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INTERVENTIONS DURING PREGNANCY AND LABOR AND OBSTETRIC OUTCOME

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Stockholm 2011

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ISBN 978-91-7457-444-9

To Martin, Kajsa, Teo and Klara

ABSTRACT

Objectives: The overall objective with the present thesis was to assess pregnancy and delivery associated risk factors for adverse pregnancy outcomes. Specific aims were : 1) to analyze the association between fetal size at the time of dating ultrasound and the risk of preterm delivery, small for gestational age birth (SGA), and macrosomia and to evaluate if the timing of ultrasound, i.e. before 14 weeks of gestation or after 16 weeks, affected this association, 2) to assess the risk of emergency cesarean section among women who were induced to labor in gestational week ≥ 41 and to evaluate if parity and mode of induction affected this association, and 3) to analyze if starting time for labor induction affected the risk of night-time delivery, and evaluate to what extent the risk was influenced by Bishop score at start of induction, mode of induction, and parity.

Study 1 and 2 were retrospective cohort studies based on an obstetrical database containing data on all obstetrical care at Danderyd Hospital from 1998-2004. The data was linked to the Swedish Medical Birth Registry. The analysis included 27 952 women. Of these, 5053 had gestational duration assessed through ultrasound before 14 weeks (early) and 22 889 after 16 weeks (late). Risks of preterm delivery, SGA and macrosomia were calculated. When the expected date of delivery was postponed after ultrasound dating ≥ 7 days, regardless of time of dating ultrasound, there was an increased risk of SGA. For preterm birth there was an increased risk for fetuses dated late. When the fetus was ≥ 7 days larger than expected at late ultrasound dating, compared to the expected size according to last menstrual period, there was an increased risk of macrosomia. Fetal size in early pregnancy is not only a function of gestational duration, but also of fetal growth. Accordingly, our studies suggest that surveillance of pregnancies with postponed estimated date of delivery may provide means for increased detection of fetal growth restriction. However, only a limited proportion of all infants born macrosomic can be detected at the time of dating ultrasound.

Study 3 and 4 were retrospective cohort studies including 23 030 women with singleton pregnancies who were delivered in gestational week ≥ 37 at Danderyd Hospital, Stockholm, Sweden, during the period 2002 - 2006. The data was linked to the Swedish Medical Birth Registry. 881 of these pregnancies were induced to labor at ≥41 gestational weeks, and 1940 at gestational week ≥37. All of the included women with induction of labor had a Bishop score of <7. Prostaglandin E2 or transcervical catheter was used for cervical ripening. Risks of emergency cesarean section and night-time delivery were calculated. Among nulliparous women who were induced at gestational week ≥ 41 there was threefold increase in risk of emergency caesarean section and an almost twofold increase in risk among multiparous compared to women with spontaneous onset of delivery. When labor is induced the high risk for emergency cesarean must be kept in mind. For nulliparae with Bishop score of 0-3 induced by transcervical catheter there was a reduction in risk for night-time delivery when inductions started in the afternoon and evening compared to inductions started in the morning. For multiparae, however, the risk of night-time delivery was highest after induction started in the afternoon and evening, respectively independent of bishop score or method of cervical ripening. Thus, the starting time of labor induction affects the risk of giving birth at night.

LIST OF PUBLICATIONS

I. Expected date of delivery from ultrasound dating versus last menstrual period – obstetric outcome when dates mismatch

Malin Thorsell MD, Magnus Kaijser MD PhD, Harald Almström MD PhD, Ellika Andolf MD PhD

British Journal of Obstetrics and Gyneacology. 2008 Apr;115(5):585-9.

II. Large fetal size in early pregnancy associated with risk for macrosomia

Malin Thorsell MD, Magnus Kaijser MD PhD, Harald Almström MD PhD, Ellika Andolf MD PhD

Ultrasound Obstet Gynecol 2010;35(4):390:4.

III. Induction of labor and the risk for emergency cesarean section in nulliparous and multiparous women

Malin Thorsell MD, Sven Lyrenäs MD PhD, Ellika Andolf MD PhD, Magnus Kaijser MD PhD

Acta Obstet et Gynecol Scandinavica Epub ahead of press 2011 17 june

IV. Starting time for induction of labor and the risk for night-time delivery

Malin Thorsell MD, Sven Lyrenäs MD PhD, Ellika Andolf MD PhD Magnus Kaijser MD PhD

Sex Reprod Healthc 2011 Aug;2(3):113-7

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LIST OF ABBREVIATIONS

BMI	Body mass index
BS	Bishop score
BPD	Biparietal diameter
BW	Birth weight
CI	Confidence interval
CRL	Crown rump length
CTG	Cardiotocography
ECS	Emergency cesarean section
EDA	Epidural anaesthesia
EDD	Estimated date of delivery
ICD	International Classification of Diseases
ITT	Intention to treat
IUFD	Intra uterine fetal death
IUGR	Intra uterine growth restriction
LGA	Large for gestational age
LMP	Last menstrual period
MBR	Swedish Medical Birth Registry
MP	Multiparous
NP	Nulliparous
OR	Odds ratio
PG	Prostaglandin
RCT	Randomized controlled trial
SD	Standard deviation
SF	Symphysis-fundal height
SGA	Small for gestational age
TCC	Transcervical catheter

1 INTRODUCTION

Pregnancy and labor are conditions that are associated with increased risk for morbidity and mortality for both mother and child. Knowledge about risks and benefits of different obstetrical examinations and interventions is important in order to improve the outcome of childbearing and birth. An adequate dating of pregnancy is essential in order to assess fetal growth in relation to the gestational length during pregnancy. The fetal growth is of crucial importance for how to handle and monitor the pregnancy and labor. The first aim of the present thesis was to study obstetrical dating ultrasound. It has been assumed rather than proven that fetal size in early pregnancy is a function of gestational age only. In studies 1 and 2 we assess the validity of this assumption.

Considering the vast number of women afflicted by induction of labor it is of great general health interest to identify risk factors and possible preventive measures to avoid complications from this procedure. The second aim with the thesis was to assess risk factors for adverse events when labor is induced.

2 BACKGROUND

2.1 GESTATIONAL DURATION

A normal pregnancy is given an estimated date of delivery (EDD) 40 weeks or 280 days from the first day of the last menstrual period (LMP). The use of LMP for this calculation assumes that all females have regular menstrual periods and that ovulation occurs on cycle day 14. Gestational age assessed by ultrasound biometry in early pregnancy has proven to be more precise in predicting date of delivery than LMP (1-4).Term pregnancies are defined as pregnancies that end between 37-42 completed weeks of gestation. In Sweden, 6% of all pregnancies end before 37 weeks of gestation (preterm birth), and 5 % of all babies are born after 42 weeks of pregnancy (postterm birth).

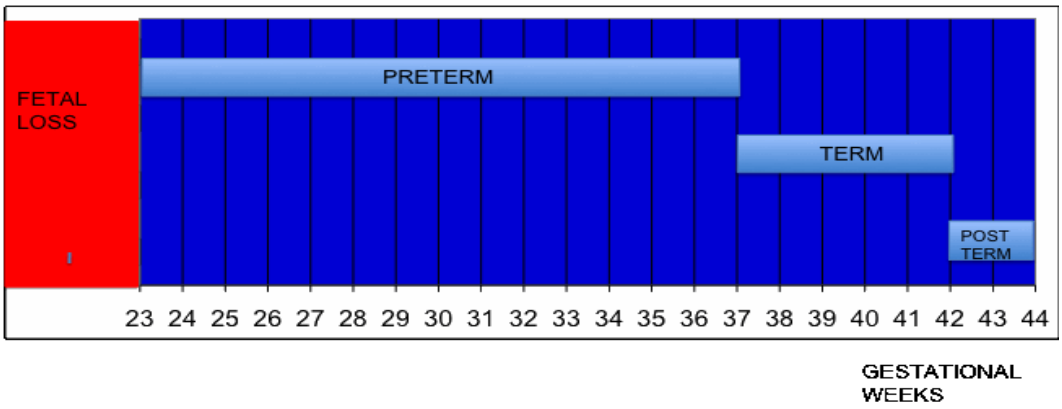

Figure 1. Definition of gestational duration.

2.2 CLASSIFICATION OF FETAL WEIGHT AND BIRTH WEIGHT

In Sweden, small for gestational age (SGA) is defined as birth weight of two standard deviations or more below the average weight for that particular gestational age and gender (5). The same definition applies for estimated fetal weight, but then it is not related to gender. SGA is thus a static concept based on comparison between the birth weight of the infant and the growth curve of the population (Fig 2A). A small for gestational age fetus or infant can either be genetically small or growth restricted. However, as many as 90% of the SGA infants experience a catch up growth during their first two years of life. This indicates that a high proportion of the SGA infants are growth restricted, why SGA can be used as a proxy for intra uterine growth restriction IUGR (6). In contrast to SGA, IUGR is a dynamic concept that refers to the deviation of growth for a fetus from its individual growth potential (Fig 2B). In order to diagnose IUGR, at least two ultrasound measurements have to be conducted. Whereas SGA can be the result of a normal gestation and a genetically small fetus, IUGR always implies pathological growth. The

term LGA, large for gestational age, has mainly been used for fetuses or infants with a weight above two SD for gestational age (7, 8). There is no international consensus on the definition of macrosomia, the most common being a birth weight above 4,500 grams (Fig 3) (9).

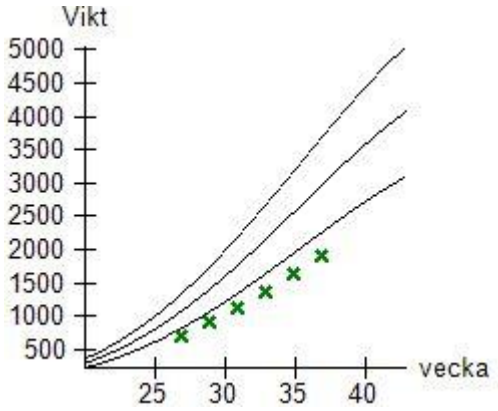

Figure 2A. Small for gestational age growth curve, fetuses with constant growth velocity.

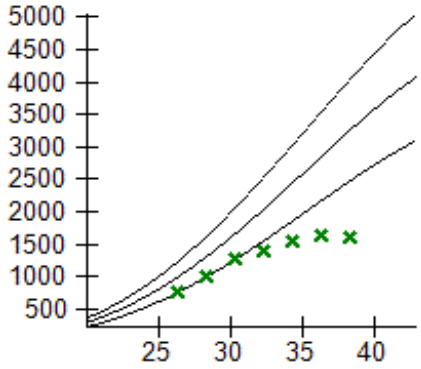

Figure 2B. Intra uterine growth restriction growth curve, fetuses with constrained growth.

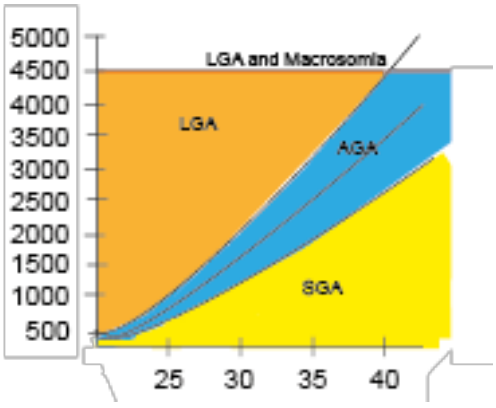

Figure 3. Definitions of fetal weight and birth weight, macrosomia, large for gestational age (LGA), appropriate for gestational age (AGA) and small for gestational age (SGA) (9).

2.3 ASSESSMENT OF GESTATIONAL DURATION AND FETAL WEIGHT

The antenatal program for pregnant women in Sweden is free of charge and virtually all women participate. The first visit includes a risk estimation of the patient so that pregnancies at high risk of developing complications are identified. Women are also scheduled for an ultrasound scan to estimate the date of delivery. Calculation of EDD is performed by measurement of crown rump length (CRL) (Fig. 4) in the late first trimester i.e. week 12-14 or femur length (FL) and biparietal diameter (BPD) (Fig. 5 and 6) in the early second trimester i.e. week 18-20. Accurate dating of pregnancy is crucial for the discovery of deviations of fetal growth. Ultrasound biometry before the 24th week of gestation is routinely used to predict EDD (1-3, 10), the underlying assumption being that fetal size in early pregnancy is a function of gestational duration. It is generally considered that differences in fetal growth at ultrasound dating compared to last menstrual period is explained by early or delayed ovulation or uncertain indication of the last menstrual period (11, 12).

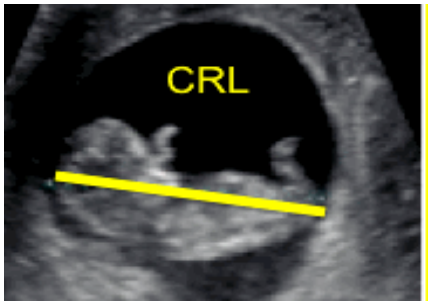

Figure 4. Crown-rump length (CRL). The ultrasonographic measurement is performed from the top of the head (crown) to the bottom of the buttocks (rump) in the sagital view of the fetus.

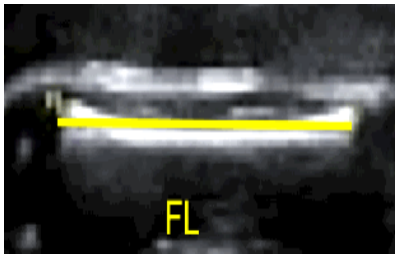

Figure 5.Femur length (FL). Measurement is performed from the outer parts of the calcified part of the femur bone.

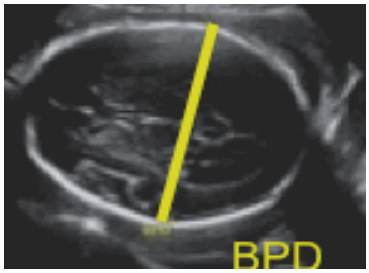

Figure 6. Biparietal diameter (BPD). Messurement is performed from the outer part of the parietal bone to the inner part of the opposite parietal bone at the level of cavum septum pellucidi.

In Sweden mainly two methods are used for antenatal detection of deviations in fetal growth, symphysis-fundal (SF) height measurement (13) and ultrasound. SF height measurement is used as a screening method to detect discrepancies in fetal growth. It is simple, inexpensive and widely used. Measurement is performed by an ordinary measuring tape from the symphysis pubis to the uterine fundus. It is used routinely in all pregnancies from gestational week 25. Pregnancies at high risk for IUGR or macrosomia and pregnancies that have deviations in the SF measurements are referred to undergo ultrasound examination for fetal biometry. However, studies have shown that both methods have rather low sensitivity. The SF-method has been shown to have a sensitivity between 16-84% (14-18). The corresponding figure for ultrasound is 50-80% (2, 19, 20). Therefore, many of the growth restricted and macrosomic infants are diagnosed after birth.

2.4 CONSEQUENCES OF FETAL AND INFANT WEIGHT

It is important to detect fetuses that are smaller than expected before birth. Fetal growth restriction is a serious complication during pregnancy associated with increased risks for asphyxia, perinatal death and neurological deficits such as cerebral palsy and mental retardation (21, 22). If detected in time, however, active surveillance and intervention can improve the prognosis substantially (23). Outcome is also improved if large fetuses are detected before delivery. Birth weight above 4000 grams is associated with an increased risk for a number of perinatal complications such as prolonged labor, shoulder dystocia with brachial palsy, facial nerve palsy, fractures of the clavicular and humeral bones, perinatal mortality and asphyxia (24-27). When the birth weight exceeds 4500 grams, the risk for these complications increases even further (8, 27). If estimated birth weight exceeds 5000 grams, the risks for complications are so high that the American College of Obstetrics and Gynecology recommends delivery through an elective cesarean section (28).

It has been shown, that small fetal size in gestational week 16-20 increases the risk of several adverse outcomes, typically associated with intra uterine growth restriction, such as perinatal death, and preterm and/or small for gestational age birth (29-32). This may suggest that small fetal size in early pregnancy is due not only to short gestational duration, but also to restricted fetal growth.

Furthermore, it has been shown that growth factors and hormonal factors known to be associated with the metabolic syndrome also influence fetal growth in the second trimester. In

large for gestational age fetuses of diabetic mothers, growth acceleration starts as early as in the 18th week (33-35). This suggests that in diabetic pregnancies, fetal macrosomia may be detected already at the time of dating ultrasound. In a recently published case-control study of macrosomia, it was found that children with a birth weight of 4500 grams or more were significantly larger at ultrasound dating in weeks 11-14 compared to neonates with a normal birth weight. This supports the assumption that fetal macrosomia can be detected in early pregnancy also in non-diabetic pregnancies (36).

Adverse fetal size in early pregnancy may therefore be a sign that these fetuses should receive attention so that measures can be taken to diminish possible future complications.

2.5 LABOR

2.5.1 Cervical ripening

The complex mechanism that initiates spontaneous labor is beyond the scope of the present thesis. A brief summary of what is known is given here in order to give a background on how methods for cervical ripening work.

A well functioning cervix is a prerequisite for delivery at term. Both in preterm birth and postterm birth cervical malfunction may be present (37). The cervix consists of connective tissue and a small amount of smooth muscle. The connective tissue is arranged in fibrils and composed of collagen type 1 to 70 percent and collagen type 3 to 30 percent (38). The fibrils are held together by proteoglycans.

It is still unknown what triggers the start of the delivery process. A gradual complex remodeling of the cervix allows the cervical canal to open in preparation for birth. The cervix changes from being closed, firm and having a posterior direction, to becoming soft and more centrally directed in the pelvic axis in late pregnancy. Just before the onset of labor the softening of the cervix enters a more rapid phase. The remodeling is achieved through changes in the quality and quantity of collagen fibers. This influences the biomechanical qualities of the cervix so that it becomes soft and more pliable to contractions during labor (39). One of the reasons for the inter-individual differences in the duration of cervical ripening is the difference in the proportion of collagen 1 and 3 and different levels of proteoglycans. On a cellular level an

inflammatory process leads to increasing uterine contractility and softening of the cervical canal.This process is influenced by oestrogen, progesterone and prostaglandins (40, 41), which in turn regulates the hundred-fold increase in cytokines such as interleukin 6 and interleukin 8 (42). The major part of the ripening process takes place during the last weeks of a normal pregnancy.

2.5.2 Induction of labor

2.5.2.1 Indications for induction of labor

If cervical ripening does not occur and if spontaneous labor has not started at a given point of time, one may choose to induce labor. Induction of labor is made for a number of fetal and maternal indications such as growth restriction, premature rupture of membranes, preeclampsia and intrahepatic cholestasis of pregnancy. The risk for impaired placental function is higher in postterm pregnancies and is therefore an indication for induction of labor (43-47). Postterm pregnancy is the most common reason for induction of labor. During the last twenty years there has been an increase in the frequency of induction of labor. In Sweden the frequency of induction in singleton pregnancies has increased from 8,1% in 1990 to 12,9% in 2009 (48). The frequency of emergency cesarean section and instrumental deliveries has increased during the same time period (49, 50). Since emergency cesarean section leads to an increased risk of maternal morbidity (51, 52) all delivery wards try to lower their rate of emergency cesarean sections. The increased rate of emergency cesarean section has not resulted in improved neonatal outcomes (53). It is therefore important to analyze factors, such as induction of labor, influencing the risk for emergency cesarean section.

2.5.2.2 Methods of induction

If cervical ripening does not occur and if spontaneous labor has not started at a given time point, one may choose to induce labor. The degree of cervical ripening affects duration of labor, risk of cesarean section, and instrumental delivery when labor is induced (54, 55). The Bishop scoring system is used to evaluate the ripening of the cervix (Fig 7) (56). According to a Cochrane analysis from 2009 the cervix is considered to be unfavorable for induction if the Bishop score (BS) is ≤6. When induction is desired in patients with an unripe cervix the first method of choice for cervical ripening, is either pharmacological, in the form of prostaglandins or mechanical in the form of an transcervical balloon catheter (TCC). Once the cervix is ripe, amniotomy can be performed and oxytocin administrated intravenously (57). Amniotomy and

oxytocin administration are also used as independent methods of induction when the cervix is ripe. There is a major difference between the pharmacological and the mechanical method of cervical ripening. Prostaglandins induce the collagen breakdown (39, 58, 59) and initiate both cervical ripening and labor. Use of the transcervical catheter only initiates cervical ripening without leading to labor induction. In an unripe cervix, Prostaglandin E2 (PGE2), dinoprostone, is the most commonly used method of induction. It can be inserted into the vagina or into the cervical canal. The drug is easy to insert in the vagina, but it is unstable in room temperature and requires refrigeration. It can cause side effects such as nausea, diarrhea and hypertonic contractions. The transcervical catheter is relatively cheap, easily available and effective. The insertion procedure is uncomfortable to some women and it is not always possible to insert the catheter if the cervix is difficult to reach or closed. Since the catheter only initiates cervical ripening, active management of labor with amniotomy and oxytocin should be administered as soon as possible.

	Score		
Parameters	0	1	2
Cervical position	posterior	mid	anterior
Cervical consistency	firm	medium	soft
Cervical effacement (%)	0	< 50%	>50%
Cervical dilatation (cm)	closed	>0.5- <1.5	≥ 1.5
Station	above the pelvic inlet	above the ischial spines	below the ischial spines

Figure 7. Bishop score, a well known method to evaluate the degree of cervical ripening.

2.5.2.3 Induction or expectant management in postterm pregnancies?

How to handle postterm pregnancies remains a controversy. In Sweden the definition of postterm pregnancy is gestational age ≥ 42 weeks. In many countries induction is performed already at ≥ 41 weeks of pregnancy (60) since perinatal morbidity and mortality increases after 40 weeks of gestation (43-46, 61-63). However this practice increases the number of inductions due to postterm pregnancy from approximately 5% to 15%. The advantages for the fetus of an earlier delivery must always be related to the increased risk of emergency cesarean section and instrumental delivery. An alternative to induction of labor in postterm pregnancies is the so called expectant management of pregnancy. In expectant management of pregnancy, repeated ultrasound examinations and CTG registrations are performed after 41 weeks of gestation to ensure the health of the fetus. At present, there is no consensus regarding which strategy to prefer. There are studies indicating that induction of labor at gestational week 41 decreases the

fetal morbidity and mortality without an increased risk of emergency caesarean section or instrumental delivery. In these studies the risks are calculated according to Intention To Treat (ITT) which means that the risk of emergency cesarean section among women induced at gestational week 41 is compared with the risk among women that go into spontaneous labor at gestational week 41 or who give birth later, either spontaneously or after labor induction (64-73). However, there are several studies that show the opposite, i.e. that induction of labor in week 41 increases the risk of emergency cesarean section (74-81). In these studies risks are estimated for induction of labor compared to spontaneous labor.

Parity as well as the degree of cervical ripening are well known factors influencing the duration and the outcome of labor (54, 82). Compared to nulliparous women, the cervical canal is more pliable in women who had a previous vaginal birth, which can lead to a faster cervical ripening and a shorter first stage of labor (83, 84). Uterine contractions are also more efficient in multiparous women compared to nulliparous (85). Accordingly, parity and cervical ripening should be included in the analysis of labor outcome after induction of labor. In the studies quoted above these two factors are not always considered.

2.5.2.4 Induction in the morning?

Spontaneous onset of labor, following a diurnal rhythm, usually starts during the night (86, 87), probably due to a higher concentration of oxytocin and to an increased level of such receptors during the night (88-90). The receptiveness of the myometrium is further enhanced as a result of a lower estradiol/estrogen ratio at night (91-93). Accordingly one would expect that cervical ripening would be more effective if it interacts with the circadian rhythm of spontaneous onset of labor. Also, several studies have reported an increased risk for early neonatal mortality, especially due to fetal asphyxia, in night-time deliveries (94-99). Therefore it is reasonable that measures should be taken to reduce the risk of night-time delivery to a minimum. The staffing situation in the delivery ward is often better during daytime. This might increase the possibility of active management of labor and thereby reduce the risk of delivery by caesarean section or instrumental delivery. Ideally, it should be possible to plan for inductions so that they fit into the daily schedule at the delivery ward. Some of studies have addressed the risk of night-time delivery after induction of labor, but the study populations differ with regard to maternal parity, gestational age, cervical status, and indication for the induction, resulting in difficulties when comparing and interpreting the results (100-102).

3 OBJECTIVES

The overall objective of the present thesis was to assess pregnancy and delivery associated risk factors for adverse pregnancy outcomes. Specific aims were:

- to analyze the association between fetal size at the time of dating ultrasound and risk for preterm delivery and small for gestational age birth, and to evaluate if the timing of ultrasound, i.e. before 14 weeks of gestation or after 16 weeks, affects this association, (Study 1).

- to assess if fetal size at the time of dating ultrasound is associated with risk of macrosomia and complications associated with macrosomia, (Study 2).

- to assess the risk for emergency cesarean section among women who were induced to labor in gestational week ≥ 41 and to evaluate if parity and mode of induction affects this association, (Study 3).

- to analyze if starting time for labor induction is associated with a risk of night-time delivery, and to evaluate if parity and/or mode of induction affects this association, (Study 4).

4 MATERIAL AND METHODS

4.1 DATA SOURCES

4.1.1 The Swedish medical birth registry

The Swedish medical birth registry (MBR) was established in 1973 and contains data from antenatal and obstetrical care in Sweden. All Swedish women are offered free antenatal care. At the first visit, scheduled before 15 weeks of pregnancy, a standardized questionnaire regarding the mother's medical and obstetrical history is completed. Infertility, maternal smoking, family status, occupation, and maternal height and weight are registered. At the first visit, EDD according to the last menstrual period is calculated. The EDD is corrected according to the ultrasound biometry, which is performed in 98% of all pregnancies in Sweden, early in the second trimester. A standardized form is completed also at the delivery ward. Parity, gestational age, birth weight and length, gender, and mode of delivery are registered. After delivery, the standardized questionnaires are forwarded to the MBR. All diagnoses during pregnancy and delivery are recorded in the MBR in accordance with the International Classification of Diseases (ICD) (103).

The MBR has been validated and is proven to have a very small proportion of missing data, only 0.5-3% (49, 104). Its objective is to provide material for analysis regarding risks for the mother and baby during pregnancy, childbirth and neonatal period. The number of births in Sweden has varied between approximately 85 000-120 000 births per year during the last decades.

4.1.2 Obstetrix

The Obstetrix medical file system is used in many hospitals and antenatal clinics in Sweden as well as in other Nordic countries. Approximately 80% of all pregnancies and births in Sweden are registered in the Obstetrix medical file system. Danderyd Hospital has used the system since 2000. The system contains a maternity module, an ultrasonic- a delivery- and a postpartal module. The ultrasound module contains functions for dating, organ screening, Doppler examinations, biometry examinations and invasive procedures. The maternity, delivery and postpartal modules contain the same standardized questionnaires that are registered in the MBR.

The system also include partograms, modules for induction, surgery and epidural anaesthesia, as well as files and diagnostic records compatible with the ICD 10, and a reporting function for the MBR. Predetermined reports from all modules, quality follow up, and raw data can be generated.

4.2 STUDY POPULATIONS

4.2.1 Study 1 and 2:

The first two studies were retrospective cohort studies. The exposures and the outcomes were based on prospectively registered information from standardized antenatal, obstetrical and neonatal records. The subjects consisted of all viable singleton pregnancies recorded at the ultrasound departments of UltraGyn Stockholm, Sweden during the Study period 1998-2004. The dating examinations were performed by trained midwives. To assess gestational age, biparietal diameter (105-107) was used before gestational week 14. In week 16-18the estimation relied on femur length and biparietal diameter (108). Exclusion criteria were the use of oral contraceptives within three months before conception, uncertain date of the last menstrual period, irregular menstrual periods, fetuses that were $\geq$ 21 days larger or smaller than expected and fetal anomalies. Possible maternal disease was not used as an exclusion criterion. In Study 2, birth before 37 or after 42 weeks of gestation was also an exclusion criterion.

Dating formulas used for estimation of gestational age (108)

BPD formula: 39.1+2.10 x BPD
BPD and FL formula: 49.0+1.21 x BPD+1.02 x FL

4.2.2 Study 3 and 4:

Study 3 and 4 were also retrospective cohort studies based on prospectively registered information from standardized antenatal, obstetrical and neonatal records from MBR and the Obstetrix system. The study population consisted of all women who were delivered at the Department of Gynecology and Obstetrics at Danderyd Hospital, Stockholm, Sweden from

2002 through 2006. Included were singleton pregnancies with cephalic fetal presentation and a gestational age of ≥ 41 gestational weeks (Study 3) or a gestational age ≥37 weeks of gestation (Study 4), according to ultrasound biometry before the 24th week of gestation. Pregnancies that were recorded with induced delivery, but which had a Bishop score of ≥7 at the time of delivery onset were excluded. Further exclusion criteria were intrauterine death, twin pregnancies and previous cesarean section. In Study 4, women with spontaneous uterine contractions at the time of delivery onset were also excluded.

If the cervix was unripe, induction of labor was either performed by vaginal gel with dinoprostone or with a transcervical catheter. The obstetrician who assessed the cervical status decided which method to use. The decision was based on the clinician's own preferences.Women who were induced by dinoprostone were treated with 1-2 mg of dinoprostone gel administrated in the posterior fornix of the vagina. The gel was placed in the vagina during manual digital examination. Women who were induced by the mechanical dilation had a catheter inserted through the cervical canal either during manual digital examination or with visualization of the cervix during speculum examination. The catheter had a 50 ml balloon, which was inflated with sterile water and taped to the patient's inner side of the thigh.

4.3 DATA CATEGORIZATION AND ANALYSIS:

4.3.1 Study 1 and 2:

In both studies obstetric outcome was assessed through linkage of the cohort to the Medical Birth Registry. In Study 1 we analyzed the outcomes: preterm delivery (= delivery at a gestational age of less than 37 completed weeks), low birth weight for gestational age, SGA (= birth weight for gestational age of more than 22% below average, i.e. below two standard deviations of a Swedish reference population (109), equivalent to the 2.3rd centile), preeclampsia (= blood pressure equal to or above 140/90 mm Hg at two consecutive measurements and proteinuria of more than 0.3g/ 24h). In Study 2 we analyzed the risk connected with a birth weight of 4000, 4500 or 5000 grams. Risks for maternal diabetes, shoulder dystocia and lacerations of the vagina and/or the anal sphincter were analyzed. In addition risks of the following diagnoses were analyzed in Study 1 and 2; fetal asphyxia,

respiratory distress, instrumental delivery, cesarean section, postpartum haemorrhage, and postterm birth. These definitions correspond to diagnoses according to the 10th revision of the International Classification of Disease (103) as follows:O60, P07, P05, O14, O24, O66, O70, P21, P22, O81, O82,O72, P08.2

We used the discrepancy between the expected date of delivery according to ultrasound and the expected date according to the last menstrual period to categorize fetal size into three groups: fetal size in accordance with the last menstrual period (defined as expected date of delivery moved less than six days), expected date of delivery moved forward seven days or more (smaller than expected) and expected date moved backwards seven days or more (larger than expected) (Fig 8). Pregnancies moved forward were further categorized as early and late ultrasound dating, i.e. between gestational weeks 11 through 13 or 16 through 20. Data were modelled using logistic regression (LOGISTIC procedure in SAS Statistical Software, version 9.1 (SAS Institute Inc., Cary, NC, USA)). Risks were expressed as odds ratios (OR) and 95 percent confidence intervals (CI).

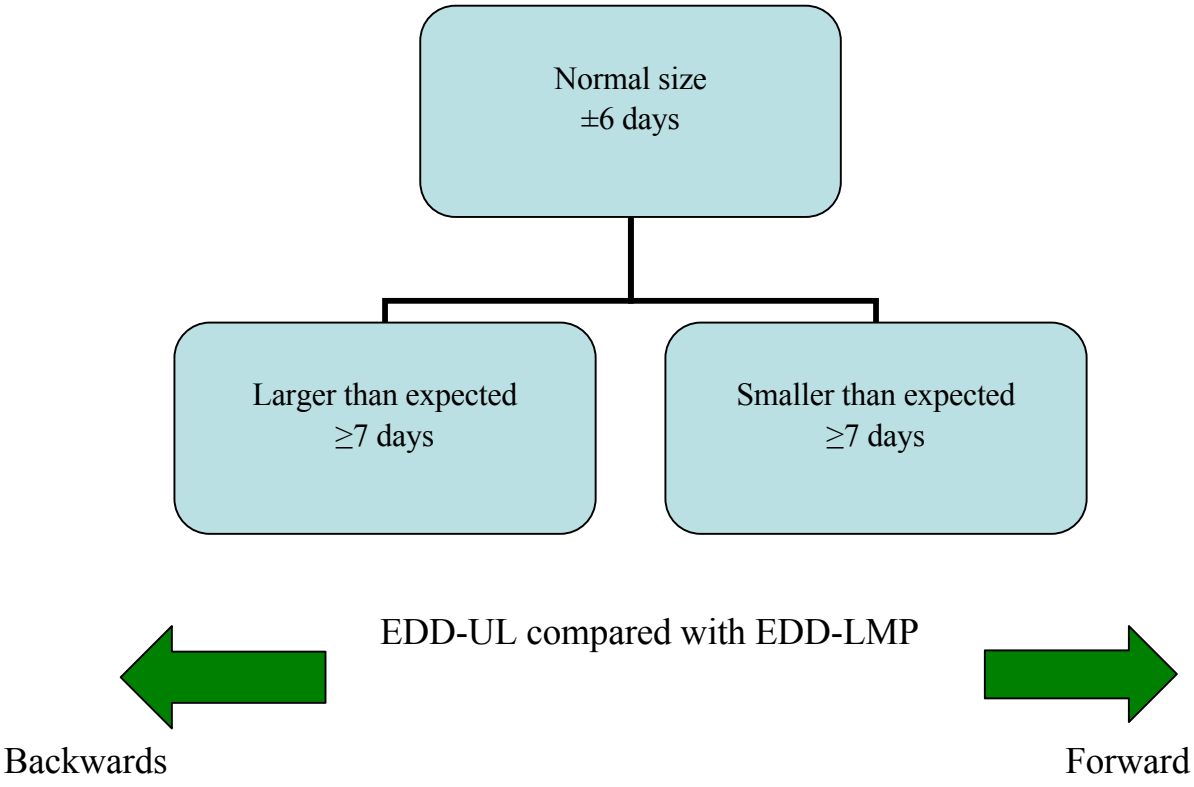

Figure 8. How the estimated date of delivery is moved according to ultrasound compared to last menstrual period.

To further assess the distribution of birth weights, we calculated birth weight expressed as number of standard deviations from the mean for each gestational week. Averages and standard deviations for birth weight for each gestational week were derived from within the cohort. This enabled us to compare the distribution of birth weights for those whose expected date of delivery was moved back at the time of ultrasound with the distribution for those whose dates were moved forward or not at all. Overall test of heterogeneity was done by the chi-square test, and tests for trend were done by the Cochran-Armitage trend tests with birth weight for gestational age categorized as a dichotomous variable (≥+2 standard deviations and ≤-2 standard deviations, respectively).

4.3.2 Study 3 and 4:

Obstetric and perinatal information on the Study population was retrieved from the Obstetrix database at Danderyd Hospital and through linkage to the Swedish Medical Birth Registry. Information from Obstetrix included time of labor induction, cervical status (Bishop score), induction method used, and the time of emergency cesarean section. Labor duration was defined as the time of the first intervention until delivery. From MBR, we gathered information on maternal height and weight, gestational length, birth weight, mode of delivery, and maternal and infant diagnoses recorded at time of delivery. Maternal BMI was calculated according to the formula BM I= maternal weight /(maternal height in metres)^2 . The diagnoses of SGA, preeclampsia, diabetes and emergency cesarean section were defined according to the 10th revision of the International Classification of Disease (103) corresponding to the codes P05, O14, O24 and O82.1, respectively. Time for start of the induction was defined as morning at (07.00-11.59) afternoon at (12.00-17.59) and evening (>18.00). We defined night-time delivery as delivery between 20.00 and 08.00.

Data were modelled using logistic regression (LOGISTIC procedure in SAS Statistical Software, version 9.1 (SAS Institute Inc., Cary, NC, USA)). First we made logistic regression to assess the association between induction of labor and emergency cesarean section. In the analysis of differences between PGE_2 and transcervical catheter, we restricted the analysis to women who were induced. Risks were expressed as OR and 95 % CI. Adjustments for maternal age, epidural anaesthesia (EDA) and body mass index (BMI) were made by adding these variables to the regression model (110). Analysis of interaction between mode of induction and maternal parity on risk of emergency cesarean section was done by adding an interaction term

to the full multivariate model. We also calculated the risk for emergency cesarean section according to the ITT model. In this model, induction of labor in, for example week 41, is compared to spontaneous deliveries in week 41 together with all deliveries after week 41, regardless of whether the later deliveries were spontaneous or not.

Odds ratios for night-time delivery were calculated for induction starting in the afternoon and evening, respectively, compared to inductions started in the morning. We stratified the analysis on factors known to influence labor duration. Adjustments for gestational duration, EDA, BMI, birth weight, maternal age, preeclampsia, SGA and diabetes were made by adding these parameters to the strata statement.

4.4 ETHICS

All studies were approved by the local ethics committee of the Karolinska Institutet. Study 1 and 2 dnr 2005/613-31. Study 3 and 4 dnr 2006/1129-31/4.

5 RESULTS

5.1 STUDY 1 AND 2:

During the study period, 28 776 singleton pregnancies meeting the inclusion criteria were measured and recorded at the ultrasound department. Of these, 824 patients were lost to follow-up (170 because of an incorrect personal identification number recorded at the ultrasound department, and 654 that were missing in the MBR). One reason for missing data in the MBR was giving birth at hospitals outside Sweden. In total, 27 952 women were included in the subsequent analysis in Study 1. Of these, 5063 were dated early and 22 889 were dated late. In Study 2, 3 433 children where born before 37 or after 42 weeks of gestation and therefore excluded from the study. Another 79 subjects were excluded due to missing information on birth weight. Thus, a total of 19 377 women were included in the subsequent analysis in Study 2. Data on smoking habits and BMI were missing in 33% and 40%, respectively, due to incomplete health history recordings at the antenatal care centre.

Among women dated early, 23% of all pregnancies were postponed, and among those dated late, 15 % were postponed (Table 1).

Dating ultrasound in gestational week					
EDD moved	11-13		16-20		∑
	n	%	n	%	N
≥ 7 days forward	1188	23.5	3376	14.7	4564
< 7 days	3858	76.2	18944	82.8	22802
≥ 7 days back	17	0.03	569	2.5	586
∑	5063	100	22889	100	27952

Table 1. Description of study subjects regarding EDD-UL compared to EDD-LMP in Study 1 and 2.

For pregnancies where the expected date of delivery was postponed seven days or more, there was a statistically significant 49% increase in risk of preterm birth when dating ultrasound was performed late (OR 1.49, 95% CI 1.27 – 1.73), whereas the 14% increase in risk for pregnancies postponed according to an early ultrasound was not statistically significant (OR 1.14, 95% CI 0.87 to 1.49) (Table 2). For both early and late ultrasounds, a postponing of the expected date of delivery was associated with an increased risk of SGA birth (OR 1.77, CI 1.13 – 2.78 and OR 2.09, CI 1.59 – 2.73, respectively) (Table 2). There was no significantly increased risk for

asphyxia, respiratory distress, instrumental delivery, cesarean section and postterm birth in any of the groups (data not shown).

		Estimated date of delivery moved											
		≥7 days forward						Within ± 6 days			≥7 days back		
		Early dating ultrasound			Late dating ultrasound								
	All	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI.
Preterm birth	1284	58	1.14	0.87-1.49	212	1.49	1.27 - 1.73	984	1	*ref*	30	1.20	0.82-1.73
SGA	327	21	1.77	1.13-2.78	70	2.09	1.59–2.73	229	1	*ref*	7	1.19	0.56–2.54

Table 2**.** Odds ratios and 95% confidence intervals for the association between changes in expected day of delivery and adverse pregnancy outcome.

There was an overlap of the diagnoses of preterm birth on the one hand, and preeclampsia and SGA birth on the other. Out of 1,284 infants born preterm, 78 (6 %) were born small for gestational age and 144 (11 %) had a diagnosis of preeclampsia (data not shown). When excluding all cases with SGA or preeclampsia from the analysis of preterm birth, however, the increased risk for preterm birth associated with postponing expected date of delivery in the late dating group was unchanged (data not shown).The associations between postponing the expected date of delivery and risk of SGA and premature birth were independent of maternal smoking status and BMI (data not shown).

When the fetus was at least seven days larger than expected at ultrasound dating, compared to the expected size according last menstrual period, there was an 59% increased risk for a birth weight of 4500 grams or more and a 145% increased risk for a birth weight of at least 5000 grams (OR 1.59 95% CI 1.12-2.24 and 2.45 95% CI 1.22-4.90, respectively). There was also a 19% increased risk for a birth weight of 4000 grams or more although it was not statistically significant (OR 1.19 95% CI 0.96-1.47). Fetuses that were smaller than expected (where expected day of delivery was postponed more than seven days) had a decreased risk of being born macrosomic (OR 0.81 95% CI 0.73-0.90, OR 0.70 95% CI 0.55-0.87 and 0.66 95% CI 0.35-1.28) for a birth weight of 4000, 4500 and 5000 grams or more respectively (Table 3).

	Expected date of delivery moved									
		≥7 days backward			± 6 days			≥7 days forward		
Birthweight (g)	**All**	**n**	**OR**	**95 % CI**	**n**	**OR**	**95 % CI**	**n**	**OR**	**95 % CI**
≥4000	4229	133	1.19	0.96-1.47	3594	1	*reference*	502	0.81	0.73-0.90
≥4500	831	37	1.59	1.12-2.24	714	1	*reference*	80	0.70	0.55-0.87
≥5000	118	8	2.45	1.22-4.90	100	1	*reference*	10	0.66	0.35-1.28

Table 3. Estimated birth odds ratios for birth weight of 4000, 4500 and 5000 grams or more respectively when expected date of delivery according to last menstrual period moved at ultrasound.

The distribution of birth weights are presented in Table 4. There was a variation of birth weight by size at the time of dating ultrasound (overall chi-square: p=0.0047). The proportion of children with a birth weight of 2 standard deviations or more above the mean for gestational week increased stepwise with increasing size at time of dating ultrasound (p=0.0079) . Likewise, the proportion of children with a birth weight of 2 standard deviations or more below the mean decreased with increasing size at time of dating ultrasound (p=0.0075).

	Expected date of delivery moved according to ultrasonography in gestational week 16-20.				
	≥7 days back % (n)	**± 6 days % (n)**	**≥7 days forward % (n)**		
Birth weight SD †				∑	p-value‡
≤-2	1.65 (8)	1.77 (285)	2.55 (72)	365	0.0075
>-2 to <+2	94.24 (458)	95.40 (15325)	95.32 (2690)	18473	
≥+2	3.92 (19)	2.86 (460)	2.13 (60)	539	0.0079
∑	485	16070	2822	19377	

‡tests for trend according to the Cochran-Armitage trend tests
†SD from the mean for according to gestational week

Table 4. Distributions of birth weight according to standard deviations.

When analyzing the outcome of all fetuses with a birth weight of more than 4000 grams, independent of size at dating ultrasound, there was an increased risk for postpartum haemorrhage, maternal diabetes, shoulder dystocia, lacerations of the vagina and/or anal sphincter, and respiratory distress. If birth weight exceeded 4500 grams, risks for cesarean section and fetal asphyxia were also increased whereas there was no statistically significant increase in risk for lacerations of the vagina and/or anal sphincter. Fetuses with a birth weight above 5000 grams had increased risk for shoulder dystocia, cesarean section and respiratory distress. For fetuses that were large at time of dating ultrasound, there was no consistent pattern

of risk increase for any of the diagnoses above (data not shown).

The association between macrosomia and large fetal size at time of dating ultrasound was independent of maternal BMI, diabetes, parity, maternal age, and gestational age at birth.

5.2 STUDY 3 AND 4:

During the period covered by the investigation, 26 358 women were delivered at our labor and delivery department. After excluding those with multiple pregnancies, intra uterine death and delivery by cesarean section in a previous pregnancy, 23 030 women qualified for inclusion in the study cohort. In Study 3, 4948 were ≥ 41 weeks of gestation, of which 881 had induction of labor with cervical ripening at a Bishop score of <7 (Fig 9). In Study 4, 21 689 were 37 weeks of gestation of which 1940 had induction of labor with cervical ripening at a Bishop score of <7 (Fig 10). Maternal and pregnancy characteristics are presented in Table 5 and 6 respectively.

	Nulliparous			**Multiparous**		
	PGE2	TCC	Spontaneous onset	PGE2	TCC	Spontaneous onset
	n= 412	n= 270	n= 2442	n= 121	n= 78	n= 1625
Age[a] (years)	32.4±8.8	32.0±8.6	30.6±8.4	34.7±7.9	34.6±9.2	33.4±8.3
BMI[a]	23.6±8.1	23.3±7.2	22.5±6.8	23.9±8.8	23.5±8.1	23.1±7.8
Parity[a]	0	0	0	2.6±1.66	2.4±1.74	2.4±1.42
BS[a] (points)	3.10±1.78	4.24±1.34	No value	3.18±1.60	3.91±1.18	No value
ECS[b]	171(42%)	115 (43%)	416 (17%)	21 (17%)	7 (10%)	116 (7%)
EDA[b]	192 (47%)	140(52%)	1168(48%)	41(34%)	26 (33%)	332(20%)
Preeclampsia[b]	24 (6%)	14 (5%)	17 (0.7%)	4 (3%)	2 (2.5%)	3 (0.2%)
Diabetes[b]	2 (0.5%)	1 (0.4%)	0	0	1 (1.3%)	0
SGA[b]	5 (1.2%)	6 (2.2%)	35 (1.4%)	0	1 (1.3%)	11 (0.7%)

[a]expressed as medians with standard deviations
[b]expressed as numbers and proportions.
Table 5. Maternal age, maternal body mass index (BMI), number of previous deliveries, Bishop score (BS), numbers of emergency cesarean sections (ECS), epidural anaesthesia (EDA), preeclampsia, diabetes, and small for gestational age (SGA) by mode of labor onset and parity among women who were delivered in gestational weeks ≥ 41.

	Nulliparae		Multiparae	
	PGE2 n= 877	TCC n= 497	PGE2 n= 331	TCC n= 235
Age[a] (years)	32.7±4.5	32.3±4.4	34.7±3.9	34.6±4.5
BMI[a] (kilograms)	23.5±4.0	23.2±3.8	23.9±4.0	23.4± 4.4
BW[a] (grams)	3620±540	3620±569	3827±556	3724±566
Parity[a]	0	0	2.6±0.9	2.5±0.81
BS[a] (points)	2.97±1.73	4.20±1.31	3.20±1.60	4.12±1.21
EDA[b]	405(46%)	249(50%)	93(28%)	76(32%)
Preeclampsia[b]	132(15%)	53(11%)	18(5%)	20(8%)
Diabetes[b]	17(2%)	7(1%)	5(2%)	7(3%)
SGA[b]	25(3%)	16(3%)	3(1%)	3(2%)

[a]expressed as medians with standard deviations
[b]expressed as numbers and proportions.
Table 6. Maternal age, maternal body mass index (BMI), Birth weight (BW), number of previous deliveries, Bishop score (BS), epidural anaesthesia (EDA), preeclampsia, diabetes, and small for gestational age (SGA) by mode of labor onset and parity among women who were delivered in gestational weeks ≥ 37.

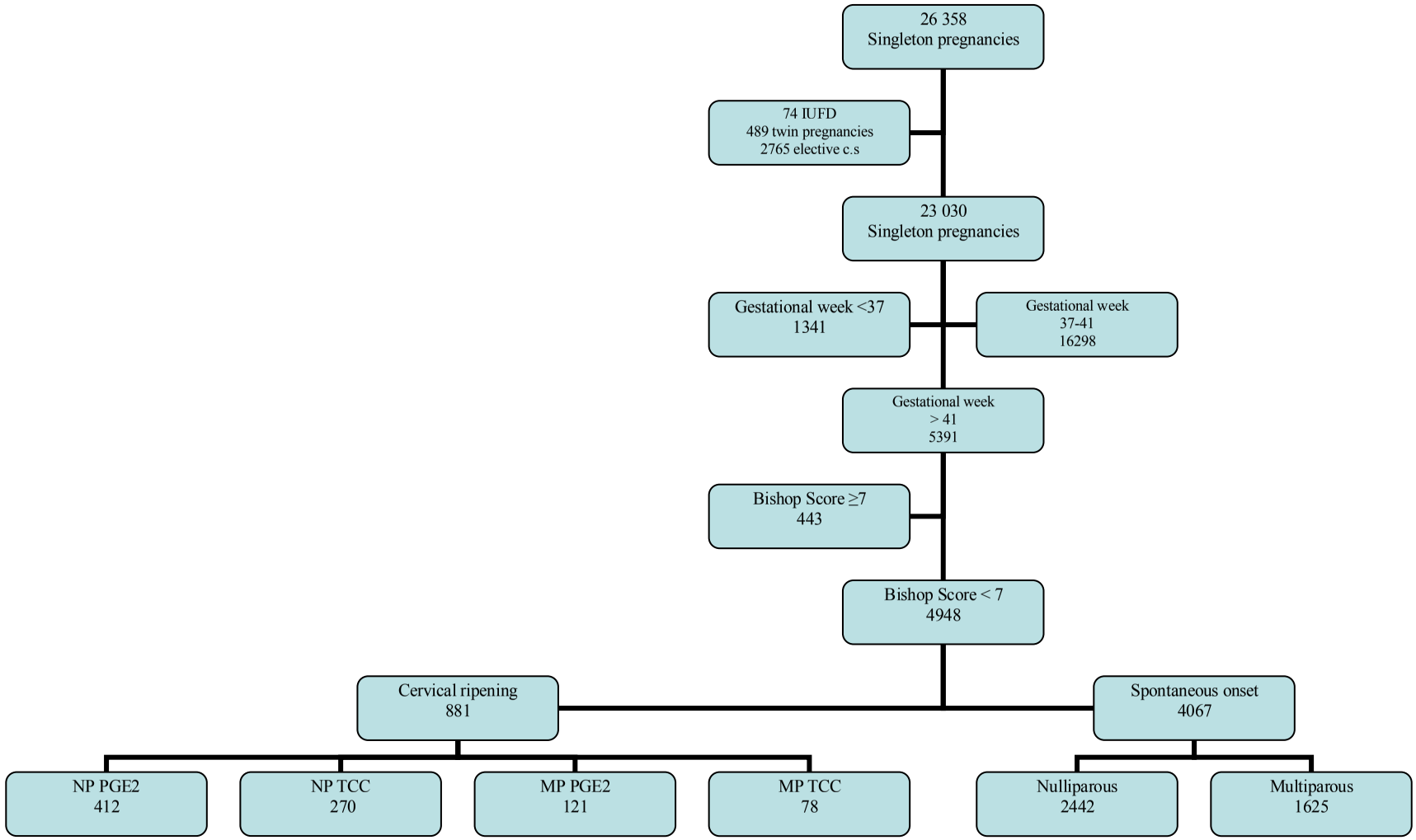

Fig 9. Flow chart of deliveries at Danderyd Hospital,2002-2006, for pregnancies with induction of labor compared to pregnancies with spontaneous labor at gestational week ≥41.

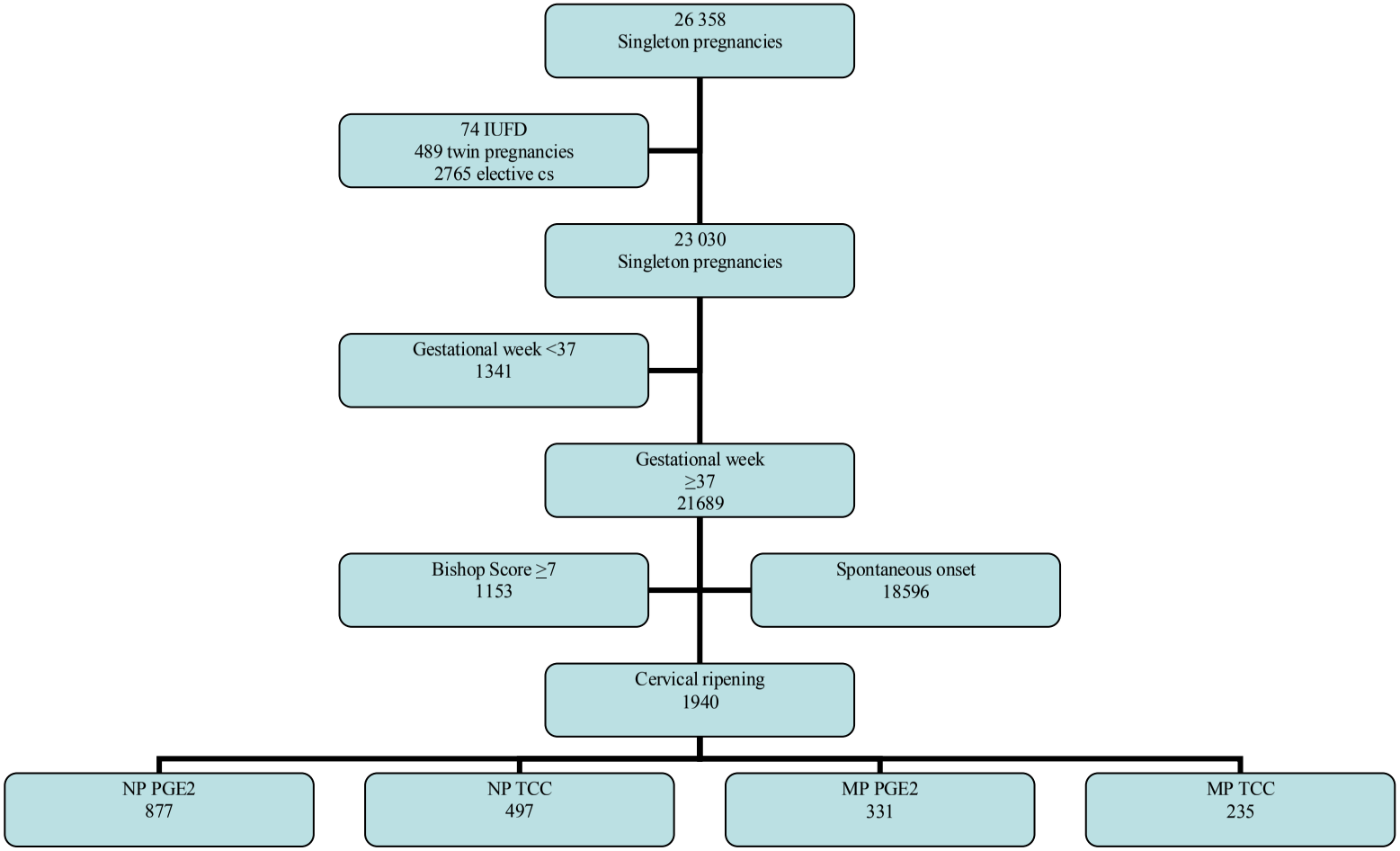

Fig 10. Flow chart of deliveries at Danderyd Hospital,2002-2006, for pregnancies with induction of labor compared to pregnancies with spontaneous labor at gestational week ≥37.

In the univariate analysis, induction of labor was associated with a more than threefold increase in risk for emergency cesarean section compared to spontaneous onset of labor. Likewise, nulliparity, a maternal age over 30 years, high maternal BMI (≥26) and EDA were also associated with an increased risk (Table 7). In the multivariate analysis there was a significant interaction between maternal parity and induced delivery on risk of cesarean section (p=0.023). We therefore present data from a multivariable model where induction to labor and maternal parity are combined to four different categories (Table 7). The emergency cesarean section rate among women with spontaneous delivery was 17% for nulliparous women and 7% for multiparous. Among women induced to delivery, the corresponding figures were 42% and 14%, respectively. The odds ratio of emergency cesarean section among nulliparous women with induction of labor was 3.34 (95% CI 2.77-4.04) compared to nulliparous women with spontaneous onset. For multiparous women, induction of labor was associated with an almost twofold increase in risk of emergency cesarean section compared to spontaneous onset (OR 1.94, 95% CI 1.24-3.02) (Table 7). In the analysis restricted to women who were induced to labor, there was no significant difference in risk of emergency cesarean section between the two methods of induction (Table 8).

	Deliveries	ECS	Crude OR	95% CI	Adjusted OR	95% CI
Maternal age						
≤ 30 years	1156	166 (14%)	1	reference	1	reference
> 30 years	3792	688 (18%)	1.32	1.10-1.58	1.50	1.23-1.82
Maternal BMI						
BMI<26	2460	377 (15%)	1	reference	1	reference
BMI≥26	540	128 (24%)	1.60	1.29-1.98	2.00	1.59-2.53
Epidural anaesthesia						
No	3049	410 (13%)	1	reference	1	reference
Yes	1899	444 (23%)	1.96	1.69-2.27	1.53	1.31-1.80
Onset of labor						
Spontaneous onset	4067	532 (13%)	1	reference	1	reference
Induced to labor	881	314 (36%)	3.67	3.11-4.33	3.06	2.57-3.63
Parity						
Multiparous	1824	144 (8%)	1	reference	1	reference
Nulliparous	3124	702 (22%)	3.39	2.80-4.10	3.08	2.51-3.77
Onset of labor by parity						
Spontaneous and nulliparous	2442	416 (17%)	1	reference	1	reference
Induced and nulliparous	682	286 (42%)	3.51	2.91-4.22	3.34	2.77-4.04
Spontaneous and multiparous	1625	116 (7%)	1	reference	1	reference
Induced and multiparous	199	28 (14%)	2.13	1.37-3.31	1.94	1.24-3.02

Table 7. Number of deliveries, emergency cesarean sections, univariate and multivariate odds ratios (OR) and 95 percent confidence intervals (CI) for emergency cesarean section (ECS) among women with singleton pregnancies at gestational week ≥ 41 by mode of labor onset, parity, maternal age, maternal body mass index (BMI), and epidural anesthesia (EDA).

	Deliveries	ECS	Crude OR	95% CI	Adjusted OR	95% CI
Maternal age						
≤ 30 years	136	38 (28%)	1	reference	1	reference
> 30 years	745	276 (37%)	1.52	1.01-2.27	1.81	1.20-2.75
Maternal BMI						
BMI<26	367	123 (34%)	1	reference	1	reference
BMI≥26	115	50 (43%)	1.76	1.17-2.66	2.38	1.51-3.73
Epidural anaesthesia						
No	482	158 (33%)	1	reference	1	reference
Yes	399	156 (39%)	1.32	1.00-1.74	1.16	0.87-1.56
Mode of induction						
PGE2	533	192 (36%)	1	reference	1	reference
Transcervical catheter	348	122 (35%)	0.96	0.72-1.27	0.97	0.72-1.30
Parity						
Multiparous	199	28 (14%)	1	reference	1	reference
Nulliparous	682	286 (42%)	4.41	2.88-6.76	5.07	3.26-7.90
Mode of induction by parity						
PGE2, nulliparous	412	171 (42%)	1	reference	1	reference
TCC, nulliparous	270	115 (43%)	1.05	0,77-1.43	1.07	0.78-1.47
PGE2, multiparous	121	21 (17%)	1	reference	1	reference
TCC multiparous	78	7 (9%)	0.47	0.19- 1.17	0.47	0.19-1.16

Table 8. Number of deliveries, emergency cesarean sections, univariate and multivariate odds ratios (OR) and 95 % confidence intervals (CI) of emergency cesarean section (ECS) among women with singleton pregnancies induced for labor ≥ 41 by mode of induction, parity, maternal age, Body Mass Index (BMI), and epidural anaesthesia (EDA).

Since maternal and fetal diagnoses of preeclampsia, diabetes, and SGA can be associated with both induction of labor and acute cesarean delivery, i.e. introducing confounding by indication, we also analyzed data with women who had these diagnoses excluded. This had no effect on the association between induction of labor and risk of emergency cesarean section (data not shown). Likewise, excluding pregnancies with missing data on BMI did not alter the results (data not shown).

In the literature it has been shown that elective induction of labor results in a decrease in emergency cesarean section compared to expectant management of labor. This analysis is made according to ITT, which is described in the introduction of this thesis. To make our data comparable also to these studies we have supplemented the analysis presented in Study 3 with risk estimation according to the ITT principle for the thesis. However, in our material

pregnancies that started spontaneously were not followed with the surveillance methods that are included in the expectant management of pregnancy. Data were stratified for BMI, maternal age and the use of EDA. The OR of emergency cesarean section, independent of parity, at gestational week 41 was 1.82 (95% CI 1.47-2.24) (Table 9). When analysis was restricted to nulliparous women the corresponding OR was 1.78 (95% CI 1.40-2.25) (Table 10). For multiparous women OR was 1.23 (95% CI 1.21-2.15) (Table 11)

Gestational week	Induction of labor ECS	Expectant group ECS	Crude OR (95% CI)	Adjusted OR (95% CI)
38	17%	11%	1.75 (1.32-2.31)	1.64 (1.24-1.18)
39	17%	11%	1.70 (1.30-2.22)	1.56 (1.19-2.04)
40	28%	12%	2.81 (2.30-3.42)	2.57 (2.10-3.15)
41	27%	16%	1.88 (1.53-2.31)	1.82 (1.47-2.24)
42	35%	21%	2.11 (1.62-2.76)	2.11 (1.60-2.77)
43	48%	0%	NA	NA

Table 9. Risks of emergency cesarean section (ECS). Induction of labor compared to expectant group independent of parity. Adjusted OR for BMI, maternal age and use of EDA. NA= non applicable.

Gestational week	Induction of labor ECS	Expectant group ECS	Crude OR (95% CI)	Adjusted OR (95% CI)
38	25%	15%	1.98 (1.42-2.76)	1.84 (1.31-2.57)
39	23%	15%	1.78 (1.31-2.41)	1.65 (1.21-2.25)
40	35%	16%	2.73 (2.16-3.44)	2.51 (1.98- 3.19)
41	33%	21%	1.84 (1.46-2.32)	1.78 (1.40-2.25)
42	44%	29%	1.94 (1.43-2.63)	1.92 (1.41-2.62)
43	52%	0%	NA	NA

Table 10. Risks of emergency cesarean section (ECS). Induction of labor compared to expectant group for nulliparous women. Adjusted OR for BMI, maternal age and use of EDA. NA= non applicable.

Gestational week	Induction of labor ECS	Expectant group ECS	Crude OR (95% CI)	Adjusted OR (95% CI)
38	9%	6%	1.38 (0.78-2.45)	1.22 (0.68-2.17)
39	8%	6%	1.33 (0.73-2.42)	1.21 (0.66-2.20)
40	16%	6%	2.94 (1.98-4.38)	2.52 (1.67-3.78)
41	14%	8%	1.35 (1.28-2.33)	1.23 (1.21-2.15)
42	15%	8%	2.11 (1.06-4.20)	1.87 (0.93-3.76)
43	25%	0%	NA	NA

Table 11. Risk of emergency cesarean section (ECS). Induction of labor compared to management group for multiparous women. Adjusted OR for BMI, maternal age and use of EDA. NA= non applicable.

For nulliparous women induced by PGE2, the starting time of labor induction did not affect the risk of giving birth at night. For nulliparous women induced by TCC with BS 0-3, the proportion of women giving birth at night was 74% when induction started in the morning and

55% when it started in the afternoon, whereas the figure was only 20% when it started in the evening. Expressed in OR, the risks of giving birth at night were 0.42 (95% CI. 0.19-0.93) when inductions started in the afternoon and 0.09 (95% CI 0.02-0.47) when they started in the evening compared to inductions that started in the morning. For nulliparous women with BS 4-6, the proportion of night-time deliveries were 63% and 68% when induction of labor started in the morning or in the afternoon, respectively, while 38% of women who were induced to labor during the evening delivered their baby during the night. Corresponding odds ratios for night-time delivery were 1.20 (95% CI. 0.75-1.86) when inductions started after noon and 0.35 (95% CI 0.17-0.71) when they started in the evening compared to inductions that started in the morning (Table 12)

For multiparae, the proportion who delivered at night was 41.9% if induction started before noon, compared to 73.2% and 66.6% when induction started in the afternoon or in the evening, respectively. Taking mode of induction and BS into account, it was found that for PGE2, a lower proportion of multiparae gave birth during the night if induction started before noon, compared to in the afternoon and evening, regardless of BS (Table 13). For multiparous women induced by TCC the risk of night-time delivery varied by BS. For BS 0-3, the proportion giving birth at night was higher when induction started in the afternoon (68%) compared to when it started in the morning (47%). For BS 4-6 the corresponding proportions were 71% when induction started in the afternoon and 63% when induction started in the evening, whereas it was 32% when it started in the morning. Compared to pregnancies induced for labor in the morning, odds ratios for night-time delivery were 2.60 (95% CI 0.89-7.55) for multiparous women with BS 0-3 induced in the afternoon and 6.03 (95% CI 2.83-12.8) for women with BS 4-6 (Table 13).

	START	Daytime birth Total n= 896 n (%)	Nighttime birth Total n= 1044 n (%)	Unadjusted OR	95% C. I.	Adjusted* OR	95% C. I.	Median duration
Nulliparous								
Bishop 0-6 PGE2 and TCC								
	06.00-11.59	350 (46.4%)	425 (53,6%)	1	reference	1	reference	13
	12.00-17.59	205 (42.8%)	273 (57.2%)	1.36	1.10-1.67	1.37	1.11-1.69	12
	18.00-05.59	68 (56.2%)	53 (43.8%)	0.93	0.66-1.31	0.92	0.65-1.30	12
Bishop 0-3 PGE2								
	06.00-11.59	160 (52.5%)	145 (47.5%)	1	reference	1	reference	14
	12.00-17.59	97 (51.9%)	90 (48.1%)	1.02	0.71-1.48	1.05	0.73-1.51	14
	18.00-05.59	18 (47.4%)	20 (52.6%)	1.23	0.62-2.46	1.22	0.61-2.44	16.5
Bishop 4-6 PGE2								
	06.00-11.59	101 (48.3%)	108 (51.7%)	1	reference	1	reference	16
	12.00-17.59	42 (40%)	63 (60%)	1.23	0.78-1.95	1.28	0.81-2.02	17.5
	18.00-05.59	17 (51.5%)	16 (48.5%)	0.76	0.37 -1.56	0.78	0.38-1.62	14
Bishop 0-3 TCC								
	06.00-11.59	19 (26.4%)	53 (73.6%)	1	reference	1	reference	14
	12.00-17.59	22 (44.9%)	27 (55.1%)	0.44	0.21-0.94	0.42	0.19-0.93	13
	18.00-05.59	8 (80%)	2 (20 %)	0.09	0.02 -0.46	0.09	0.02-0.47	16.5
Bishop 4-6 TCC								
	06.00-11.59	70 (37%)	119 (63%)	1	reference	1	reference	12
	12.00-17.59	44 (32.1%)	93 (67.9%)	1.24	0.78-1.97	1.20	0.75-1.86	12
	18.00-05.59	25 (62.5%)	15 (37.5%)	0.36	0.17-0.72	0.35	0.17-0.71	13.7

*Adjusted for gestational duration, epidural anaesthesia (EDA), body mass index (BMI), birth weight, maternal age, preeclampsia, small for gestational age (SGA) and diabetes.

Table 12. Risk of night-time delivery after induction of labour among women who delivered in gestational weeks ≥ 37 depending on parity and cervical ripening.

	START	Daytime birth Total n= 896 n (%)	Nighttime birth Total n= 1044 n (%)	Unadjusted OR	95% C. I.	Adjusted* OR	95% C. I.	Median duration
Multiparous								
Bishop 0-6 PGE2 and TCC								
	06.00-11.59	202 (58.1%)	146 (41.9%)	1	reference	1	reference	9
	12.00-17.59	59 (26.5%)	123 (73.5%)	3.21	2.39-4.31	3.53	2.57-4.83	7
	18.00-05.59	12 (33.4%)	24 (66.6%)	7.67	4.11-14.22	8.49	4.45-16.19	6
Bishop 0-3 PGE2								
	06.00-11.59	64 (54.6%)	53 (45.4%)	1	reference	1	reference	11
	12.00-17.59	18 (35.3%)	33 (64.7%)	2.21	1.12-4.37	2.18	1.08-4.38	10
	18.00-05.59	3 (20%)	12 (80%)	4.83	1.30-18.0	5.32	1.41-19.97	10.5
Bishop 4-6 PGE2								
	06.00-11.59	48 (53.3%)	42 (46.7%)	1	reference	1	reference	11
	12.00-17.59	16 (34%)	31 (66%)	2.21	1.06-4.60	2.29	1.07-4.87	9
	18.00-05.59	4 (36.4)	7 (63.6%)	2.00	0.54-7.31	2.23	0.60-8.36	8.5
Bishop 0-3 TCC								
	06.00-11.59	20 (52.6)	18 (47.4%)	1	reference	1	reference	10
	12.00-17.59	9 (32.1%)	19 (67.9%)	2.34	0.85-6.49	2.60	0.89-7.55	8
	18.00-05.59	2	0	-	-	-	-	-
Bishop 4-6 TCC								
	06.00-11.59	70 (68%)	33 (32%)	1	reference	1	reference	9
	12.00-17.59	16 (28.6%)	40 (71.4%)	5.30	2.60-10.81	6.03	2.83-12.8	8
	18.00-05.59	3 (37.5%)	5 (62.5%)	3.53	0.80-15.69	3.42	0.75-15.65	9

*Adjusted for gestational duration, epidural anaesthesia (EDA), body mass index (BMI), birth weight, maternal age, preeclampsia, small for gestational age (SGA) and diabetes.

Table 13. Risk of night-time delivery after induction of labour among women who delivered in gestational weeks ≥ 37 depending on parity and cervical ripening.

6 DISCUSSION

During pregnancy and delivery both mother and child are at risk of suffering from various complications. The goal of this thesis was to find tools to possibly prevent some of these complications. In this thesis all studies are observational studies. Scientists have a great potential to perform observational research in Sweden since all Swedish residents are assigned a unique national registration number which is referred to in all medical records and official documents. Scientists working in Sweden also have access to large registry databases which allow for observational studies of rare outcomes with high statistical precision.

6.1 DISCUSSION OF MATERIALS AND METHODS:

6.1.1 The Swedish Medical Birth Registry

All studies in this thesis use data from the Medical Birth Registry (MBR). There are always shortcomings in data derived from several different sources and the MBR is no exception. The most recent quality review of the MBR was performed in 2002 (48). Incorrect diagnoses and ICD codes were found. In some cases, data had been lost or incorrectly registered when the data was transferred from the medical record to the registry. In other cases the criteria for a specific diagnosis were different between hospitals. When data were evaluated over time there were trend differences in the diagnosis that was chosen. When data were evaluated, some differences were found regarding how different diagnoses were used over time. The overall evaluation, however, found the validity of the data to be high (48). In our studies we have supplemented with data from patient records in cases where information was inadequate from the MBR.

6.1.2 Study 1 and 2

One advantage of the first two studies is that we retrieved all viable singleton pregnancies recorded at the ultrasound department of UltraGyn Stockholm during the study period. Another

advantage is that all ultrasound examinations were performed by a limited number of specially trained midwifes, reducing the risk for interobserver variation.

As for disadvantages, one limitation is that we used the last menstrual period to estimate the date of conception. This assumes that ovulation occurs on day fourteen of the menstrual cycle, day one being the first day of the last menstrual period. This is true for most women, but ovulation can actually occur at any time during the menstrual cycle. There are also inter-individual differences in the length of the menstrual cycle. A shorter cycle leads to underestimation of fetal size and vice versa. This is why ultrasound biometry before the 24th week of gestation is recognized to be more reliable than LMP as a predictor for the date of delivery (1, 3, 4). To overcome the shortcomings of using LMP as a predictor of EDD and to reduce misclassification in our study, women with possibly undefined ovulation were excluded. Thus women having used oral contraceptives within three months before conception, women with an uncertain date of the last menstrual period or irregular menstrual periods and fetuses that were $\geq$ 21 days larger or smaller than expected were excluded from the study. Furthermore, the misclassification of date of conception will be non-differential, and the bias introduced can only dilute the underlying associations. We therefore do not consider that the use of LMP has undermined the validity of our results. Another source of misclassification is the fact that the mathematical formulas (111) used for clinical management to estimate the date of delivery according to ultrasound biometry underestimate gestational age by a mean of 3 days when dating is performed at 12-14 weeks and 0.8 days at 16-20 weeks (106). The misclassification of date of conception and estimated delivery according to ultrasound will also be non-differential and the bias introduced can only dilute the underlying associations.

Gestational age was assessed from the biparietal diameter (105-107) before gestational week 14 and from femur length and biparietal diameter in weeks 16-18 (108). The reason for not relying on the more precise method for estimating fetal size in the first trimester, on CRL, was that the accuracy of this method has been reported to decrease by the end of the first trimester (105-107). Since the potential misclassification introduced by using a less precise method of measuring fetal growth in early gestation is again non-differential, it is unlikely that the association between SGA and postponing expected date of delivery in the early dating group is due to the use of BPD instead of CRL.

Another risk of misclassification in Study 1 and 2 is due to missing data. The MBR lacks information on maternal smoking during pregnancy in approximately 5 – 10 % of the

pregnancies, whereas in our study, data on smoking was missing in one third. Data on maternal BMI were missing in 40% in our study, in the MBR in general the corresponding figure is 25%. The results were the same, however, when analyses were restricted to pregnancies for which we had smoking information and controlling for maternal smoking status did not affect the results. Neither was the outcome affected when we excluded pregnancies with missing data on maternal BMI. It is therefore unlikely that missing data on BMI and smoking should have influenced our results.

6.1.3 Study 3 and 4

Studies 3 and 4 were based on data on women who were delivered at the Department of Gynecology and Obstetrics at Danderyd Hospital, Stockholm, Sweden from 2002 through 2006. In Study 3 all singleton pregnancies with cephalic fetal presentation and a gestational age of more than 41 gestational weeks, according to ultrasound biometry before the 24th week of gestation were included. In Study 4 corresponding gestational age for inclusion was ≥ 37 weeks of gestation. Pregnancies that were recorded with induced delivery but had a Bishop score of ≥7 were excluded. Further exclusion criteria were intrauterine death, twin pregnancies and previous cesarean section. In Study 4 pregnancies with spontaneous uterine contractions at the time of delivery onset were also excluded from the analysis.

The results of Study 3 could be influenced by confounding, assuming that the person who decides on the induction of labor and delivery also made the decision about a cesarean section. This seems unlikely, however, when the elapsed time between the two interventions makes it unlikely that it is the same individuals who decide about the two different interventions.

The observational design of Study 4 may have introduced selection bias when the method of induction was chosen, and at what time of day or night to induce labor. However, during the study period, the time for cervical ripening was determined by the workload on the labor ward. There was to our knowledge no notion among obstetricians at our clinic that the starting time for cervical ripening was of any importance for the risk of giving birth during the night, nor was there any apprehension that risk of night-time delivery should be influenced by the method of induction. Accordingly, it is unlikely that our results are due to confounding by indication, selection bias or any other systematic error.

Another potential shortcoming of studies 3 and 4 is that cervical status was assessed digitally by several different investigators, which could introduce measurement bias. Using narrow inclusion criteria such as, for example Bishop score of 1-2, could therefore, hypothetically, lead to some investigators being disproportionally represented in the cohort. By using seven points as cut off we have included the majority of induced women and, hopefully, reduced this problem to a minimum. In addition, when Bishop score of 0-3 and 4-6 were analyzed separately in Study 4, there was no suggestion of our results being due to measurement bias. The use of two different methods for induction of labor could possibly introduce confounding by indication. The median BS was lower in women induced by dinoprostone. However, there is no difference in risk for emergency cesarean section when the two methods were compared.

6.2 DISCUSSION OF THE RESULTS:

6.2.1 Study 1 and 2

In Study 1 we found that pregnancies with expected date of delivery moved forward seven days or more at time of dating ultrasound faced a twofold increase in risk of SGA birth. Furthermore, this increase in risk was present also when dating ultrasound was performed in gestational weeks 11 to 13. In the late dating group there was an increased risk for premature delivery but not in the early dating group. In Study 2, we found that fetuses that were at least seven days larger than expected at time of dating ultrasound compared to the expected size according last menstrual period had an increased risk of birth weights above 4500 and 5000 grams. We also found that the proportion of children with a birth weight of two SD or more above the mean for gestational week increased with increasing size at time of dating ultrasound. These studies suggest that fetal size in early pregnancy may be due not only to gestational duration, but also to fetal growth.

Before dating by ultrasound was introduced, expected date of delivery was based on LMP. It assumes that ovulation occurs on day fourteen of the menstrual cycle, where day one is the last menstruation's first day. This is true is true in most cases, but ovulation can actually occur at any time during the menstrual cycle. There are also inter-individual differences in menstrual cycle length. A short cycle leads to overestimation of fetal size and vice versa. Since the advent of ultrasound dating it has been assumed that fetal growth during the first half of the pregnancy is similar for all fetuses giving rise to relatively small variations in the pattern of fetal growth.

Ultrasound biometry before the 24th week of gestation is recognized to be more reliable than LMP as predictor for the date of delivery (1, 3, 4). Several trials have shown that the use of ultrasound biometry reduces the rate of postterm pregnancies. Since 1990, all pregnant women in Sweden are offered an ultrasound scan in early second trimester to determine the expected delivery date, and 98% of all women accept this offer (112).

A number of authors have reported that if the EDD is postponed more than seven days after ultrasound dating in the second trimester, the risk for a SGA fetus increases (29-32).This was found also for pregnancies dated in the first trimester, in a study by Smith et al (113). In a recent study of pregnancies conceived as a result of assisted reproduction, the finding was further corroborated (114). Hackmon et al presented data that showed an increased risk of birth weight of 4500 grams or more in IVF pregnancies for fetuses that were larger than expected in gestational weeks 11-14 (36). Our findings in studies 1 and 2 are in line with these findings although our findings concern spontaneous pregnancies. Reduced fetal size in the first trimester does not necessarily lead to growth restriction later in pregnancy. The fetus may be genetically small or experience catch-up growth. This could explain the reduced frequency of pregnancies that have their estimated date of delivery postponed in the late ultrasound compared to the early, 14.7% versus 23.5%. Another explanation could be the error in the mathematical formulas used in ultrasound biometry, underestimating the gestational length by 3 days in the first trimester and by 0.8 days in the second trimester. Fetal size is also related to ethnicity (115, 116). Ethnicity was not registered in our studies. The catchment area of Danderyd Hospital is still very homogenous regarding ethnicity, most are of Caucasian origin. A small fetal size at dating can further stand for a fetal malformation and/or a chromosome aberration. Because of this, fetuses with malformations were excluded from the study.

We found an association between postponing the EDD more than 7 days and the risk of preterm birth which was confined to the late dating group (Study 1). An explanation for this increase in risk may be iatrogenic interventions, or spontaneous birth due to the condition of the fetus. An argument against such an explanation, however, is that exclusion of subjects with SGA and/or preeclampsia, two of the major underlying conditions for delivery before term, had no effect on the results. A more plausible explanation is therefore misclassification of gestational duration. A fetus that is small at time of dating ultrasound, either naturally or because of growth restriction, may be incorrectly categorized as having a short gestational duration. Accordingly, since there was no increase in the risk of preterm birth among those dated early, such an explanation would

imply that misclassification of gestational duration is more common in the late dating group. This, in turn, would be consistent with fetal size being increasingly due to fetal growth, rather than to gestational duration. It would also imply that in the late dating group, birth weight for gestational age is overestimated and that the association between postponing the expected date of delivery and the risk of SGA may be underestimated in our study.

There are several differences between male and female fetuses. Female fetuses are usually smaller than male, and postponing pregnancies increases the risk of IUFD if the fetus is female but not if it is male (117). In spite of this, we did not control for fetal sex in our studies. This is because in Study 1, our outcome measure was SGA, which is derived from sex dependent growth curves. Accordingly, fetal sex is taken into account through the diagnosis. In Study 2, our outcome was a birth weight above cut off values of 4000, 4500 and 5000 grams. Whether there are any differences between the sexes in risk of birth weight above these cut off values can not be calculated from our study. This, however, does not put in question the validity of our overall finding of an association between fetal size at the time of dating ultrasound and birth weight.

6.2.2 Study 3 and 4

Study 3.

In the decision making of whether or not to induce in gestational week 41 one has to weigh the risk of emergency cesarean section against the risk of intrauterine fetal demise and perinatal morbidity. Currently there are two competing opinions in obstetrics on how to balance these risks. One is advocating the so-called expectant management of pregnancy, often including a non-stress test and controls of the biophysical profile of the fetus, commonly twice a week until delivery (118-121). The purpose of expectant management of labor is to await spontaneous contractions and at the same time increase pregnancy monitoring to avoid adverse consequences such as IUFD. Induction is performed in case of CTG-changes or oligohydramniosis. The other opinion is advocating elective induction at 41 weeks of gestation since this decreases the risk of emergency cesarean section and adverse fetal outcome (64-72). In the literature, there is no consensus whether induction of labor at ≥41 weeks of gestation decreases the risk of emergency cesarean section or not (64-72) (74-81). Our study adds to the literature that puts in question the

benefit of induction in week 41 since we found that induction is associated with an increased risk of emergency cesarean section.

There are several possible explanations for the discrepant results between our study and the meta-analyzes, the RCT's and the observational studies that have shown a decrease in risk of emergency cesarean section in the group that had elective induction of labor. In most these studies, the risk of emergency cesarean section is calculated according to intention to treat (ITT), those that are categorized as induced to labor are either induced or go into spontaneous labor while waiting for induction. The induced women are compared with women awaiting spontaneous labor, however some of the women categorized as spontaneous labor are actually induced to labor for various reasons. The risk of emergency cesarean section increases with gestational age (122). Accordingly, a high risk of emergency cesarean section after labor induction in later gestational weeks may increase the risk of emergency cesarean section in the reference category i.e. awaiting spontaneous labor. Induced delivery in week 41 may therefore appear to be more beneficial than it actually is. In addition, women starting with spontaneous contractions have a lower risk of emergency cesarean section. The inclusion of women with spontaneous contractions in the induced group since may underestimate the risk of cesarean section among women that are induced.

Another possible explanation for the discrepancy in result is the general difficulty entailed in non-blinded intervention studies. Included women are informed about the study and then randomized either to induction or to have expectant management of labor i.e. assessment by ultrasound and non-stress tests, typically twice a week. If the tests are reassuring the pregnancy is allowed to continue until spontaneous contractions starts or reaches ≥42 weeks of gestation. If, on the other hand, the non-stress test show signs of non-reassuring pattern of the fetal heart rate, if olighydramnniosis is diagnosed, or if the mother so requests, the pregnancy is terminated either with induced delivery or elective cesarean section. Since the women by participating in the study are informed about the risks of pregnancies that continue after 41 weeks of gestation in terms of fetal mortality and morbidity, the indication maternal request for induction of labor is thereby probably at risk of increasing as the pregnancy proceeds. Likewise, the clinician interpreting the CTG registration and ultrasound examination is also aware of the risks which may influence the decision making regarding mode of delivery. Therefore, even though the internal validity may be excellent in these randomized trials, the external validity, i.e. the generalizability to other populations, may be questionable.

On the other hand there are a number of observational studies showing that induction of labor in ≥ 41 weeks of gestation leads to increased risk of emergency caesarean section (74-81). However these observational studies, as well as Study 3, do not take into account the fact that pregnancies that are not induced will not all start spontaneously. Indeed, women who proceed in their pregnancy will face either spontaneous labor or induction of labor at a more advanced gestational age. The risk of emergency cesarean section increases with gestation (122). This is the main argument used by several authors to explain the increase in risk of emergency cesarean section in observational studies. We therefore calculated the risk of emergency cesarean section in our study according to ITT. In these risk calculations we still found an increase in risk for emergency cesarean section. This is not in line with the meta-analysis or with the RCT´s. The reason for this discrepancy could be that we restricted the analysis to inductions of labor at Bishop score of <7 and cervical ripening with PGE2 or transcervical catheter. Further the pregnancies that proceeded were not managed according to expectant management of pregnancy, therefore neither the patient nor the clinician could have been influenced in their decision making nor in their handling of the labor. The lack of surveillance may also have masked a deteriorating fetal condition evident only at spontaneous contractions or at induction after 42 weeks thus mediating a higher risk of emergency cesarean section.

In our study we have chosen to analyze the risk for emergency cesarean section after induction of labor at ≥ 41 weeks of gestation. Induction in this gestational week has become common worldwide after the publication of a Canadian study showing a decreased risk of emergency cesarean section after induction of labor compared to expectant management of labor. The perinatal mortality was also lower but the result was not statistically significant (67). Meta-analyses have shown a decrease in risk of perinatal mortality without an increase risk in emergency cesarean section (66, 73). These studies are hampered by the fact that the Canadian study has a large impact on the result and by the fact that the perinatal losses are not convincingly due to gestational age. The perinatal mortality increases as the placenta ages and is at 41 weeks around 1/500 (43-47) . The number of elective inductions of labor in order to prevent each loss is therefore very large. To our knowledge, no single study has been able to show a decrease in perinatal mortality by elective induction of labor at 41 weeks of gestation, illustrating the problem in studying rare outcomes. Thus since elective induction hasn't lead to a decrease in perinatal mortality rate this management of pregnancies at 41 weeks of gestation must be questioned.

Study 4

We found that nulliparous women induced with transcervical catheter had an increased risk of giving birth during the night. This was at Bishop score 0-3 and if they were induced in the morning instead of in the afternoon or in the evening. If cervical ripening was performed with vaginal dinoprostone gel, the time of induction did not affect the risk. For multiparous women, on the other hand, induction in the morning reduced the risk of night-time deliveries regardless of whether cervical ripening was done by transcervical catheter or dinoprostone.

Dodd et al presented a study in which they studied the duration of labor for women induced with prostaglandins (misoprostol or dinoprostone) (101). They concluded that if cervical ripening was required with prostaglandins it should preferably be given in the morning at admission. The aim of that study was not to reduce the number of deliveries during the night, but to reduce the need for oxytocin infusion and epidural analgesia. In another study the authors concluded that there is no benefit in starting induction with dinoprostone in the evening compared to the morning (102). The study only includes 126 women, and the lack of statistically significant results could be due to lack of power. To our knowledge there is no previous study in which the risk for cervical ripening with a transcervical catheter and the risk for giving birth at night has been evaluated.

There are a number of reasons for trying to reduce deliveries during the night, one of the most important is that perinatal morbidity and mortality is lower for deliveries during daytime (94-99, 123). One might speculate on whether the increase in risk of fetal asphyxia during the night is biased by a higher proportion of high risk pregnancies delivered at night. In 2003 a study showed that delivery of high risk pregnancies were more common during the day and that the risk for early neonatal death in night-time deliveries increased after adjustment for high risk pregnancies (98). It has been shown that the work during the night is associated with an increased amount of errors due to sleepiness compared to work during the day (124, 125). The staffing situation in the delivery ward is often better during daytime. There are fewer midwives during the night and junior doctors have to make more complicated decisions since more competent physicians are not immediately available. It is therefore reasonable to plan inductions so that night-time deliveries are avoided. Thus the possibility of active management of labor is optimized and the risk of delivery by caesarean section or instrumental delivery decreased.

6.3 IMPLICATIONS

Small for gestational age is associated with a number of adverse outcomes such as asphyxia and perinatal death. Since early detection may improve the prognosis, finding means for increasing the detection is essential. The screening method used today, SF-measurement has low sensitivity for detection of deviations of fetal growth. Our study suggests that a more active surveillance of pregnancies with postponed EDD could be one possible way to detect high risk pregnancies early, especially in the late dating group.

It has been shown that children who are smaller than expected at the dating ultrasound have an increased risk of intrauterine death in post date pregnancies. This could implicate that pregnancies with a postponed EDD would benefit from induction of labor before 41 weeks of gestation.

Since induction of labor after 41 weeks of gestation increases the risk of emergency cesarean section substantially, this risk has to be balanced against the risk of fetal comprise. The maternal age, the BMI of the mother, parity and the degree of cervical ripening should also be considered.

In the daily work in the maternity ward, it makes sense to plan the work as far as possible to avoid night-time delivery. Our results suggest that starting time of labor induction is a factor that influences the risk of night-time delivery. Nulliparous should be induced later in the day than multiparous in order to avoid night-time delivery

6.4 FUTURE PERSPECTIVES:

Study 1 and 2 of this thesis underline the importance of the first part of the pregnancy. Previously, the first visit to the antenatal care centre was geared towards information to the mother. A history was also obtained to evaluate the risk for complications. Lately screening for chromosome aberrations has been introduced in the first trimester and early detection of preeclampsia has also been discussed. The perspective introduced here is that fetal growth deviations can also possibly be detected at this early stage. Since altered placentation is involved in many pregnancy complications their detection is mandatory before the placenta is fully developed i.e. before gestational week 24. The symptoms and signs of these complications usually develop after that particular week. We know today that abnormal proteins are

synthesized as a cause or a result of these complications. We also know that placental transport of growth factors and nutrients contribute. In the future diagnosis and treatment may be possible through administration of needed substances or by blocking others.

Study 3 and 4 underlines the importance of the last weeks of pregnancy.
It is generally considered that it is of no benefit for the fetus to stay in the uterus after gestational week 39. Instead the perinatal mortality increases. The argument against induction of delivery is fear of maternal complications. Previous history, maternal age, maternal BMI, cervical status, gestational week and predicted fetal weight all contribute to the success of induction. Through investigation of these risks an algorithm could be created to evaluate the true chance that induction in a particular week on a particular mother could be successful. Only then can the benefit for the fetus be balanced against the risks for the mother.

7 CONCLUSIONS

Study 1

We have found that early growth retardation may be present as early as in the first trimester. Accordingly our study suggests that surveillance of pregnancies, whose expected day of delivery is postponed, regardless of whether dating was performed early or late, may provide means for increasing the detection rate of fetal growth restriction. However, late dating seems to be more efficient than early dating for the detection of pregnancies at increased risk of SGA, premature delivery and preeclampsia than early dating, with a higher odds ratio in spite of a lower rate of postponed pregnancies.

Study 2

Fetuses that are larger than expected in the second trimester have an increased risk of macrosomia. This emphasizes that fetal size in early pregnancy is not only a function of gestational duration, but also of fetal growth. However, only a limited proportion of all infants born macrosomic can be detected at time of dating ultrasound.

Study 3

Compared to spontaneous onset of delivery, induction of labor is associated with an increased risk of emergency cesarean section both among nulliparous and multiparous women. When labor is induced the high risk of emergency cesarean must be kept in mind.

Study 4

Starting time of labor induction affects the risk of giving birth at night. For nulliparae induced by TCC, starting the induction in the evening instead of during the day may reduce the number of night-time deliveries substantially. For multiparae, however, our data suggest that induction of labor should take place in the morning.

8 SUMMARY IN SWEDISH

-sammanfattning på svenska

Som kliniskt verksam läkare inom förlossningsvården på Danderyds sjukhus ställs jag dagligen inför kvinnor som på ett eller annat sätt drabbats av komplikationer i samband med graviditeten, under eller efter förlossningen. Många områden inom obstetriken är fortfarande outforskade eller skulle vinna på ytterligare kartläggning.

Studie 1 och 2:

För att kunna uppskatta fostrets storlek är det nödvändigt att ha en adekvat bedömning av graviditetslängden. Idag erbjuds alla gravida kvinnor i Sverige en ultraljudsundersökning under graviditeten för att fastställa förlossningsdatum samt utesluta anatomiska missbildningar hos fostret. Man har länge ansett att fostrets storlek under första trimestern endast är beroende av graviditetslängden. Att med ultraljud fastställa graviditetslängden har setts som mer tillförlitligt än att beräkna förlossningsdatum utifrån sista menstruationens första dag. Eventuella skillnader i fetal storlek vid ultraljudsdatering, jämfört med förväntad fosterstorlek enligt sista menstruationen, har ansetts bero på osäkra mensdata eller tidig respektive sen ägglossning. Därför har dessa graviditeter behandlats som normala. Variationer i barnets födelsevikt har tillskrivits orsaker under andra hälften av graviditeten. Men en mindre eller större fosterstorlek än förväntat kan också stå för en tidig tillväxthämning eller en accelererad fostertillväxt. Det finns studier som antyder detta. Genom att utifrån ultraljudsundersökningen senarelägga förväntat förlossningsdatum hos ett foster som i själva verket har en tidig tillväxthämning kommer detta att resultera i att graviditeten anses yngre än vad den är. Det kan i sin tur resultera i att man inte reagerar på de tecken som antyder att fostret är tillväxthämmat eller att man reagerar för sent.

I Sverige använder vi idag två metoder för att bedöma fostrets storlek under graviditeten: symfys-fundus mätning och ultraljudsundersökning. SF-måttet används som screeningmetod from graviditetsvecka 25. Graviditeter som löper en stor risk för avvikelser i fosterstorlek samt graviditeter där SF-kurvan avviker undersöks med ultraljud för att man skall få en bättre uppfattning om fostrets storlek. Båda mätmetoderna har dock visat sig ha relativt låg sensitivitet för att upptäcka avvikelser i fostertillväxten. Detta gör att många av de foster med en accelererad tillväxt eller tillväxthämning inte upptäcks förrän efter förlossningen.

Barn som är mindre än två standardavvikelser från medelvärdet för graviditetslängd och kön kallas lågviktiga barn (small for gestational age, SGA). Makrosomi (stort barn), definieras i Sverige som en födelsevikt på mer än 4500 g oavsett graviditetslängd. Det är viktigt att upptäcka om ett foster är lågviktigt innan förlossningen startar. Fetal tillväxthämning är en känd riskfaktor för en rad allvarliga komplikationer för fostret. Det tillväxthämmade fostret har en ökad risk för syrebrist i samband med förlossningen, perinatal död samt neurologiska resttillstånd. Man har i studier kunnat påvisa att förlossningsutfallet förbättras avsevärt om man känner till tillväxthämningen innan förlossningen startar. Även en accelererad fostertillväxt är viktig att känna till innan förlossningsarbetet startar. Födelsevikt ≥4000 gram är förenat med en ökad risk för utdraget förlossningsarbete, att skuldrorna fastnar i förlossningskanalen, för skelettskador och att barnet dör i nyföddhetsperioden. När födelsevikten är ≥4500 gram ökar dessa risker ytterligare. Om den förväntade förlossningsvikten är ≥ 5000 gram är riskerna för negativa konsekvenser för mamma och barn så stora att man rekommenderar förlossning med planerat kejsarsnitt.

Syftet med studie 1 och 2 var att utvärdera huruvida fostrets storlek i samband med ultraljudsdateringen, jämfört med förväntad storlek enligt sista menstruationen, påverkar risken att födas för liten respektive för stor för tiden. Syftet med studierna var också att utvärdera om tidpunkten för ultraljudsdateringen, före graviditetsvecka 14 (tidigt) respektive efter graviditetsvecka 16 (sent), påverkar den risken. I studie 1 utvärderades också om foster som var oväntat små hade en ökad risk att födas för tidigt (prematurt).

Studie 1 och 2 är retrospektiva kohortstudier som utgår från en databas på Danderyds sjukhus från åren 1998-2004. 27 952 graviditeter ingår i studien. Av dessa är 5053 daterade tidigt och 22 889 daterade sent. Studie 1 visade att det fanns en överrisk för SGA om fostret var ≥ 7 dagar mindre än förväntat jämfört med förväntad fosterstorlek enligt sista mens, oavsett om ultraljudsdateringen gjorts tidigt eller sent. Risken för tidig födsel var endast ökad hos foster som var små för tiden vid den grupp som daterades sent d.v.s. efter vecka 16. Studie 2 visade att foster som var oväntat stora vid det sena dateringsultraljudet löpte en ökad risk att födas stora. Antalet foster som var större än förväntat vid det tidiga ultraljudet var för få för att man skulle kunna beräkna risken för makrosomi.

Studie 3 och 4:

Att sätta igång förlossningsarbetet s.k. induktion har blivit en av de vanligaste interventionerna inom förlossningsvården idag. I genomsnitt 12-15% av alla graviditeter avslutas på detta vis. De främsta orsakerna är havandeskapsförgiftning, högt blodtryck, diabetes, tillväxthämning och överburenhet, varav överburenhet är den vanligaste orsaken. I Sverige är definitionen på överburenhet ≥ 42 graviditetsveckor. I många andra länder är istället 41 graviditetsveckor gränsen för igångsättning. Motivet till denna ändring är att man har funnit att en ökad risk för perinatal morbiditet och mortalitet efter denna vecka. Denna förändring innebär att antalet induktioner har ökat kraftigt.

Det finns olika metoder för att sätta igång ett förlossningsarbete. Om livmoderhalskanalen anses omogen kan man applicera prostaglandiner i vagina, medicinsk induktion, alternativt kan man föra upp en typ av ballongkateter i livmoderhalskanalen, mekanisk induktion. Det finns ett stort antal studier beträffande förlossningsutfall vid induktion. Trots detta har man i litteraturen inte kunnat enas om huruvida igångsättning av förlossningsarbetet vid ≥ 41 graviditetsveckor leder till en ökad risk för kejsarsnitt, jämfört med spontan förlossning, eller ej**.**

Det är känt att förlossning nattetid innebär en ökad risk för fostret att drabbas av syrebrist under förlossningen. På många förlossningskliniker väljer man att påbörja induktionen på morgonen eller förmiddagen eftersom bemanningen är bättre på dagtid. I litteraturen har man funnit att mediantiden från induktionstillfället tills att barnet är fött är 12-25 timmar. Detta borde alltså resultera i att induktion av förlossningsarbetet på morgonen ökar risken för nattlig förlossning.

Syftet med Studie 3 var att analysera om risken för akut kejsarsnitt ökar vid förlossningsinduktion i graviditetsvecka ≥41 jämfört med spontan vaginal förlossning hos först- respektive omföderskor. Syftet var också att undersöka om risken påverkades av valet av induktionsmetod.

Syftet med Studie 4 var att undersöka om tidpunkten på dygnet då induktionen påbörjades påverkade risken för nattlig förlossning i fullgången graviditet, samt om det var någon skillnad i denna risk mellan först- och omföderskor.

Studie 3 och 4 är retrospektiva kohortstudier som utgår från en databas på Danderyds sjukhus från åren 2002-2006. 23 030 kvinnor med förlossning efter vecka 37 ingår i studien. Av dessa inducerades 1940 efter ≥ 37 graviditetsveckor och 881 efter vecka 41 med prostaglandingel eller kateter i livmoderhalskanalen p.g.a. att livmoderhalskanalen ansågs omogen. I studie 3 fann vi att det förelåg en ökad risk för akut kejsarsnitt både för först- och omföderskor efter igångsättning. Det fanns dock ingen skillnad i riskökning mellan de två undersökta induktionsmetoderna. I studie 4 fann vi att risken för nattlig förlossning var högre för förstföderskor som satts igång med kateter på morgonen jämfört med de förstföderskor som inducerats på kvällen. För omföderskor rådde omvända förhållanden, d.v.s risken för nattlig förlossning var högre för de omföderskor som inducerats på eftermiddagen eller kvällen.

9 ACKNOWLEDGEMENTS

I would like to express my sincere gratitude and appreciation to everyone who has helped and supported me throughout the years I have worked with this thesis and making it possible. Especially,

Associate Professor Ellika Andolf, my principal supervisor and co-author, who introduced me to research in obstetrics. You have always been supportive and helpful. For your wonderful sense of humor. For getting to know you as a clinician, researcher and friend. I have really enjoyed our travels together and our discussions.

Associate Professor Magnus Kaijser, my co-supervisor and co-author. This had not been possible without you. For introducing me to epidemiology. For answering my e-mails late at night when the statistical struggles have been overwhelming. For all the time at your kitchen table discussing science, family and other things that are important.

M.D. PhD. Harald Almström, my co-supervisor and co-author. Chief executive operating manager of BB Stockholm. For encouraging and supporting me. Making my education in ultrasonography possible.

M.D. Anna Marsk , Head of UltraGyn, for valuable help with the data bases. For constructive criticisms of the manuscripts regarding fetal growth. Responding to emails faster than the wind. For your support and friendship.

M.D. PhD. Ann Hjelm, Head of BB Stockholm, who through timetabling made it possible to finish my thesis.

Associate Professor Jan Zetterström, my mentor, for interesting discussions, god advices and friendship, for believing in me.

Associate Professor, Sven Lyrenäs, co-author in Study 3 and 4, for a good collaboration.

To all my friends and colleagues at UltraGyn always being supportive, creating and forming the Department to what it is today, an outstanding place to work, with nice and pleasant atmosphere, with vivid discussions and a lot of laughter. In short a good place to work in.

To all my friends and colleagues at BB Stockholm, for a dynamic work environment, with plenty of work satisfaction and the never-ending desire of wanting to learn more. I feel pleased when I go to work.

To all my friends and colleagues at the Department of Obstetrics and Gynaecology at Danderyd Hospital, for all the years of cooperation. I am sincerely grateful for al years in close collaboration. I also truly appreciate all the knowledge and expertise that I have been given the opportunity to take part of.

To beloved my father Tomas and my mother Annica. Through your love and support you have helped me become who I am today. You taught me that everything is possible.

To my dear sister, Jenny Lorefors, for sharing the joys and sadness in life with the same presence and compassion, for being my friend. To Klas. Alva and Ellen, you enrich my life.

To Cecilia Magnusson, my sister, thank you for all the joy and happiness you have given me. I am so happy that you are you.

To my grandmother, Iris Magnusson, I think of you daily and carry your voice within me. "One should always celebrate if there is something to celebrate, and it always is," I am glad and grateful that you were my friend.

To my grandfather, Alvar Hedmo. You taught me to see life in another perspective. I will always remember your patience and kindness.

To my "family in law", Gunnar, Anna Lena, Magdalena, Kristina, John, Walter and Folke for your kindness and your love. For your loyalty in helping us through everyday life, for never saying no to all of our ideas.

To my dear friend, Pia Fagerstöm, for always being there. You are a true friend in the truest sense. Life would not be the same without you. "MOPÄB". To Saga and Hjalmar for letting me be a part of your lifes.

To Camilla Stocklassa, my friend and colleague, for always being there, for all the laughter and sharing life and the daily work with me. You always turn things to the better.

To Fredrik, Gabi, Miranda, Noel and Esther Jäderling, for all the support, friendship and loyalty when I have needed it most, for sharing the contents of life. I love and highly appreciate our macaroni and meatball dinners on a regular Monday.

To Johan, Åsa, Viktor, Simon and Anna Borulf Berséus, for their inspiring ability to make adventures home or away. For all the fun and all the laughter. I hope we will continue to share the adventure and the fun for the rest of our lives.

To Filip, Ylva, Vera and Sebastian Bjurström, and Fredrik, Pernilla, Alexander and Hugo Lagerman, for wonderful brakes in my research, always being there sharing dinners and adventures in my time of. I hope we will have more time for that now.

To Jan, Lina, Alexandra, Agnes and Christopher Teorell, despite long distance always very present in our thoughts and lives. For stimulating conversations about what makes life precious.

To Joakim, Idun and Disa. You always add that little extra that makes me feel good. For always making the effort to make the parties even more fun. Jocke, you made this thesis more readable.

To Mattias, Helen, Klara and Axel Magnusson, for all the good times during our friendship. For all your kindness and never ending hospitality.

To my friends and colleagues Sophia Ehrström, Karin Wikström, Ulrika Johanesson and Åsa Hammar; for accompanying me down the slopes, at the shopping sprees, interesting discussions about life and work in a delightful mix.

To my friends and colleagues Elisabeth Wikström Schemer and Helena Kopp Kallner, for all your understanding and support over the years that I struggled with this thesis. I have really appreciated our “research dinners” when we shared experiences regarding our education but also life in general.

To my friend and colleague, Jan Rapp, for your enthusiasm to all my ideas. For your commitment when ever I want to have a party. Because you only see the possibilities

Karolinska Insitutet and Capio research foundation for financial support

And finally the most important and precious persons in my life, there are no words that can express how dear you are to me,

To my beloved husband Martin, being with you is like being fed with sunshine every day. You are the one that makes everything worth living for.

My wonderful beloved children; Kajsa, Teo and Klara, for being you. For the constant reminder of what’s important in life.

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