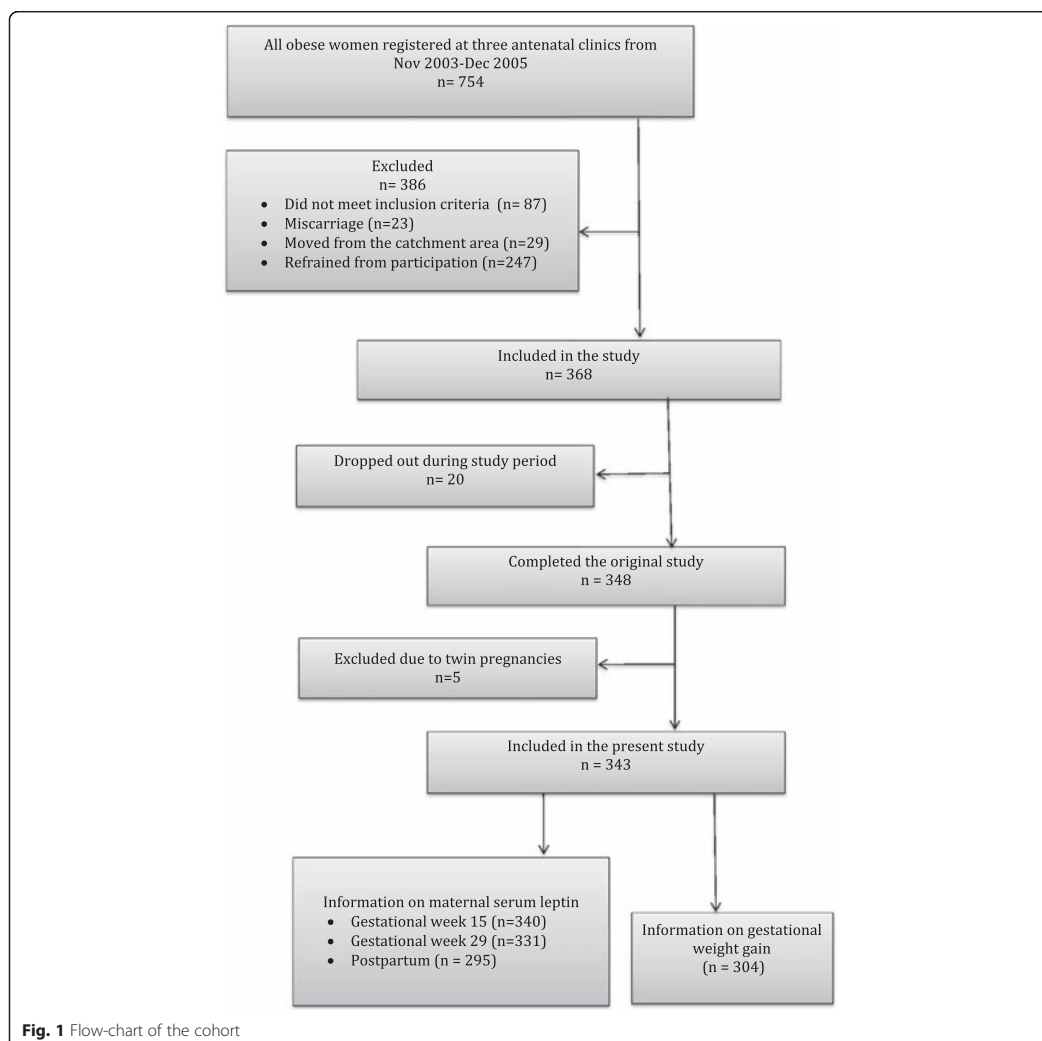
Data were collected as part of a prospective cohort study on obese pregnant women [29]. Between November 2003 and December 2005, all obese pregnant women ($n = 754$), consecutively registered in early pregnancy in three antenatal clinics in Sweden, were approached to the study [29]. The inclusion criteria were early pregnancy BMI ≥ 30 and knowledge of the Swedish language. The exclusion criteria were pre-pregnant diagnosis of diabetes mellitus, thyroid dysfunction or psychiatric disease treated with neuroleptic drugs. A flow chart of the study is presented in Fig. 1. Out of the 615 women who were eligible and invited to participate, 368 women were included in the study and 348 completed the study. Additionally five women, who expected twins, were excluded, leaving 343 women with singleton pregnancies as the present study population.

The study-population was categorized in three obesity classes of early pregnancy BMI, based on the WHO definition; class I obesity = BMI 30–34.9, class II obesity = BMI 35–39.9 (morbid obesity) and class III obesity = BMI ≥ 40 (morbid obesity) [30]. BMI was defined as body weight in kilograms divided by height in meter squared (kg/m^2). All women had their weight and height recorded in the gestation week eight to ten, which enabled calculation of BMI.

The study-population was also divided into three groups of GWG: < 5 kg, 5–9 kg and > 9 kg. In 2009 the IOM published guidelines advising optimal weight gain during pregnancy, based on pre-pregnancy BMI. According to these guidelines, the recommended GWG for obese women is 5–9 kg [28]. To calculate GWG we used maternal weight in delivery week minus early pregnancy weight. If maternal weight in delivery week was missing, the weight 1 or 2 weeks before delivery, was used. A total number of 304 women had information on GWG. Gestational age was calculated based on fetal biometry at the first trimester ultrasound. Data on maternal characteristics and pregnancy complications were retrieved from computerized patient records.

Maternal plasma leptin levels were measured in week 15 and 29 of gestation and 10 weeks postpartum. The women fasted prior to sampling of maternal blood. Maternal blood was collected in the morning in all patients.

For leptin analyses blood was collected in a test tube with a clot activator and gel for serum separation. One



hour after sampling, the blood was centrifuged, aliquoted and serum was stored at -70° Celsius until analyses.

The maternal plasma leptin concentration was measured using a direct sandwich based ELISA (Millipore, Billerica, USA). Human leptin was captured by a polyclonal antibody on a 96-well microtiter plate and unbound material washed away. A secondary monoclonal biotinylated antibody was added to the captured human leptin complex followed by streptavidin-horseradish peroxidase. The enzyme activity was measured spectrophotometrically (Victor 3, PerkinElmer, Waltham, MA, USA) at 450 nm after a last step of acidification of the sample products.

Increased absorbance was directly proportional to the amount of captured human leptin in unknown samples derived from a generated standard-curve. In a sample size of 25 μ L, the limit of sensitivity of the assay was 0.2 ng \pm 2 SD. The within and between assay variation was 4.6 and 6.2 % respectively. The specificity of the assay was 100 % for human leptin. No cross-reactivity was found for human pro-insulin, insulin, insulin-growth factor I and II or Glucagon.

Differences in categorical demographic variables as well as obstetric outcomes, between maternal obesity class I-III, were analysed using Pearson's Chi-square test

and ANOVA was used for analysing differences in continuous variables and outcomes (maternal age, birth weight, GWG and gestational length in weeks.) Categorical variables and outcomes were expressed as numbers (percentage) and if continuous as mean (SD).

The mean value and confidence interval of plasma-leptin during and after pregnancy in women with obesity class I-III and in obese women in three different GWG groups were analysed with a two-way ANOVA model. (Bonferroni adjusted within each gestational week).

Interaction effect between Maternal BMI and GWG was tested with a two-way ANOVA model.

General linear models were used to test possible confounding in addition to the main effect model of BMI and gestational weight gain.

All analyses were performed using IBM SPSS version 23 (IBM Inc, Armonk, NY). A *p*-value <0.05 was considered statistically significant.

The Regional Ethical Review Board in Linköping, Sweden approved this study (No 03–231).

Results

Out of the 343 women included in the study, 223 (65.0 %) were classified as obesity class I, 77 (22.4 %) were defined as obesity class II and 43 (12.5 %) as obesity class III. Of these 343 women, 304 (88.6 %) women had information that enabled calculation of gestational weight gain. A total number of 50 (16.4 %) women gained less than 5 kg (low GWG), 87 (28.6 %) gained 5–9 kg (recommended GWG) and 167 (54.9 %) exceeded the IOM gestational weight gain guidelines, i.e. more than 9 kg.

Maternal demographic characteristics, pregnancy outcome and complications over the BMI strata are presented in Tables 1 and 2. No differences in mean maternal age, parity, mean gestational age, birth weight, smoking and alcohol usage in first trimester were found between the groups. Mean GWG, was significant lower in obesity class III compared to obesity class I and class II. The distribution of GDM and hypertension before pregnancy did not differ substantially between the obesity classes. The prevalence of PE increased with increasing BMI.

In gestational week 15, samples from 340 (99.1 %) women were available for measurement of leptin levels and in gestational week 29, 331 (96.5 %) women. At 10 weeks post partum, leptin levels were measured in 295 (86.0 %) women (Fig. 1).

The median week, 25th and 75th percentiles and the lowest and highest value of pregnancy week or week postpartum when blood was drawn for leptin analyses, are presented in Table 3. There was no significant correlation between gestational week, when blood was drawn for leptin analyses, and the value of leptin, within each time-period of leptin measurement (week 15 *p* = 0.33, week 29 *p* = 0.45 and 10 weeks postpartum *p* = 0.70). Since there was no significant correlation between gestational week at leptin analyses and the value of leptin, within each time-period of leptin measurement, the leptin analyses have not been adjusted for gestational week at time of leptin measurement.

No significant interaction was found between maternal BMI and GWG, therefore the analyses on leptin and GWG-group were not adjusted for BMI and vice versa.

The mean maternal plasma leptin concentrations and 95 % confidence interval in the three obesity classes are presented in Fig. 2. Mean maternal leptin concentrations during and after pregnancy seem to be associated with degree of maternal obesity. The mean maternal leptin concentrations were significantly higher in women with obesity class III compared to women in obesity class I, at all times when plasma leptin were measured. The mean leptin concentrations were also significantly higher in women with obesity class II compared to women in obesity class I, except in gestational week 29. Postpartum the mean leptin concentrations were higher with increasing obesity category, although not reaching statistically significant difference between women in obesity class II and III.

The mean maternal plasma leptin concentrations and 95 % confidence interval, in the GWG groups are presented in Fig. 3. Mean maternal leptin concentrations during and after pregnancy do not seem to be associated with degree of GWG. There was no significant difference in plasma-leptin levels during and after pregnancy in obese women classified according to degree of

Table 1 Maternal characteristics and pregnancy outcome in relation to maternal obesity class. Continuous variables Mean (Std)

	Obesity class I <i>N</i> = 223	Obesity class II <i>N</i> = 77	Obesity class III <i>N</i> = 43	<i>P</i> -value
Maternal age (years)	30.0 (4.7)	30.4 (4.4)	29.0 (5.3)	0.322
Gestational length (full weeks)	39.2 (2.0)	39.8 (1.4)	39.0 (2.6)	0.076
Birth-weight (gram)	3708 (594)	3713 (448)	3670 (811)	0.920
Weight gain during pregnancy (kg)	10.6 (5.6)	9.6 (6.0)	7.7 (6.1)	0.015
	<i>N</i> = 203	<i>N</i> = 66	<i>N</i> = 35	

P < 0.05 statistical significance in difference between obesity class I-III groups

Table 2 Maternal characteristics and pregnancy outcome in relation to maternal obesity class. Categorical variables *N* (%)

	Obesity class I	Obesity class II	Obesity class III	<i>P</i> -value
Parity				0.714
Nulliparous	96 (43.0)	36 (46.8)	21 (48.8)	
Multiparous	127 (57.0)	41 (53.2)	22 (51.2)	
Smoking in pregnancy				0.059
No	206 (93.2)	72 (94.7)	35 (83.3)	
Yes	15 (6.8)	4 (5.3)	7 (16.7)	
Alcohol in first trimester				#
No/rarely	223 (100.0)	77 (100.0)	43 (100.0)	
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
Pre-term (<37 weeks)				0.046
No	209 (94.6)	76 (100.0)	38 (90.5)	
Yes	12 (5.4)	0 (0.0)	4 (9.5)	
Post-term (≥42 weeks)				0.993
No	206 (93.2)	71 (93.4)	39 (92.9)	
Yes	15 (6.8)	5 (6.6)	3 (7.1)	
GDM				0.505
No	211 (94.6)	75 (97.4)	40 (93.0)	
Yes	12 (5.4)	2 (2.6)	3 (7.0)	
Pre-eclampsia				0.009
No	211 (94.6)	68 (88.3)	35 (81.4)	
Yes	12 (5.4)	9 (11.7)	8 (18.6)	
Hypertension pre-pregnancy				#
No	221 (99.1)	77 (100.0)	42 (97.7)	
Yes	2 (0.9)	0 (0.0)	1 (2.3)	

GDM = Gestational diabetes mellitus

P < 0.05 statistical significance in difference between obesity class I-III groups

= Assumption for chi²-test not fulfilled

GWG, with one exception. Obese women with > 9 kg GWG had significantly higher mean plasma leptin concentration in pregnancy week 29 compared to obese women with recommended GWG (5–9 kg).

No significant confounding was found using general linear models. The resulting model included only the main effects of BMI and GWG (data not shown).

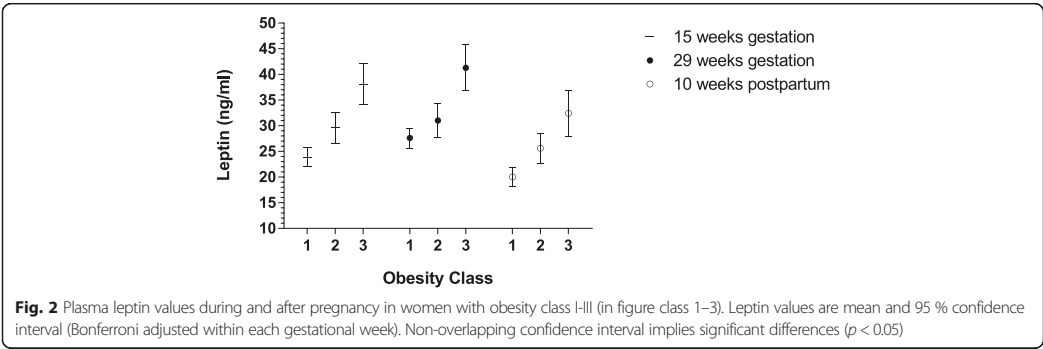
Table 3 Gestational week and weeks postpartum at leptin measurements

	Gestational week at measurement 1 <i>N</i> = 340	Gestational week at measurement 2 <i>N</i> = 331	Weeks postpartum at measurement 3 <i>N</i> = 295
Min	10	24	6
25 percentile	14	28	9
Median	15	29	10
75 percentile	16	30	12
Max	22	33	28

Discussion

This large study included 223 women in obesity class I and 120 women with morbid obesity (obesity class II and III) and showed higher leptin levels during and after pregnancy in women with morbid obesity, compared to women in obesity class I. Thus, at each leptin measurement during and after pregnancy maternal leptin levels were significantly higher among women in obesity class III compared to obesity class I women. There was no significant difference in maternal leptin levels at 15 weeks gestation and postpartum between low, recommended and excessive GWG. At 29 weeks gestation measurement women with excessive weight gain had a significantly higher leptin levels than women in obesity class II.

It is well described in epidemiological studies that the risk-estimates of adverse obstetric and neonatal outcome vary substantially between obesity class I and obesity class III [8, 31]. Leptin and other adipokines have been studied in relation to different adverse outcomes as well and have been found to be elevated in complicated pregnancies

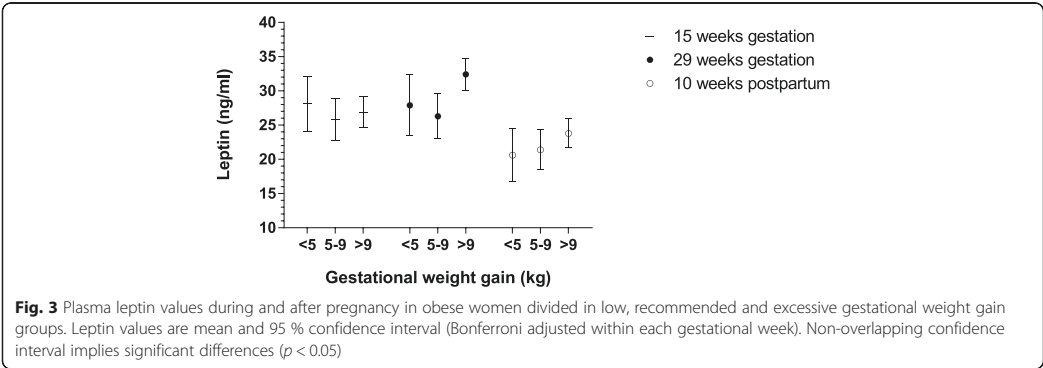


[12, 17, 19, 20]. Increased leptin levels have been found in women with PE [19, 20]. If such proteins are involved in the well described step-wise increased risk of adverse outcomes for both the mother and the infant for each higher obesity class, the levels of the adipokines should vary substantially with the degree of obesity. Results in this study add knowledge on this issue by showing a significant difference in leptin levels between the three degrees of obesity.

There are some previous studies indicating that maternal leptin levels are associated with maternal pre-pregnancy BMI [19, 22, 24-26]. Misra et al. studied the longitudinal effects of maternal pre-pregnancy BMI on serum leptin concentrations during pregnancy in 143 women, categorized as non-overweight or overweight/obese. Leptin levels were analysed five times during pregnancy. Leptin concentrations were higher in the overweight/obese group but increased at a significantly lower rate across gestation, compared to normal weight [24]. Similar results were presented in Brazilian study including 42 women, categorized as normal-weight or overweight/obese, according to their pre-pregnancy BMI [25] Yang et al. reported that serum leptin concentrations in 114 women, with a normal

singleton pregnancy, correlated with gestational age, maternal bodyweight and BMI in the three trimesters of pregnancy [22]. This is in accordance with findings in the present study. However there are differences. The majority of previous studies were based on relatively small cohorts and often analysed obese and overweight women as one group or with few obese individuals included.

This study showed that there was no difference in maternal plasma leptin levels during and after pregnancy in obese women with excessive GWG, compared to obese women with recommended GWG, with one exception. Among women with excessive weight gain in gestational week 29, women in obesity class III had significantly higher leptin levels compared to those in obesity class II. Although the confidence limits are close to each other but not overlapping. It is possible that excessive weight gain in late second trimester contributes to significantly higher leptin levels. It seemed though that the degree of weight gain during pregnancy in obese women is of minor importance for the actual serum leptin value during and after pregnancy compared to early pregnancy BMI. Walsh et al. prospectively studied serum leptin concentration in 621 pregnant women, subdivided into those



who did ($n = 267$) and those who did not ($n = 354$) exceed the IOM gestational weight gain guidelines, regardless of BMI in early pregnancy. Maternal plasma leptin concentrations were measured in early pregnancy and in gestational week 28. The leptin levels were significantly higher in women with excessive weight gain in gestational week 28 but not in early pregnancy [27].

Excessive GWG has previously been shown to increase risk factors related to obstetric and neonatal outcome in obese women [9], although to a lower magnitude than risks associated with morbidly obesity. Epidemiological data have shown that the most favourable obstetric and neonatal outcome among obese women is related to low GWG, except for birth of small for gestational age infants [32, 33].

This study has certain strengths and limitations. One of the strength is the large number of obese individuals included, which enabled analyses of three subgroups of obesity. In addition, BMI was based on measured weight in week eight to ten of gestation. The IOM guidelines are based on pre-pregnancy weight. However during the first two months of pregnancy, the weight gain is minimal [34]. Further, information on GWG was available in a majority of the obese women included, which enabled a division into three groups according to degree of GWG. A thorough baseline evaluation on maternal comorbidity and demographic variables and continuous registration of maternal complications in all study subjects were also available. This information made it possible to demonstrate that there were no major differences between the different obesity classes concerning variables that could have influenced the maternal leptin levels.

There are limitations of this study. The postpartum measurement of leptin could only be performed in 86 % of the study subjects since not all women attended the proposed postpartum control. Apart from this, almost all study subjects (98.5 %) had complete information on leptin concentration during pregnancy. It must also be kept in mind when interpreting the data, that although a large sample size in the study-population, numbers in certain subgroups were low. Another limitation is the lack of data on maternal leptin at time of delivery.

Conclusions

In conclusion, this study demonstrated that maternal plasma leptin levels during and after pregnancy differed significantly between the women with obesity and morbid obesity. Further no major differences in leptin levels were defined between women with low, recommended and excessive GWG. That is in concordance with observations done in epidemiological studies where the most severe complications during and after pregnancy occur among morbidly obese women and the amount of GWG could alter these risks marginally.

Ethics approval and consent to participate

The Regional Ethical Review Board in Linköping, Sweden approved this study. (No 03–231.) Written informed consent was received from all study participants.

Consent for publication

Not applicable.

Availability of data and materials

Data supporting our findings can be sent upon request.

Abbreviations

BMI: body mass index; GWG: gestational weight gain; GDM: gestational diabetes mellitus; PE: pre-eclampsia; IOM: Institute of Medicine; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IMB, GS, AJ contributed to the original study design. IMB contributed to measurements. AT contributed to leptin analyses. SC, MBLO, JB contributed to the present study design. SC, MBLO and MBLA contributed to data analysis. SC wrote the manuscript under the supervision of MBLO. JB helped with construction of manuscript. All authors read and approved the final manuscript.

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PAPER IV

Maternal plasma leptin levels in relation to the duration of the active phase of labor.

Running headline: Maternal leptin and duration of labor.

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Conflicts of interest statement: The authors declare no conflicts of interest.

Abstract

Introduction: Obese women have increased leptin levels and longer duration of labor compared to normal weight women. Leptin has an inhibitory effect on myometrial contractility *in vitro*. Our purpose was to examine whether maternal leptin levels in active labor were associated with the duration of the active phase of labor.

Material and methods: This prospective cohort study included 914 women. Maternal blood samples were collected in active labor. The plasma-leptin concentration was obtained using a direct sandwich-based ELISA. Bivariate and multiple linear regression analyses were used to study the association between leptin levels and the duration of labor.

Results: A one ng/ml increase in maternal plasma leptin was associated with a 0.015 hour increase in duration of labor ($p < 0.007$). This association was not statistically significant in the adjusted analyses or when analyzing nullipara and multipara separately. In women with spontaneous labor ($n = 766$) leptin was not associated with an increase in duration of labor in the adjusted analyses.

Conclusions: There was no significant association between leptin levels and duration of the active phase of labor. Leptin *in vivo* might display a similar dose-response effect on myometrial contractility as demonstrated in *in vitro* studies. Future studies need to explore the association between leptin levels and time in labor in obese women with high leptin levels to evaluate a possible dose-response effect.

Key words: Leptin, duration of labor, active phase of labor, obesity, delivery.

Abbreviations: BMI=body mass index, GWG=gestational weight gain, GDM=gestational diabetes mellitus.

Key message: Duration of the active phase of labor increased with maternal leptin levels measured in active labor, however the increase was not significant in the adjusted analyses.

Introduction

The increasing worldwide prevalence of maternal obesity is concerning considering the strong association with complications for the obese mother and her child (1-3). As regards the majority of obesity-related complications during pregnancy and labor, the risks seem to increase with a higher degree of obesity (2-4). Obese women more often have a dysfunctional labor pattern compared to normal weight women and the duration of labor increases with maternal body mass index (BMI) (5, 6). Many studies have demonstrated that there are no associations between BMI and the length of second stage of labor suggesting that the effect of maternal overweight and obesity on time in labor is restricted to the active phase of labor (6-8). Post-dated pregnancies and induction of labor are more common in obese women, who also require more oxytocin for augmentation than normal weight women (9, 10).

The exact mechanism of dysfunctional labor in obese women is not fully understood and presumably is multifactorial. Impaired myometrial contractility has been proposed to be of importance. It has been demonstrated that the myometrium of obese women contracts with less force and frequency *in vitro* than myometrial fibers of normal weight women (11).

Adiposity-related hormones such as leptin, an adipokine mainly produced by white adipose tissue, might affect uterine contractility. Leptin receptors have been identified in the myometrium as well as in other reproductive tissues (12). During pregnancy, the placenta is a major source of leptin production and contributes to the elevated levels seen in all pregnant women (13). Maternal leptin levels increase during gestation, peak in late second or early third trimester, decrease towards the end of the pregnancy in normal weight women and decline drastically postpartum, suggesting an important role during gestation (13-15). Obese pregnant women seem to have increased leptin levels compared to normal weight women (16) and morbidly obese women have the highest leptin values (17). Leptin has been reported to depress human myometrial contractility *in vitro* (18, 19) and to maintain uterine quiescence by inducing myometrial proliferation (20). These findings have led to speculations about whether leptin could be used as a tocolytic agent (20, 21).

Since pregnant obese women display elevated levels of leptin, and seem to have less effective myometrial labor contractions, we hypothesized that high leptin values might contribute to the

dysfunctional labor often observed in obese women. To our knowledge, there are no previous published studies on the predictive effect of maternal plasma leptin on the duration of labor. In this study we therefore aimed to examine whether maternal leptin levels were associated with the duration of the active phase of labor in the total study population as the primary outcome, and in women restricted to a spontaneous start of labor as a secondary outcome.

Materials and methods

Study design and participants

This prospective cohort study, including 914 pregnant women who delivered between April 1, 2014 and December 10, 2015, was conducted at Linköping University Hospital, Sweden. At the first antenatal visit in gestational weeks six to ten, all pregnant women in Linköping aged 18 years or older, were informed and asked to participate by attending a local biobank (register number 185, at the department of Obstetrics and Gynecology, Östergötland County Council) for collection of maternal blood samples during pregnancy and labor. In Sweden, 95 % of all women attend an antenatal clinic during the first trimester. After giving informed written consent the women, consecutively recruited to this biobank in early pregnancy, were included in the present study. Women with multiple pregnancies, diabetes mellitus, intrauterine fetal death, premature labor (gestation week < 37+0), elective caesarean section, missing leptin value or incomplete information on the time estimates of the active phase of labor, were excluded. Hence, all women who had undergone an emergency cesarean section during the active phase of labor (before pushing efforts started) were excluded (Figure 1).

Variables and parameters included in study

Maternal height and weight were measured at the baseline visit in gestation weeks six to ten. Maternal socio-demographic data, medical history, pregnancy complications, maternal weight on admission to the delivery ward, and data on labor and birth were prospectively recorded in standardized medical records (Obstetrix[®], Cerner) by midwives or doctors at the department of Obstetrics and Gynecology, Linköping University Hospital. BMI was calculated using maternal weight and height data, which were recorded in early pregnancy. Gestational weight gain (GWG) was defined as maternal weight gain in kg from weight at the baseline visit in early pregnancy to measured weight on admission to the delivery unit. The study population was sub-classified into

three GWG groups; below recommended, recommended, or excessive weight gain based on the American Institute of Medicines guidelines on weight gain during pregnancy, in relation to pre-pregnancy BMI (22). Onset of active labor was, at the time of the study, defined as regular painful uterine contractions, three to four per ten minutes, and a cervical dilatation of three cm or more. The midwife at the delivery ward prospectively recorded the time when active labor and pushing efforts started. The active phase of labor was defined as from the start of active labor until the start of the pushing efforts.

Analysis of plasma leptin

Maternal plasma was collected shortly after the women had arrived to the delivery ward as soon as she was assessed to be in active labor. For leptin analyses blood was collected in a test tube with a clot activator and gel for plasma separation. One hour after sampling, the blood was centrifuged, aliquoted, and plasma was stored at -70 degrees Celsius in the local biobank (register number 185, at the department of Obstetrics and Gynecology, Östergötland County Council) until further analyses. The plasma leptin concentration was obtained using a direct sandwich-based ELISA (Catalogue # EZHL-80SK; Merck-Millipore, Solna, Sweden) according to the manufacturer's instructions. Human leptin was captured by a polyclonal antibody on a 96-well microtiter plate, followed by addition of a secondary monoclonal biotinylated antibody. Streptavidin-horseradish peroxidase was then added to the biotinylated antibodies, and in the final step prior to measuring enzyme activity. The enzyme activity was measured spectrophotometrically (Victor 3, PerkinElmer, Waltham, MA, USA) at 450 nm after acidification of the sample products stopping the enzymatic reaction. In between each step the wells were washed three to five times to eliminate unbound material. Increased absorbance was directly proportional to the amount of captured human leptin in unknown samples, and quantification was derived from a generated reference curve with reference calibrators of known concentrations. In a sample size of 25 μ L, the limit of sensitivity of the assay was 0.17 ng + 2 SD. The within and between assay variation was 3.8 and 6.2 %, respectively. The specificity of the assay was 100 % for human leptin. No cross-reactivity was found for human pro-insulin, insulin, insulin-growth factor – I and – II, or glucagon. All samples were run in duplicates and a CV cut-off of 15% was set for each duplicate.

Data management and statistical analyses

Time in the active phase of labor in relation to leptin levels and maternal and fetal characteristics were analyzed in the total study population as well as in nulliparous and multiparous women separately. Furthermore, 766 women with a spontaneous start of labor were analyzed separately after excluding women with induced labor. Maternal BMI in early pregnancy, GWG, parity, maternal age, birth-weight, gestational week at delivery, smoking, pre-eclampsia, gestational diabetes mellitus (GDM), induction of labor, epidural anesthesia and usage of oxytocin (for either induction or augmentation of labor) were regarded as potential confounding factors. Bivariate and multiple linear regression analyses were used to study the association between maternal leptin levels and duration of the active phase of labor. The first multivariable model included leptin levels and variables considered as possible confounding factors with $p < 0.2$ in the bivariate analyses and the final restricted multivariable model included leptin levels and variables with $p < 0.2$ in the first full multivariable model. The dataset was restricted to case records with known leptin levels and length of the active phase of labor. Missing data on GWG were handled using multiple imputation (number of imputed data sets = 20). A Kaplan-Meier analysis was performed and a graph produced in order to illustrate the association between maternal BMI, leptin levels in active labor and time in the active phase of labor. Women who were normal-weight or underweight with levels below or similar to/above the leptin value of the third quartile (37 ng/ml) were compared to women who were overweight or obese with leptin levels below or similar to/above the third quartile leptin value (37 ng/ml). All analyses were performed using IBM SPSS version 23 (IBM Inc, Armonk, NY). A p-value < 0.05 was considered statistically significant.

Ethical approval

The Regional Ethical Committee in Linköping, Sweden approved this study (Dnr 2010/296-31 date of approval 2010-10-13, Dnr 2013/378-32 date of approval 2013-09-27).

Results

The study-population included 914 women with information on maternal plasma leptin levels in active labor and duration of the active phase of labor. In this study population 48.8 % of the women were nulliparous and 51.3 % were multiparous, 24.5 % were overweight and 8.8 % were

obese. Labor started spontaneously in 83.8 % (766) of the women. The mean time and 95 % confidence interval (CI) in the active phase of labor was 8.7 (CI; 8.3-9.2) hours in nulliparous women and 4.6 (CI; 4.3-4.9) hours in multiparous women. Descriptive data on maternal and fetal characteristics during pregnancy and labor and maternal leptin levels (ng/ml) in median and quartiles are presented in Table 1. The median leptin values were higher with increasing maternal BMI. The median leptin levels were lower in women with a GWG below recommendations compared to women with recommended GWG, and increased in women with excessive GWG. Figure 2 shows a Kaplan-Meier graph, illustrating the cumulative chance to end the active phase of labor at a certain time point, by maternal BMI category and leptin value in active labor. There was no overall statistically significant difference between the groups ($p = 0.296$). However, from the figure a difference is seen between the groups after 10 hours duration of active labor, when normal-weight/underweight women with lower leptin levels (below the third quartile/ < 37 ng/ml) had a greater chance to end the active phase of labor at a given time point compared to overweight/obese women with high leptin levels (≥ 37 ng/ml).

The time in the active phase of labor in relation to maternal leptin levels, and maternal and fetal characteristics in the total study population are presented in Table 2. A one ng/ml increase in maternal plasma leptin was associated with a 0.015 hour increase in duration of labor ($p < 0.007$) in the unadjusted analyses. In women with morbid obesity (BMI ≥ 35) the median leptin value were 50 mg/ml, which would mean that time in the active phase of labor increased 0.75 hours. Nulliparous women, those who used epidural anesthesia and those who received oxytocin during labor had statistically significantly longer duration of the active phase of labor compared to their counterparts in the unadjusted analyses. Furthermore, the time in labor increased statistically significantly with gestational age and birth-weight. GWG but not BMI was associated with time in the active phase of labor in the unadjusted analyses. In addition, the active phase of labor was statistically significantly shorter in women with induced labor compared to those with spontaneous onset of labor.

In the adjusted analyses the statistically significant association between leptin levels and duration of the active phase of labor did not persist. In the final multivariable analyses nulliparity, birth-weight and usage of epidural anesthesia or oxytocin were statistically significantly associated

with increased duration of the active phase of labor and induction of labor was statistically significantly associated with a shorter duration of the active phase of labor (Table 2).

When nulliparous and multiparous women were analyzed separately, no significant associations between the time in the active phase of labor and maternal leptin levels were found in any of the groups. Results not shown.

In the 766 women with a spontaneous onset of labor, a one ng/ml increase in maternal leptin level was associated with a 0.016 hours increase in duration of the active phase of labor ($p < 0.005$) in the unadjusted analyses (Table 3). However, this association was not significant when adjusting for confounding factors or when analyzing nulliparous and multiparous women with spontaneous labor separately. Results not shown.

Discussion

Here, we present a first study examining correlations between plasma leptin levels from mothers in early active labor and duration of the active phase of labor. At the onset of this study we anticipated that high leptin levels would have an antagonistic effect on the duration of the active phase of labor. In this study population of 914 women, with a low prevalence of obesity, we found a significant effect of leptin on time in the active phase of labor in the bivariate analyses but not in the multivariate adjusted analyses. This could mean that in our study-population, other birth related factors were of more importance than leptin, in influencing the time in the active phase of labor.

To our knowledge there are no previous published reports on maternal leptin levels measured in active labor in relation to labor duration. Logan et al found a significant association between the increased duration of labor and higher cord blood leptin levels. Maternal leptin levels were not included in the analyses (23). In the same cohorts with a smaller number of participants, maternal leptin levels were measured 24 hours postpartum and correlated with cord blood leptin levels (24). However, as maternal leptin levels decrease rapidly after delivery (13), and we do not know how maternal leptin levels during active labor differ from maternal leptin levels shortly after delivery, our results are difficult to compare.

There are several *in vitro* studies suggesting that leptin might play a role in the regulation of myometrial activity (12, 18-20, 25). Two separate studies demonstrated an *in vitro* inhibitory effect of leptin on contractions in myometrial biopsies from non-laboring pregnant women (18, 19). Leptin may also prevent remodeling of myometrial extracellular matrix, which is necessary for effective uterine contractions during labor (25), and inhibit myometrial apoptosis, which is of importance for uterine smooth muscle to change from a proliferative to contractile status (12). Leptin has also been shown to be able to induce human myometrial proliferation and maintain uterine quiescence and thereby oppose the mechanisms that trigger labor and myometrial contractions (20). It has been speculated that if leptin has the same function in the uterine smooth muscle cells as in vascular smooth muscle and reduce intracellular calcium [Ca^{2+}] release, it could impair the contractile ability of the myometrium (26). This idea was supported by Zhang et al. who demonstrated reduced frequency and amplitude of contractions in myometrium from obese pregnant women *in vitro*. The tocolytic effect was explained by less [Ca^{2+}] flux observed in the myometrium of obese women compared to normal weight women (11). With this large number of preclinical studies demonstrating a tocolytic activity by leptin, one might speculate why no association between maternal leptin levels in early active labor and duration of active labor was found in the present study.

Perhaps the results would be different if more obese women were included, as median levels were higher in the obese women and maybe there were too few women with high leptin levels to demonstrate a statistically significant effect in the adjusted analyses. Several authors demonstrate that the *in vitro* myometrial relaxant effect of leptin is cumulative and more pronounced with increasing leptin concentrations (18, 19). This raises the question of whether the inhibitory effect of leptin on uterine contractility only exists at high leptin levels, as is observed in obese women? In normal weight women, maternal leptin concentrations increase from early pregnancy but start to decrease towards the end of pregnancy (14). Considering the *in vitro* relaxant effect of leptin, high leptin levels at the time of delivery would have an antagonistic effect on the myometrium. It is possible that although placental production of leptin decreases close to parturition, leptin levels derived from adiposity tissue in obese women might still be high enough to affect the myometrial contractility.

In our study population, a number of birth related factors other than maternal leptin were significantly associated with duration of the active phase of labor. Parity, birth-weight and the use of epidural anesthesia and oxytocin had the most pronounced effect on time in labor. Being nulliparous or delivering a large for gestational age child are known risk factors for increased duration of labor. Those strongly correlated factors to duration of labor might have concealed the effects of leptin. Another possibility is that a longer duration of the active phase of labor influenced the decision to use oxytocin or to give an epidural anaesthesia and therefore could explain the association between those factors and duration of labor. In contrast to several other studies, maternal BMI in our study-population was not significantly associated with duration of the active phase of labor (5-8). This could be explained by the low prevalence of obese women in our study-population.

The strength of this present study is the large number of participants with information on the actual maternal leptin value when the outcome, time in the active phase of labor, was measured. We chose to restrict the analyses on the association between leptin levels and duration of labor to the active phase of labor, as previous studies indicate that the dysfunctional part of labor in obese women seem to be restricted to the active phase of labor (7, 8). Furthermore, uterine contractility and maternal pushing ability during the second stage do not seem to be dependent on maternal BMI (27). The prospective design enabled us to follow the cohort from early pregnancy, with a thorough baseline evaluation on maternal co-morbidity and socio-economic factors and continuous registration of maternal complications during pregnancy, consequently adjusting the statistical analyses for possible confounding factors. The size of the study population also enabled us to analyze subgroups based on parity and onset of labor.

Information on GWG was missing in 27.8 % of the women. Multiple imputation was used to deal with missing information in the adjusted analyses, which included GWG as a potential confounding factor.

There are certain limitations. Our study population, restricted to those who agreed to participate in the biobank, may not be representative of the total population. The women in the biobank have so far not been described elsewhere. The number of obese women in the present study (BMI >30)

was 8.8 % compared to 13.6 % in the total pregnant population in Sweden 2015 (28). This may limit the generalizability of our results.

As it is unknown whether maternal leptin levels change during active labor, the sample time of maternal plasma might be an important potential confounding factor. Unfortunately, we had no information on the exact time of maternal plasma sampling. For most women sampling was done as soon as they arrived to the delivery-ward and were assessed to be in active labor.

Since we only included women with information on the active phase of labor and the end of the active phase of labor was defined as the start of pushing efforts, 67 women with missing information on the time when pushing phase started were excluded. This could have biased our results since all women with an emergency cesarean section during the active phase of labor were thus excluded. The small number of cesareans performed after pushing has begun is a result of the implementation of a “nine-item list” of structured organizational and cultural changes at the delivery unit, where one of the efforts was to increase the staff confidence in handling instrumental delivery (29). The measurement of cervical dilatation and defining the start of regular contractions were subjective. If the study population is large, the estimation of these parameters may not be uniform across the study population, but the variation is probably not related to maternal leptin levels. Another limitation is our definition of the start of active labor. We have used the definition that was nationally accepted in Sweden at the time of this study. However, recent studies have shown that latent labor may last until up to six centimeters of cervix dilatation has occurred, and that there can be great variation in the duration of latent labor (30). This may limit the generalizability of the present study.

In conclusion, this study could not demonstrate a significant association between leptin levels and duration of the active phase of labor. A positive association between increasing maternal leptin levels and longer time in the active phase of labor in the total study population as well as in women with a spontaneous onset of delivery was found in the bivariate analyses. However, this association was not statistically significant when adjusting for confounding factors or when analyzing nulliparous- and multiparous women separately. It is possible that leptin, as a single putative factor, may not cause a clinical negative effect on the contractile ability of the myometrial fibers during the active phase of labor, such as the inhibitory effect of leptin on myometrial contractility demonstrated in *in vitro* studies. On the other hand, leptin *in vivo* might

display a similar dose-response effect as *in vitro*, which not could be demonstrated in this study population, with a low prevalence of obese women. Whether the association between maternal leptin levels and duration of labor is different in obese women needs to be investigated in future studies.

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Table 1. Maternal and fetal characteristics during pregnancy and labor and maternal plasma leptin levels in active labor. (N = 914)

Characteristics	N	%	Maternal leptin levels (ng/ml) – median and quartiles			
			25%	Median	75%	
Maternal characteristics						
Age < 25 (years)	88	9.6	18.1	25.4	43.2	
Age ≥ 35 (years)	173	18.9	12.7	23.4	35.1	
Para 0	445	48.6	15.4	25.0	40.9	
Para 1+	469	51.3	13.6	21.8	34.5	
Smoking yes	18	2.0	18.0	27.4	33.3	
Smoking no	896	98.0	14.3	23.4	37.1	
BMI <18.5 (kg/m ²)	17	1.9	6.04	13.8	22.5	
BMI 18.5-24.9 (kg/m ²)	591	64.7	13.2	20.2	30.8	
BMI 25.0-29.9 (kg/m ²)	224	24.5	19.9	30.9	42.5	
BMI 30.0-34.9 (kg/m ²)	61	6.7	20.5	36.2	51.1	
BMI ≥35 (kg/m ²)	19	2.1	30.5	50.0	65.0	
Missing BMI	2	0.2				
Below recommended GWG	141	15.4	10.6	16.4	25.6	
Recommended GWG	256	28.0	14.5	23.1	34.6	
Above recommended GWG	263	28.8	21.4	33.0	48.4	
Missing GWG	254	27.8	12.6	20.1	33.1	
Pre-eclampsia yes	19	2.1	21.6	29.4	55.6	
Pre-eclampsia no	895	97.9	14.2	23.2	36.9	
GDM yes	12	1.3	22.5	25.8	46.9	
GDM no	902	98.7	14.3	23.3	37.0	
Delivery characteristics						
Gestational age 37-38 weeks	147	16.1	13.5	21.5	35.0	
Gestational age 39-40 weeks	515	56.3	14.1	23.3	37.8	
Gestational age ≥41 weeks	252	27.6	16.0	23.9	37.8	
Induction yes	148	16.2	15.4	24.9	36.8	
Induction no	766	83.8	14.3	23.1	37.0	
Epidural yes	419	45.8	15.6	24.9	38.8	
Epidural no	495	54.1	13.3	22.0	36.1	
Oxytocin yes	442	48.4	16.0	25.8	38.3	
Oxytocin no	472	51.9	13.3	21.4	36.1	
Vaginal, non-instrumental	846	92.6	14.2	23.1	36.8	
Instrumental delivery	65	7.1	17.3	30.0	46.1	
Emergency cesarean section	3	0.3	20.9	22.7	24.7	
Fetal characteristics						
Birth-weight <2500g	12	1.3	14.4	25.3	33.4	
Birth-weight ≥4500g	28	3.1	16.7	27.0	37.5	
Female gender	449	49.1	14.4	22.6	55.6	
Male gender	465	50.9	14.4	23.8	59.8	
Apgar score 5 min <7	11	1.2	14.4	23.1	46.4	
Apgar score 5 min ≥7	903	98.8	14.3	23.4	36.9	

BMI= body mass index in early pregnancy, GDM = gestational diabetes mellitus

GWG = gestational weight gain according to IOM's recommendations

Table 2. Time in the active phase of labor (h) in relation to maternal and fetal characteristics and maternal leptin levels (ng/ml). Results from bivariate and multiple linear regression analyses (N=914).

Characteristics		Crude estimate		Estimates from first multivariable model ^a		Estimates from final restricted multivariable model ^b	
		Beta-coefficient ^c	p-value	Beta-coefficient ^c	p-value	Beta-coefficient ^c	95% confidence interval
	Age (per one year increment)	-0.19	<0.001	-0.03	0.259		
	Parity (0 vs. 1+)	4.05	<0.001	2.08	<0.001	2.19	1.68-2.69
	Smoking (yes vs. no)	0.39	0.711				
	Maternal BMI (per one kg/m ² increment)	0.04	0.235				
	Pre-eclampsia (yes vs. no)	0.04	0.970				
	GDM (yes vs. no)	-0.72	0.575				
	GWG (per one kg increment)	0.10	0.002	-0.01	0.819		
	Gestational age (per one week increment)	0.08	<0.001	0.03	0.068	0.03	0.00-0.06*
	Induction (yes vs. no)	-2.15	<0.001	-3.37	<0.001	-3.37	-4.02 to -2.72
	Epidural (yes vs. no)	4.03	<0.001	2.38	<0.001	2.39	1.89-2.89
	Oxytocin (yes vs. no)	3.55	<0.001	2.65	<0.001	2.63	2.10-3.16
	Birth-weight (per 100g increment)	0.06	0.041	0.10	<0.001	0.09	0.04-0.14
	Leptin levels (per one ng/ml increment)	0.015	0.007	0.004	0.326	0.004	-0.004 to 0.013

^a Includes leptin levels and variables with p < 0.2 in the bivariate analyses.

^b Includes leptin levels and variable with p < 0.2 in the first full multivariable model.

^c The beta coefficients represents the slope, the change in maternal duration of labor per one unit increment of each evaluated factor (as specified above).

BMI = body mass index

GDM = gestational diabetes mellitus

GWG = gestational weight gain

*Non-significant

Table 3. Time in the active phase of labor (h) in relation to maternal and fetal characteristics and maternal leptin levels (ng/ml) in women with a spontaneous start of labor. Results from bivariate and multiple linear regression analyses. (N=766)

Characteristics		Crude estimate		Estimates from first multivariable model ^a		Estimates from final restricted multivariable model ^b	
		Beta-coefficient ^c	p-value	Beta-coefficient ^c	p-value	Beta-coefficient ^c	95% confidence interval
	Age (per one year increment)	-0.20	<0.001	-0.05	0.123	-0.05	-0.11 to 0.01
	Parity 0 vs. 1+	4.08	<0.001	1.73	<0.001	1.69	1.09-2.27
	Smoking (yes vs. no)	1.66	0.179	0.44	0.645		
	BMI (per one unit increment)	0.07	0.076	0.04	0.204		
	Pre-eclampsia (yes vs. no)	-0.61	0.734				
	GDM (yes vs. no)	-0.16	0.920				
	GWG (per one kg increment)	0.10	0.003	0.01	0.647		
	Gestational age (per one week increment)	0.10	<0.001	0.06	0.001	0.06	0.03-0.09
	Epidural (yes vs. no)	4.47	<0.001	2.41	<0.001	2.43	1.88-2.98
	Oxytocin (yes vs. no)	4.74	<0.001	2.79	<0.001	2.82	2.26-3.39
	Birth-weight (per 100g increment)	0.04	0.21				
	Leptin levels (per one unit increment)	0.016	0.005	0.003	0.564	0.005	-0.004 to 0.013

^a Includes leptin levels and variables with $p < 0.2$ in the bivariate analyses.

^b Includes leptin levels and variable with $p < 0.2$ in the first full multivariable model

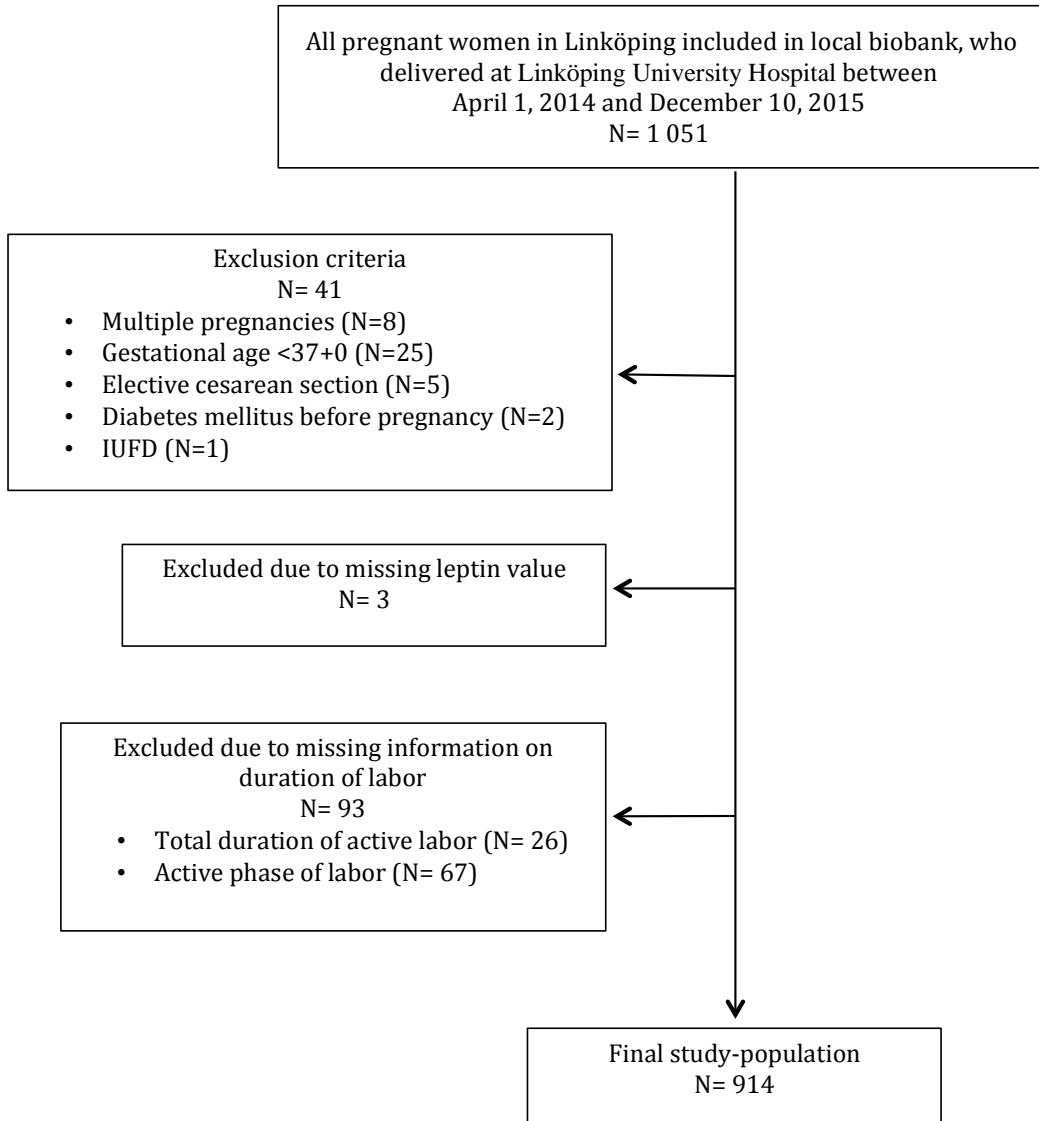
^c The beta coefficients represents the slope, the change in maternal duration of labor per one unit increment of each evaluated factor (as specified above).

BMI = body mass index

GDM = gestational diabetes mellitus

GWG = gestational weight gain

Figure 1: Flow chart of the included and excluded women in the cohort.



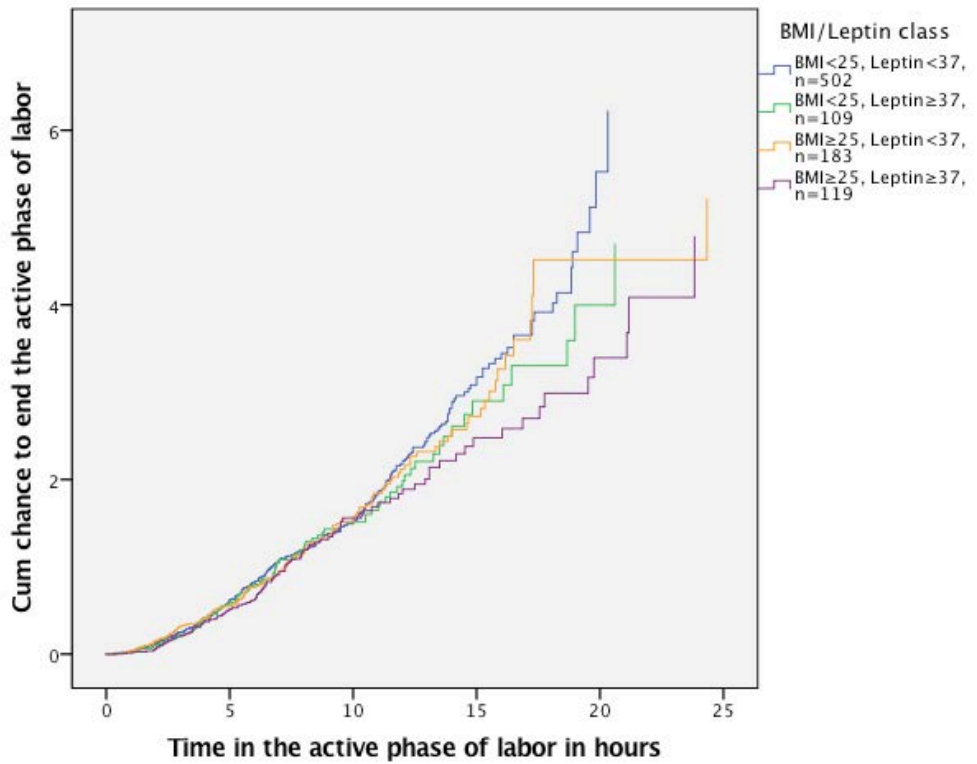


Figure 2. Cumulative hazard plot of the study population (N=914). The chance to end the active phase of labor at certain time point, in relation to early maternal BMI and leptin value in active labor, below or similar to/above the third quartile of leptin (37 ng/ml) in all women. Event was defined as end of active phase of labor. $p=0.296$.