Individualized management in term pregnancies. Action point decisions based on gestational duration considering parity and BMI.

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Individualized management in term pregnancies

Action point decisions based on gestational duration considering parity and BMI

Lina Lindegren, MD

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle: Individualized management in term pregnancies. Action point decisions based on gestational duration considering parity and BMI.

Abstract

Introduction: The overall purpose is to investigate the impact of maternal BMI and parity in relation to gestational duration on adverse maternal and neonatal outcome among women with singletons in cephalic presentation in term pregnancies. **Methods and Material:** Retrospective studies on data from the Swedish Medical Births Register, 1998-2017. **Results: I**: Primiparous, but not multiparous women handled at more active managed maternity units, had a reduced risk of a child with Apgar score <7, AOR=1.27 (95%CI: 1.16-1.41) at five minutes and meconium aspiration AOR=1.49 (95%CI: 1.14-1.95). Caesarean section (CS) rates increase after induction, regardless of parity. **II**: No subgroup of multiparous women with improved neonatal or maternal outcome after induction was detected. Success rates of vaginal birth in a second delivery is highly dependent on first delivery mode, vaginal or CS, and from diagnosis or conditions present at first CS. **III:** Children to primiparous women born at 41^{+3} weeks or more were at increased risk of stillbirth or neonatal death before 45 post-menstrual weeks compared to children born at 39^{+0}-40^{+2} weeks (ARR=1.29 95%CI: 1.10-1.52). No significant risk increase with gestational age was detected for multiparous women, regardless of BMI. **IV:** Children to obese primiparous women had an increased risk of Apgar score <7 at five minutes (AOR=1.36 (95%CI: 1.27-1.45) from 39^{+3} and for stillbirth or neonatal death before 45 post-menstrual weeks throughout the study period, 39^{+0}-41^{+6} (AOR= 1.26 (95%CI: 1.07-1.48).

Conclusions: The risk of adverse neonatal outcome in addition to advancing gestational duration in term pregnancies is affected from both parity and BMI. For obese primiparous women the risk for Apgar score <7 at five minutes is increased from 39^{+3}, compared to the baseline incidence. Regardless of gestational duration, primiparous women who were overweight or obese were at increased risk of having a child who died perinatally or had low Apgar score <7 at five minutes compared to women with normal weight. For multiparous women the risk of having a child with adverse neonatal outcome in term pregnancies were low, and the risk did not increase with advancing gestational duration. Recommendation on management in term pregnancies would benefit from individualized assessments on action point decisions from gestational duration with addition from parity and BMI, especially for primiparous women who are overweight or obese.

Key words Parity, BMI, Induction, Caesarean section, term and late term pregancy.

Classification system and/or index terms (if any)

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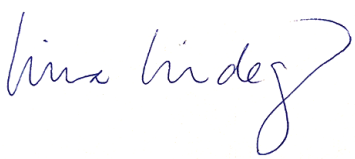
Signature  Date 2021-10-21

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To women giving birth

Table of Contents

Original Papers

This doctoral dissertation thesis is based on the following papers which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I. Improved neonatal outcome after active management of prolonged pregnancies beyond 41^{+2} weeks in nulliparous, but not among multiparous women. Lindegren L, Stuart A, Herbst A, Källén K. Acta Obstet Gynecol Scand. 2017. Dec;96(12):1467–1474.

II. Retrospective study of maternal and neonatal outcomes after induction compared to spontaneous start of labour in women with one previous birth in uncomplicated pregnancies ≥ 41+3. Lindegren L, Stuart A, Carlsson Fagerberg M, Källén K. J Perinat Med. 2020 Aug 24;49(1):23–29.

III. Stillbirth or neonatal death before 45 post-menstrual weeks in relation to gestational duration in pregnancies at 39 weeks or beyond: the impact of parity and body mass index. A national cohort study.Lindegren L, Stuart A, Herbst A, Källén K. BJOG. 2021 Oct 12. Epub ahead of print.

IV. Relation between perinatal outcome and gestational duration in term nulliparous pregnancies stratified by body mass index.Lindegren L, Stuart A, Herbst A, Källén K. Submitted.

Abstract

Introduction and aim: During the last two decades the regional differences in Sweden of management of late to post-term pregnancies have radiated towards active management at 41^{+0} to 42^{+0} weeks to reduce maternal and neonatal adverse outcome. This is in line with international recommendations for pregnant women. The recommendations are for all women without consideration of the heterogenicity in characteristics of pregnant women. The overall purpose of this thesis is to investigate the impact of maternal BMI and parity in relation to gestational duration on adverse maternal and neonatal outcome among women with singletons in cephalic presentation in term pregnancies.

Methods and Material: Four retrospective register studies from the Swedish Medical Births Register. Included are women with singleton in cephalic presentations from 1998 to 2017. Descriptive and logistic regression analysis are calculated. Parity is studied for primiparous and multiparous women separately and BMI in classes (BMI<25, BMI 25-29.9, and BMI≥30). Outcome measures studied are maternal mode of delivery, vaginal or caesarean section (CS) and neonatal Apgar score <7 at five minutes, meconium aspiration, stillbirth and stillbirth or neonatal death before 45 post-menstrual weeks.

Results: Study I: Primiparous, but not multiparous women handled at a more active managed maternity unit, had a reduced risk of a child with Apgar score <7 at five minutes, AOR=1.27 (95%CI: 1.16-1.41), and meconium aspiration AOR=1.49 (95%CI: 1.14-1.95). Regardless of parity, CS rates increase after induction.

Study II: No subgroup of multiparous women with improved neonatal or maternal outcome after induction of labour was detected. Success rates of vaginal birth in a second delivery are highly dependent on first delivery vaginal or CS birth, and of diagnosis and/or conditions present. Vaginal success rates vary from 97.8% (first vaginal delivery with second labour spontaneous start) to 47.9% (first delivery emergency CS with following second labour induction). The risk of emergency CS second labour, after induction vs spontaneous start, regardless of first delivery mode was AOR = 2.11 (95%CI: 2.00-2.23).

Study III: Children to primiparous women, regardless of BMI class, born at 41^{+3} weeks or more were at increased risk of stillbirth or neonatal death before 45 post-menstrual weeks compared to children born at 39^{+0} to 40^{+2} weeks (ARR=1.29 95%CI: 1.10-1.52), with the highest incidence detected for primiparous women with BMI ≥30, ARR=1.52 (95%CI: 1.10-2.10). No significant risk increase with gestational age was detected for multiparous women, regardless of BMI class.

Study IV: Children to primiparous women with BMI ≥30 had an increased risk of Apgar score <7 at five minutes (AOR=1.36 (95%CI: 1.27-1.45) from 39^{+3}, and stillbirth or neonatal death before 45 post-menstrual weeks throughout the study

period, 39^{+0}-41^{+6} (AOR= 1.26 (95%CI: 1.07-1.48). For children to women with BMI <25 no association between gestational duration and risk of stillbirth or neonatal death was indicated.

Conclusions: The risk of adverse neonatal outcome in relation to advancing gestational duration in term pregnancies is affected by both parity and BMI. For obese primiparous women the risk of a child with Apgar score <7 at five minutes is increased from 39^{+3}, at which non-medial induction isn´t considered. Regardless of gestational duration, primiparous women who were overweight or obese were at increased risk of having a child who died perinatally or had low Apgar score <7 at five minutes compared to women of a normal weight. For multiparous women the risks of having a child with adverse neonatal outcome in term pregnancies were low, and the risk did not increase with advancing gestational duration

The result from our analyses emphasises parity and BMI as risk factors to be considered in term pregnancies. Individualized management of risk factors in association with gestational duration could be a way to lower the numbers of adverse neonatal outcomes even further.

Summary in Swedish - Populärvetenskaplig sammanfattning

En graviditet räknas som fullgången mellan 37 veckor och 0 dagar (37^{+0}) till 41 veckor och 6 dagar (41^{+6}). Därefter är graviditeten per definition överburen vilket inträffar för ungefär 6 procent av gravida svenska kvinnor. Att vara gravid mer än två veckor efter beräknat förlossningsdatum medför ökade risker för försämrat mående både för mamman och barnet. Ökad kunskap kring riskerna med överburenhet har medfört att regionala riktlinjer för igångsättning av friska gravida tidigareläggs till mellan 41^{+0} och 42^{+0}. Riktlinjerna baseras enbart på graviditetslängden och beaktar inte kvinnans individuella förutsättningar inför en förlossning.

Syftet med avhandlingen är att undersöka betydelsen av paritet, har den födande kvinnan tidigare fött barn, och kvinnans body-mass-index i relation till fortsatt graviditet vid fullgången tid. Studerade utfall för mamman är förlossningssättet, vaginalt eller kejsarsnitt. Studerade utfall för barnet är risken för att svälja fostervatten nedsmutsat av mekonium, Apgarpoäng mindre än sju vid fem minuters ålder, att födas dödfödd, avlida under förlossningen eller under första veckorna i livet. Apgar är ett poängsystem som bedömer barnets vitalitet vid 1, 5 och 10 minuters ålder.

Förhoppningen är att avhandlingens resultat kan lämna ett bidrag till en minskad förekomst av komplikationer hos den födande kvinnan eller hos barnet genom individualiserad handläggning av friska fullgångna graviditeter baserat på information om kvinnans paritet och BMI som komplement till graviditetslängd.

Avhandlingen består av fyra registerstudier baserade på data från Medicinska Födelseregistret (MFR). Alla mödrahälsovårdsmottagningar, förlossningskliniker och neonatalavdelningar i Sverige skickar digitalt information om den gravida, förlossningen och det nyfödda barnet till registret. Digital överföring medför att alla förlossningar rapporteras och att det över tid bildas ett register med förutsättningar att studera och analysera resultat med stor säkerhet även för ovanliga händelser som dödföddhet.

I den första studien undersöks hur paritet påverkar utfallet för barnet i graviditeter efter 41^{+3}. Förlossningsenheter delades in i mer eller mindre aktiva, beroende på andelen gravida som inte var förlösta innan 42^{+3} av alla gravida vid 41^{+3}. Resultaten visar att barn till förstföderskor, som handlades vid förlossningsenheter med mer aktiv handläggning mådde bättre efter förlossningen men för kvinnan ökade risken för kejsarsnitt. För omföderskor handlagda på en aktivare förlossningsenhet sågs inget förbättrat mående för barnet men däremot en ökad risk för kejsarsnitt.

I den andra studien studeras enbart omföderskor. Gruppen omföderskor delades upp utifrån hur varje kvinnans första förlossning avslutades, vaginalt eller med

kejsarsnitt. Kvinnorna grupperades även utifrån om den andra förlossningen startade spontant eller med igångsättning och hur det påverkade förlossningsutfallet. I de fall kvinnan förlöstes med ett kejsarsnitt vid första förlossningen undersöktes även om diagnosen för det första kejsarsnittet påverkade den andra förlossningens utfall. Förlossningssättet vid den andra förlossningen påverkades, med hög risk för upprepning av hur den första förlossningen avslutades. För omföderskor kunde inga vinster med igångsättning för barnet eller kvinnan identifieras under den studerade graviditetslängden (41^{+3}–42^{+6}).

Övervikt och obesitas (fetma) ökar bland gravida. Detta medför ökad risk för den gravida att gå över tiden och för ett försämrat mående hos barnet efter förlossningen. Studierna tre och fyra undersöker hur risken för dödföddhet samt låg Apgar poäng påverkas av kvinnans paritet och BMI utöver graviditetslängden.

Studie tre inkluderade nästan 900 000 gravida mellan 39^{+0} till 42^{+2}. Barn till obesa förstföderskor efter vecka 41^{+3} hade högst risk för Apgarpoäng <7 vid 5 minuter, för att födas dödfödd, avlida under förlossningen eller under första veckorna i livet. Risken för dödföddhet ökade för gruppen obesa förstföderskor från 0.8 till 4.0 promille mellan 40^{+2}–40^{+6} och 42^{+0}–42^{+2} och var dubbelt så stor för förstföderskor som för omföderskor. För omföderskor och normalviktiga förstföderskor ökade risken för att barnet ska dö i magen med ökande graviditetslängd, men sakta och måttligt jämfört med för överviktiga eller obesa förstföderskor.

Fokus i studie fyra är den absoluta risken för förstföderskor att föda ett barn med Apgar poäng <7 vid 5 minuter, ett dödfött barn eller ett barn dör innan 45 veckor i relation till graviditetslängden och BMI. För att kunna jämföra risken mellan BMI-klasser beräknades bakgrundsrisken för alla kvinnor vid 41 veckor fram. Resultaten visar att barn till normalviktiga kvinnor uppnådde den bakgrundsrisken för Apgarpoäng <7 vid fem minuter vid en graviditetslängd på 41^{+3} dagar, kvinnor med övervikt vid 40^{+4} dagar och kvinnor med obesitas vid 39^{+3}. Övervikt och obesitas medför ökad risk för försämrat mående hos barnet efter förlossningen vid kortare graviditetslängd än för normalviktiga förstföderskor. Risken för att barnet föds dödfött, avlider under förlossningen eller under första veckorna i livet var högre för obesa förstföderskor under hela den studerade graviditetsperioden (39^{+0}–41^{+6}).

Den senaste internationella Cochranerapporten rekommenderar att vid friska fullgångna graviditeter ska alla gravida kvinnor få hjälp med igångsättning av förlossningen vid 41 veckor. Sverige har haft en relativt oförändrad incidens av dödfödda i fullgångna graviditeter, men efter ökad medvetenhet och en mer samstämmig handläggning verkar incidensen sjunka. Avhandlingen indikerar att det bland gravida finns betydande riskskillnader. Dessa riskskillnader, paritet och BMI, bör beaktas och prioriteras för att uppnå ytterligare hälsovinster för barnet och kvinnan. Barn till förstföderskor med högt BMI kan ha nytta av igångsättning före 41 veckor men det finns även grupper av gravida, omföderskor, där igångsättning enligt våra resultat endast medför ökade risker för den blivande mamman och

barnet. Genom en ökad individanpassning av förlossningsvården med individuella bedömningar avseende paritet och BMI hos i övrigt friska fullgångna gravida finns potentialen för en förbättrad förlossningsvård.

Abbreviations

ACOG	American College of Obstetrics and Genecology
AOR	Adjusted Odds ratio
ARR	Adjusted Risk ratio
BMI	Body Mass Index (kg/m^2)
BPD	Biparietal diameter
CI	Confidence interval
CRL	Crown Rump Length
CS	Caesarean Section
EDD	Estimated Due Date
ENAP	Every Newborn Action Plan
ERCS	Elective Repeated Caesarean Section
IOL	Induction of Labour
LMP	Last menstrual period
MAS	Meconium Aspiration Syndrome
MBR	Medical Birth Register
OR	Odds Ratio
RCT	Randomized Controlled Trial
RR	Risk Ratio
TOL	Trial of Labour
TOLAC	Trial of Labour after Caesarean section
UNICEF	United Nations Children´s Fund
VBAC	Vaginal Birth after Caesarean section
WHO	World Health Organization

Introduction

Definitions of term, late, and post-term pregnancy

This thesis is about women with singletons in cephalic presentation in term to post-term pregnancies. The focus is on gestational duration and the impact of parity and BMI on maternal and neonatal outcomes.

When a woman recognises that she is pregnant, the expected date of delivery or the due date (EDD) is of great interest both for personal planning and for medical reasons, as different stages in pregnancy have different challenges and risks. To estimate the due date of a pregnancy is more complex than adding 9 months from the first day of the last menstrual period (LMP). The German obstetrician Naegel (1778-1851) came up with the 'rule of Naegel' to define EDD. The rule subtracts three months from the first day of the LMP, then adds a year and seven days. This formula is only correct if a woman has an exact menstrual circle of 28 days (Lawson 2021). In the 1970's, when ultrasound was introduced, the EDD became more accurate for women regardless of different menstrual periods. In early gestation ultrasound dating is based on measurement of crown-rump-length (CRL), and from weeks 12-14 on biparietal diameter (BPD) if BPD = 21 to 55 mm, and on femur length (FL) if BPD is not possible (i.e., acrani) (H.P Robinson 1973, Campbell 1969, Selbing and Kjessler 1985, Sladkevicius et al., 2005, SFOG råd, 2019). When BPD >55mm no ultrasound EDD should be done, and the LMP still be used (SFOG råd, 2019).

Ultrasound dating based on BPD at 12-14 weeks is more accurate than dating based on CRL. Saltvedt et al. found that compared to IVF pregnancies with known conception, the algorithm recommended in Sweden (Selbing and Kjessler 1985) showed a mean difference of -0.4 days, with a standard deviation of 1.9 days (Saltvedt et al., 2004). Dating with the same algorithm at 15-20 weeks also showed a low mean difference (-0.2 days) compared to IVF dating, but the standard deviation was 3.25 days. Thus, the true gestational duration of a pregnancy dated to be 41+3 weeks may have a 95% probability to be between 40^{+6} and 42^{+0} if dating was done in week 12-14, and a 95% probability to be between 40^{+0} and 42^{+2} if dated in gestational week 15-20. Systematic bias of ultrasound-based gestational duration estimations has been reported due to foetal sex, intrauterine growth restriction and

maternal BMI (Källén 2002, Simic et al., 2010). In Sweden, over 97% of all pregnancies are dated by ultrasound.

In Sweden and from WHO (1976), the expected duration of median pregnancy is set to 280 days. With more accurate EDD by ultrasound the normal pregnancy duration is presumed to be longer; Tunon et al reports a median of 281 days; Saltved et al. reports a mean and median at slightly 282 days; and Kessler et al a median pregnancy duration of 283 days (Tunon et al., 1996, Saltved et al., 2004, Kessler 2019).

The definition of term pregnancy was specified by WHO in 1976 and defines a term pregnancy to be 37^{+0} to 41^{+6} (259 to 293 days). After 42^{+0} ($\geq$294 days) the pregnancy is defined as post-term (WHO 1976). In 2013 the ACOG practice bulletin contributed with definitions within the 'term pregnancy' period. Early term pregnancy from 37^{+0} to 38^{+6} (259 to 272 days); term from 39^{+0} to 40^{+6} (273 to 286 days); and late term from 41^{+0} to 41^{+6} (287 to 293 days) (ACOG 2013). This clarification was made because of observed difference of neonatal respiratory morbidity within the five-week period of term pregnancies.

Maternal risks in late and post term pregnancies

Pregnancies proceeding into late term or post term imply increased maternal risks such as labour dystocia, disproportion, perineal lacerations III and IV, emergency caesarean section, prolonged labour, postpartum bleeding, and puerperal infections (Olesen et al., 2003, Caughey et al., 2007, Linder 2017). In 2019, the National Board of health and welfare reported a Swedish post-term incidence of 6% (SOS 2019).

Neonatal risk in late and post term pregnancies

Adverse neonatal outcomes such as: asphyxia, umbilical cord complications, meconium aspiration syndrome (MAS), sepsis, shoulder dystocia, traumatic injuries, pneumonia, neonatal convulsions, and peripheral nerve damage increase gradually after 40 weeks of gestation (Olesen et al., 2003, Bruckner et al., 2008, Linder et al., 2017). It has been indicated that the risk of neonatal encephalopathy increases significantly in new-borns delivered in the late and post term period (Badawi et al., 1998).

Apgar score is an expression of the infant's physiological condition at one, five- and ten-minutes of age. The skin colour, heart rate, reflex irritability, muscle tone, and respiration is valued at a score of 0 to 10. If the Apgar score total at 5 minutes equals 7 or higher it is unlikely that peripartum hypoxia-ischemia caused neonatal encephalopathy (ACOG 2015). Children born post-term have, in follow-up studies of long-term effects, shown to be overrepresented with diagnoses such as

developmental delay, behavioural, emotional, and neuropsychiatric problems and were also more likely to have attention deficit hyperactivity disorder symptoms (Lindstrom et al., 2005, El Marroun et al., 2012).

Recommendation on late and post-term pregnancies

The latest review from the Cochrane systematic review on 'Induction of labour in term pregnancies' has the aim to summarise the benefits of induction at or beyond 37 full weeks compared to expectant management - spontaneous start indefinitely or until a later gestational age when a maternal or foetal indication for induction of labour arises - on pregnancy outcomes for the infant and the mother. The primary aim is to reduce stillbirth rates (Middleton et al. 2020). The meta-analyse concludes that for stillbirth or neonatal death during the first week of life there is a decreased risk of perinatal death with intervention, relative risk (RR)=0.31 (95%CI: 0.15-0.63), resulting in a number needed to treat of 544 to prevent one perinatal death. When analysing stillbirth per se, the relative risk from intervention (induction) decreased the risk RR=0.30 (95%CI: 0.12-0.75) compared to expectant managment. For caesarean section (CS) the evidence is moderate and the authors conclude that induction probably results in fewer CS, RR= 0.73 (95%CI: 0.85-0.95). Analysis on neonatal outcome showed that the risk of Apgar score <7 at five minutes was reduced in the induction group, RR=0.73 (95%CI: 0.56-0.96). In a subgroup analysis parity had no influence on the neonatal outcomes. Authors conclude that althoug the absolute risk rate for stillbirth is low, induction (compared to expectant management) reduced the risk from 4 to 0.3 per 1000 births (Middleton et al., 2020).

In Sweden, the Region of Stockholm changed their guideline for management of post-term pregnancies from induction at 43^{+0} to 42^{+0} weeks in 2005. The change resulted in a 48% reduction of perinatal deaths before 45 post-menstrual weeks, AOR=0.52 (95%CI: 0.31–0.83), of meconium aspiration with 51%, and for Apgar score $\leq$6 at five minutes with a 31% reduction. No change in operative deliveries was detected (Grünewald et al., 2010).

With the aim to investigate how to manage late term to post perm pregnancies, a Randomized Controlled Trial (RCT) - SWEPIS (Swedish Post-term Induction Study) - was started in May 2016. The intention was to include 10,038 pregnant women. The study was stopped for safety reasons when 2,760 were included. A significantly higher rate of perinatal death in the expectant management arm (six versus 0) was observed and thus the steering committee recommended an end to the study. The composite perinatal outcome did not vary between the groups; 2.4% in the induction group versus 2.2% in the expectant management group (Wennerholm et al., 2019). A meta-analysis on SWEPIS with two other RCTs (Gelisen et al., 2004, Keulen et al., 2019) was made by Alkmark et al., 2020. The conclusion of the meta-analysis was that compared with expectant management until 42 weeks, induction

of labour (IOL) at 41 weeks improves severe adverse perinatal outcome, RR=0.43 (95%CI: 0.21-0.91). The number needed to treat was 175 to reduce one severe adverse perinatal outcome. No difference in CS rate between IOL and expectant management was identified, RR=0.98 (95%CI: 0.83-1.16). Prespecified subgroup analyses on severe adverse perinatal outcomes showed decreased risk for nulliparous women in the IOL group, RR=0.2 (95%CI: 0.07-0.60). The authors conclude that the risk reduction remains uncertain, but that women overall should be informed of the parity specific risk to make an informed choice.

As an alternative to induction for 'women overall' the region of Stockholm made a retrospective follow-up on routine ultrasound examination at 41 completed weeks (on every pregnant woman), compared to a maternity unit with only indicated ultrasound examinations at 41^{+0}. The conclusion was that indicated ultrasound examination increases the risk for adverse neonatal outcome compared to routine examination at 41^{+0}, OR=1.48 (95%CI: 1.06-2.1) (Lindqvist et al., 2014). The Stockholm region reports low stillbirth rates, for women with a foetus alive at 41^{+0} the incidence was 0.15/1000 pregnancies between 2014-2018 (Åmark et al., 2021).

At present, Region Skåne recommends primiparous, and multiparous women with risk factors, an assessment at 41 weeks. The assessment includes a clinical evaluation, assessment of the foetal heart rate pattern, and ultrasound assessment of amniotic fluid volume. According to the present guidelines, women with normal findings are offered induction within three to six days. Parous women without risk factors are offered IOL at 42^{+0} weeks.

With altered management for 'women overall' in late and post-term pregnancies, the incidence of perinatal morbidity and neonatal morbidity is already improving. New, more sensitive approaches could be a way to decrease the incidence even further when compared to general guidelines.

Induction of labour

Methods for induction of labour

There are two ways to perform a labour induction; mechanically and pharmaceutically. The preferred method is decided by how ripe the cervix is when induction is started. The cervical status is described using the bishop score system, which utilises the cervical dilation, effacement, consistency, position, and station of foetal presenting part (Bishop 1964, Edwards et al 2000). If the score is lower than 5, the recommendation is pharmacological ripening of the cervix or mechanical induction by catheter insertion through the cervix (SFOG 2016). If the score is six or above in nulliparous and five or above in multiparous women, then amniotomy

(rupturing of the membranes) is the method of choice (ACOG 2009, G. NICE, 2008, SFOG 2016).

The mechanical method uses a transvaginal balloon catheter that is inserted through the cervix with the inflatable part just above the internal os. There are single and double balloons, and in the case of the double, the second balloon is placed caudal of the external os. The balloon(s) are inflated with 30–80 mL NaCl. The pharmaceutical induction uses low dose synthetic prostaglandin administered orally or vaginally. The prostaglandins used are orally misoprostol (Cytotec®, Angusta®), and vaginally dinoprostone (Minprostin®, Propress®).

To induce labour in women with a previous uterine scar (e.g., CS) the mechanical way using the balloon catheter is recommended (SFOG riktlinjer., 2016, de Vann et al., 2019). The balloon catheter is safer but not as effective as Misoprostol, and if Misoprostol still is used (not recommended), it demands careful monitoring (SFOG riktlinjer., 2016).

When inducing women who are obese no dose change is recommended for pharmacological IOL compared to the doses used for women who are of normal weight (SFOG riktlinjer., 2016). It has been indicated that women who are obese have altered parturition physiology described by changes in the placenta, cervix, amnion, and myometrium that could alter labour preparation, contraction, and endurance (Carlsson et a., 2015).

Induction guidelines in late and post-term pregnancies

In line with internationally changed guidelines for induction of labour (IOL) in the late term to post term period, the induction rate has increased. Guidelines from WHO recommends IOL at 41^{+0} (WHO 2018), UK, Canada and Denmark recommend delivery between 41^{+0} to 42^{+0}, and the United States between 41^{+0} to 42^{+6} (NICE 2008, SOGC 2017, DSOG 2011, ACOG 2014).

Sweden has had no national guideline on how to manage late to post term pregnancies. Currently, some regions offer all women induction in the first days from 41^{+0}, while other regions offer induction at 42^{+0} weeks. Some regions, such as Stockholm and Skåne, use an examination at 41^{+0} to identify possible indications for IOL. From the Medical Birth Register (MBR) it is evident that IOL in Sweden has increased at gestational durations of 39^{+0} to 42^{+0} (figure 1), but there are regional differences. The induction rate for nulliparous women with singletons in cephalic presentation after 37^{+0} weeks differed in 2019 from 13.5% to 25.6% between regions, with the largest differences in the management of pregnancies after 41^{+0} (SOS 2019). The national differences in induction rates can be noticed from two decades ago, with a trend of uniformity around active management from 41 completed gestational weeks (Lindegren et al., 2017). Figure 1 shows induction

rates for singletons in cephalic presentation derived from MBR. Data from Graviditetsregistret indicates that the induction rate has increased even further after our study period, (Figure 2), without increasing CS rates after 41^{+0}.

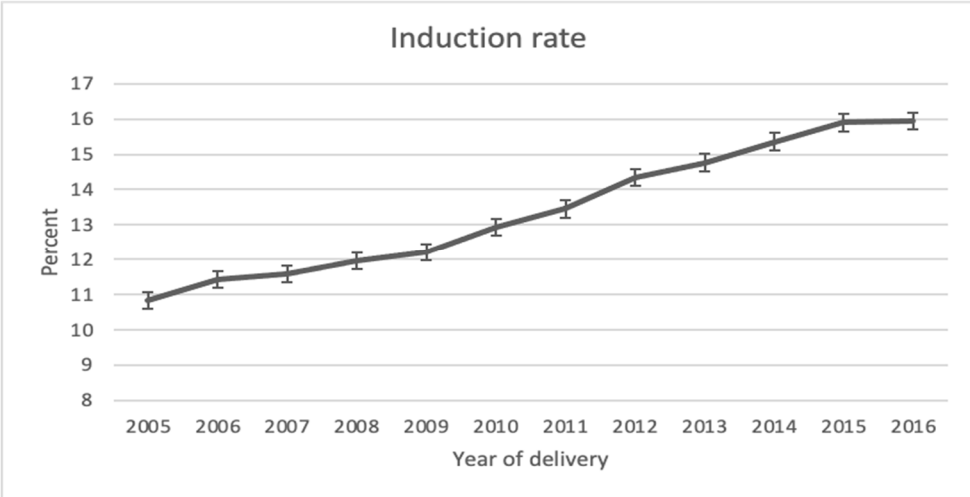


Figure 1: Induction rate for women with singletons in cephalic presentation from 39^{+0} to 41^{+6} between 2005-2016 (the time studied for this thesis). Bars showing confidence intervals (unpublished data from study 3, MBR 2005-2016).

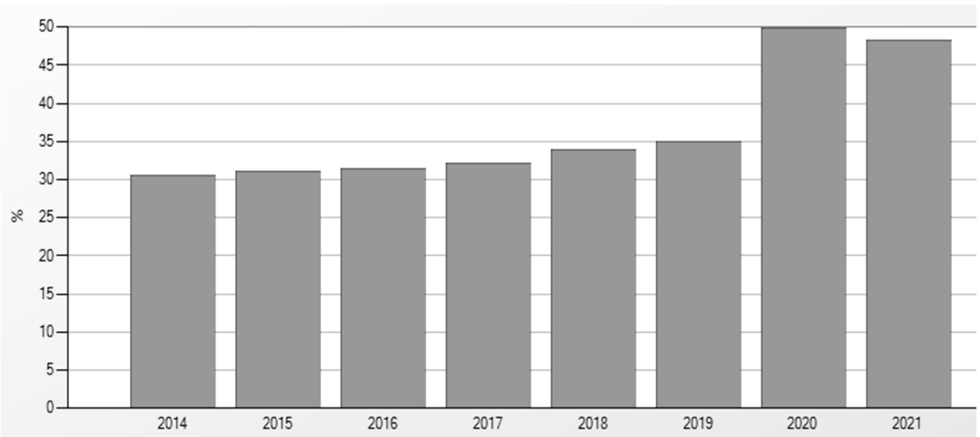


Figure 2: Annual induction rates in Sweden for pregnancies from 41 completed weeks or longer (Graviditetsregistret).

Potential maternal benefits and risks from induction

In the latest version of the Cochrane review (2020) on induction in term pregnancies induction seems to lower the incidence of CS, RR=0.9 (95%CI: 0.85-0.95) but not the incidence of operative vaginal birth RR= 1.03 (95%CI: 0.96-1.10). In the review, three individual studies identified significantly lowered CS rates (Hannah et al.,1992, Dyson et al., 1987, Grobman et al.2018). In a Norwegian RCT from 2007, there was no finding of increased CS rate with induction at 41^{+2} compared to expectant management (Heimstad et al., 2007).

Some observational studies have indicated increased risk of CS with IOL compared to expectant management in term pregnancies, Dublin et al. (2000) report an ARR= 1.77 (95%CI: 1.50-2.08) among nulliparous women but not for multiparous women. A Swedish cohort study showed a tripled risk of CS for nulliparous and doubled risk for multiparous women, OR 3.34 (95%CI: 2.77-4.04) and OR 1.94 (95%CI: 1.24-3.02) respectively (Thorsell et al., 2011). A retrospective study on multiparous low risk pregnancies also reported an increased risk for CS, OR=1.93 (95%CI: 1.63-2.29) (Jacquemyn et al., 2012). To conclude, CS is an operative procedure that has short and long-term complications and must be judged against the benefits from induction on neonatal outcome in late to post-term pregnancies.

Short-term complications

The most frequent maternal complication after birth is infection, and endometritis is overrepresented in women with planned or emergency CS (Burrow et al., 2004, Liu et al., 2010). CS increases the risk for postnatal venous thromboembolism by three to five times, and two thirds of life-threatening pulmonary embolisms are associated with CS (Bonnar et al., 1999, Lindqvist et al., 1999, Jacobsen et al., 2008, Galamboise et al., 2017). In a publication from the Netherlands, the risk for maternal death after CS (any gestational age) compared to vaginal birth was three times higher following exclusion of deaths that had no association with surgery (Kallianidis et al., 2017).

Despite these associations, thromboembolism, and especially maternal deaths are rare events, and CS is considered a safe procedure.

Long-term complications

The most important maternal long-term complication to CS is abnormal placentation including placenta previa and invasive placenta in subsequent pregnancies (Silver 2012). Previa is associated with increased risk for haemorrhage, blood transfusion, hysterectomy, sepsis, and thromboembolism (Crane et al., 2000, Silver 2015). For the diagnosis of placenta increta/percreta/accrete, an associated risk is reported for increased maternal morbidity due to large blood loss - the average blood loss has been reported to 2500-5000 ml, (Rosen et al., 2008, Eller et al., 2009, Bauer et al., 2009).

Rupture of the uterus in a subsequent pregnancy following a CS is a rare event, but nevertheless a factor to consider especially when IOL is considered for non-medical reasons. A retrospective analysis reported the risk for uterine rupture at spontaneously started Trial of Labour After Caesarean Section (TOLAC) compared to planned repeated CS to RR=3.3 (95%CI: 1.8-6.0), compared to induction without prostaglandins to RR=4.9 (95%CI: 2.4-9.7), and for induction with prostaglandin to RR=15.6 (95%CI: 8.1-30.0) (Lydon-Rochelle 2001). However, it is not clear whether the prostaglandin, or the presumably unfavourable cervix status present when prostaglandin is used, is the predictor of uterine rupture or the success of vaginal birth after caesarean section (VBAC) (Bujoild 2004, Kayani 2005, Landon et al., 2005). The Cochrane report on the subject concludes that both induction and repeated CS implies risk of harm for the pregnant woman, and that all results should be interpreted with caution when drawn from non-randomised trials (Dodd et al., 2017).

Reproductive complications such as a scar pregnancy are obviously linked with a previous CS. The number of scar pregnancies has increased with increasing CS rates and these women are at high risk of recurrence and for placenta accrete (Rosen 2008, Morlando et al., 2020).

Potential benefits

Elective induction of labour (IOL) at 39 weeks has, in low-risk populations resulted in lower CS rate, lower rates of maternal morbidity, fewer stillbirths and neonatal deaths, and lower rates of neonatal morbidity, compared to expectant management with IOL for medical or obstetric reasons, or at 41 weeks (Sinkey et al., 2018). A decrease in maternal hypertensive disorders has also been detected from elective IOL from 39 completed weeks (Gibson et al., 2016, Hersh et al., 2019., Migliorelli and Martinez., 2020). It has been indicated that obese women have a decreased risk of emergency CS after elective IOL in term pregnancies from 39 weeks, compared to expectant management, without increasing the risks of other adverse outcomes (Lee 2016, Palatnik and Kominiarek, 2020).

The risk for stress urinary incontinence, overactive bladder, and pelvic organ prolapse is reduced by CS when compared to after vaginal deliveries (Blomquist et al., 2018, Keag et al., 2018).

Potential neonatal benefits and risks from induction

When discussing induction in term pregnancy with the expectation to reduce the number of perinatal deaths, it is important to offer reassurance that it can be achieved without the negative impacts of being born too early (Blencowe et al., 2013, Natarajan and Shankaran., 2016, Williams and Pugh., 2018). There are studies providing information that gestational duration after 39^{+0} has no additional benefits

for the neonate. Instead, gestational duration around 39^{+0} to 40^{+0} is indicated to be the best time for neonates to be born and thus elective CS are recommended to take place around 39^{+0} weeks (Cheng et al., 2008, Clark et al., 2009, Green 2009, ACOG 2013, Rosenstein et al, 2013). Chen et al. (2017) showed higher risk of adverse composite neonatal outcome with delivery at 40^{+0} versus 39^{+0} weeks, ARR=1.18 (95%CI: 1.15-1.22). Heimstad et al. report no increased risk of Apgar score <7 at five minutes or umbilical cord pH <7 when comparing induction at 41^{+2} versus expectant management (Heimstad et al., 2007). Alkmark et al. (2020) report decreased neonatal risks with induction at 41^{+0} versus expectant management for Apgar score <7 at five minutes, RR= 0.65 (95%CI: 0.43-1.00), for admittance to neonatal care unit for four days or longer, RR=0.53 (95%CI: 0.32-0.85), and for children born with macrosomia (weight >4500g) RR=0.59 (95%CI: 0.46-0.76).

A low rate of adverse neonatal outcome is used as a measure of good obstetric management. The challenge for inductions in term pregnancies is to predict an optimal timing for induction which may be altered due to individual maternal characteristics and optimising allocations of resources (Alavifoud 2019, Middleton et al., 2020).

To my knowledge, no studies have evaluated the risk of poor neonatal outcome stratified by maternal parity and BMI. It has been reported that infants of primiparous women are at increased risk of poor neonatal outcome compared to infants of multiparous women (Ingmarsson and Kallén., 1997, Hilder et al., 2007).

Stillbirth, perinatal and neonatal death

With approximately 5 million perinatal deaths, stillbirth and neonatal death occurring globally each year this is an important 'issue on the international public health agenda' (Blencowe et al., 2016, Liu et al., 2015, WHO/UNICEF 2014). The World Health Organization (WHO) and UNICEF has an 'Every Newborn Action Plan (ENAP)' with the goal to decrease preventable stillbirths and neonatal deaths and to reduce the stillbirth rates to 12 or less per 1000 births by 2030 (WHO/UNICEF, 2014). In countries with frequent stillbirth the perinatal deaths are poorly recorded and therefore the ICD - perinatal mortality (ICD-PM) - was constructed for identifying the time of and classifying the cause of the death. Stillbirth is defined as dead before contractions started, perinatal death antepartum, intrapartum, or neonatal death within 7 days after birth, and neonatal as death within 28 days from birth (WHO – ICD PM, 2016). The Lancet series 'preventing stillbirth' states that by identifying substandard care a reduction of stillbirth by 20-30% is possible (Flenady et al., 2016).

Stillbirth can occur at any gestational length and WHO uses the definition of intrauterine death for pregnancies $\geq 28^{+0}$ weeks. In Sweden, the definition of

intrauterine death was changed in 2008 to pregnancies $\geq 22^{+0}$ weeks. The stillbirth rate, independent of pregnancy duration, was 3.6 of 1000 pregnancies in 2016 (SOS, 2018).

Stillbirth rates in high income countries have remained relatively constant during the recent decades (The European Health Report 2015, Flenady et al., 2011). WHO states that in 2019, 128 high income countries reached the goal of less than 1.2 stillbirth per 1000 deliveries (WHO-stillbirth). From the MBR, used in our studies, we present a figure of the stillbirth rates during 2005 to 2016 at gestational duration of 39^{+0} to 42^{+0} weeks (figure 3). The incidence is near the WHO goal of 1.2 or less per 1000 births and has, as mentioned above, remained relatively constant.

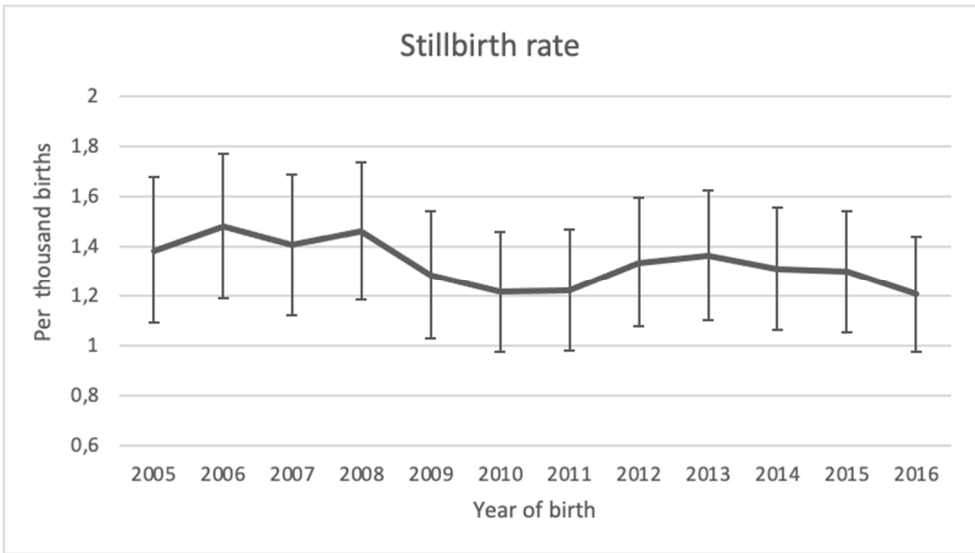


Figure 3: The incidence of stillbirth in singletons with cephalic presentation from 39^{+0} to 41^{+6}, 2005-2016. Bars indicating confidence intervals (unpublished data from study 3, MBR 2005-2016).

Advancing gestational duration and especially the post term period are known, and well-studied, risk factors for stillbirth (Olesen et al., 2003, Nakling et al., 2004, Heimstad et al., 2008, Muglu et al., 2019). A Swedish randomized trial and a Danish retrospective study report increased risk for stillbirth in pregnancies in the late term period (Wennerholm et al., 2019, Lidegaard et al., 2020). The Danish study report a strong relationship from increasing gestational duration and an increasing cumulated risk of intrauterine foetal death from 0.16 to 1.25 per 1000 ongoing pregnancies between 41^{+0} - 41^{+6} (Lidegaard et al., 2020). The stillbirth rate in 2011/12 versus 2017/18 was in the Danish study 0.38 and 0.74 per 1000 pregnancies respectively with the induction rate of 44% in 2011/12 and 39% 2017/18 (Lidegaard et al., 2020). In the region of Stockholm, an incidence of stillbirth of 0.5/1000

pregnancies from 41^{+0} gestational weeks during 2014-2018 was reported (Åmark et al., 2021). An American study reported improved overall mortality risk with induction from 39 gestational weeks compared to expectant management for each additional week (Rosenstein et al., 2012). Other considered risk factors for stillbirth in term pregnancies are primiparity, country of birth (low-income countries), low level of education, overweight/obesity, smoking, and advanced maternal age (Olesen et al., 2003, Kristensen et al., 2005, Flenady et al., 2011, Tennant et al., 2011 Page et al., 2013, Aune et al., 2014, Waldenstrom et al., 2015, Jacob et al, 2016).

A key risk factor for stillbirth independent of gestational duration is foetal growth restrictions, due to placenta dysfunction (Divon et al, 1998, Flenady et al., 2011). A Swedish study indicated that the most frequent cause for stillbirth after 41^{+0} was foetal infection (Åmark et al., 2021).

Parity

A woman who is pregnant for her first time is considered primipara (or nullipara) whereas a woman who has had a delivery, vaginal or by CS, is defined multipara. In 1997, Ingmarsson and Kallén, reported increased risk for neonates of primiparous women for stillbirth and an increased association between neonatal death and post-term pregnancies for primiparous, but not for multiparous women. Multiparous women with a prior CS are a disadvantaged group, especially when labour induction is needed as the methods of choice are fewer (deVann et al., 2019). A factor connecting primiparous and multiparous women is that after a CS the cervix has not been fully dilated as during a vaginal birth, hence the expression 'vaginal nullipara'.

In term pregnancies, a significant interaction between primiparity and gestational duration in relation to stillbirth and perinatal death has been reported (Ingmarsson and Kallén., 1997, Hilder et al., 2007, Lindegren et al., 2017). From the conclusion in the latest Cochrane review on subgroup analyses there are no apparent differences from timing of induction in term pregnancies by parity (Middleton 2020). In a meta-analysis by Alkamark (2020) the improved perinatal outcome was indicated only for nulliparous women.

The group of multiparous women contains great differences due to their 'birth history' from the first delivery. The second labour success rate for vaginal delivery was 94% if the first birth was vaginal and 50% if the first birth CS (Carlsson Wallin et al, 2010). A previous CS is not *per se* an indication for elective repeated caesarean section (ERCS). Among multiparous women with one previous CS, 70% had an ERCS and 30% had a trial of labour (TOL) (Fagerberg et al., 2012). In attempts to predict the possibility of a vaginal birth after caesarean section (VBAC), information from first CS increases the accuracy of the model (Grobman et al., 2007,

Fagerberg et al., 2015, Lakra et al., 2020). To minimise adverse maternal and neonatal outcomes after a first delivery CS, TOL followed by emergency CS should be avoided. This indicates the importance of individualized decisions of planned management, TOL or ERCS, for this group (Dinsmoor et al., 2004, Grobman et al., 2009, Guis et al., 2010, Landon et al, 2005, ACOG 2019).

Body Mass Index

WHO concludes that more people die from obesity than from starvation and concludes that the world stands ahead of a new obesity pandemic. With a trend of decreasing numbers of smoking among pregnant women, the quantity of pregnant women who are overweight or obese increases (EuroPeristat 2015).

Obese pregnant women should be considered a high-risk population, with IOL as the start for increased risk of complications intra and post-partum (Kira et al., 2005). Obesity has been identified as a risk factor for longer gestation duration, post term pregnancies, decreased likelihood for spontaneous onset of labour at term, and increased likelihood of complications (Denison et al., 2008, Heslehurst et al., 2017). Other studies on elective IOL for obese or severely obese pregnant women from 39 completed gestational weeks versus expectant management show reduced CS risk (Glazer et al., 2020, Palatnik and Kominiarek, 2020) and even an improvement on neonatal morbidity (Gibbs et al., 2018).

The increased prevalence of obesity is seen among pregnant women in Sweden (figure 4). From the MBR, the rate of obese women increases in gestational duration of $\geq 39^{+0}$ from 11.0% to 13.6% between 2005 and 2016.

Figure 4: The incidence of pregnant women with BMI ≥30kg/m^2 in pregnancies 39^{+0}-41^{+6}. Bars indication confidence intervals (unpublished data from study 3, MBR 2005-2016).

During pregnancy, an overweight or obese women have an increased risk of hypertensive disorders, gestational diabetes, and CS (Denison et al., 2013, Knight-Agarwal et al., 2016). Obesity was associated with nearly 25% of the stillbirths that occurred in a study of term pregnancy (37 to 42 weeks' gestation) (Yao et al., 2014).

Neonates of women with morbid obesity (BMI>40) were at increased risk for adverse neonatal outcomes independent of mode of delivery (Blomberg 2013). A meta-analysis on the subject concludes that BMI is a risk factor for adverse neonatal outcomes which needs to be considered in weight management guidelines for pregestational counselling (Aune et al 2014).

Aims

As mentioned above there are both pros and cons to consider with induction. There are ongoing discussions on induction of labour in term and late term pregnancies and on how to make the recommendations more sensitive to individual risk factors. Today, there are a lack of analyses of gestational duration combining parity and BMI as potential risk factors in term pregnancies.

The purpose of this thesis is to investigate the impact of gestational duration in relation to parity and BMI on pregnancies from 39^{+0} to 42^{+2}, and thereby contribute to decrease adverse maternal and neonatal outcomes.

The specific aims of the individual studies:

I. To assess the obstetric management in prolonged pregnancies at each maternity unit level in Sweden, by comparing maternal and foetal outcome depending on the timing of delivery in prolonged pregnancies among primiparous and multiparous women separately.

II. The association between induction and neonatal and maternal outcome among two-parous women in uncomplicated pregnancies ≥ 41+3, was studied, stratified by first labour mode of delivery and conditions present. Second aim, to explore if the information regarding conditions present at the first delivery could be used to estimate the chance of a second delivery induction resulting in a vaginal delivery of a healthy child.

III. To study the impact of advancing gestational age beyond 39+0 weeks and the impact from body mass index (BMI) and parity on the mortality rate measured as all deaths (foetal or neonatal) before 45 post-menstrual weeks (primary aim) or measured as stillbirth rates (secondary aim).

IV. To investigate the combined association of BMI and advancing gestational duration on neonatal outcome among children to nulliparous women in singleton pregnancies ≥39+0 weeks.

Material and Methods

Epidemiological studies

Epidemiology is the research for knowledge of the spread of diseases or risk of adverse events in a population due to lifestyle or increased exposure of environmental or genetical factors. An epidemiological survey can be observational, cross-sectional, cohort and case-control (Björk 2015). When performing epidemiologically studies the risk of systematic bias are higher than in experimentally studies as the group investigated has raised naturally. Systematic biases can be categorized in three; selection bias - the sample is distorted and therefore not representative, information bias - inaccuracies in data collection, and confounding bias - lack of comparability in the groups examined (Delagadoo-Rodrigues & Llorca 2004).

In a cohort analysis, the prevalence of cases is measured over time and compared between two groups (cohorts). In large register studies, case control studies are made by arranging the cohorts from individual factors.

When register data is split into different groups these are named 'strata' and for every stratum power measure can be calculated. Strata are for example made to visualize the incidence and incidence rate by exposure (e.g., BMI class or gestational duration).

Data source

'The results of a study can never be better than the data on which it is based'

The four studies in this thesis uses the same data source, the Medical Birth Register (MBR). The MBR is managed by the Swedish national board of health and welfare. The register contains information from almost all Swedish pregnancies and deliveries since the start in 1973. Delivery units in Sweden are by law obligated to report data to the MBR. All women in Sweden are offered free care, antenatally, during delivery, and paediatrically. Standardized record forms from antenatal units' report on maternal number of pregnancies, smoking habits, previous delivery/ies, gestational duration at delivery, mode of delivery, and use of anaesthesia.

Furthermore, the record forms report on neonatal diagnosis, neonatal gender, weight, head circumference and on Apgar score (registered according to International Classification of Disease (ICD)), (Region Skåne, basprogram BMC). Sweden has 90 000 to 120 000 deliveries every year and 97 - 99% is covered by the MBR (Cnattingius 1990, SOS Statistics*).* After 2008, maternity units report data electronically directly from the patients´ medical records. Data on BMI and smoking registered at a first trimester maternity visit are included in the register since 1983.

The quality of a register can be measured by the probability of recorded diagnosis in cases (sensitivity of the outcome), of the probability that exposed individuals are classified as exposed (sensitivity of exposure), by the probability that references not are falsely diagnosed (specificity of the outcome), and by the probability that not exposed individuals being diagnosed as non-exposed (specificity of exposure). When the exposure information is gathered prospectively, i.e., BMI in first trimester and parity, the putative miscalculation could be expected not to vary with exposure – non-differential misclassification. Non-differential miscalculations will always bias the estimate towards the unity (Gullen et al., 1968). As the MBR obtains reliable estimates on specificity and sensitivity, both for the outcome and for the exposure, adjusted OR (or RR) for specificity and sensitivity can be calculated without the risk of inclusion bias in the register (Copeland et al., 1977).

Invalid and missing data is a problem in register studies. If the lack of information is random, the impact on risk estimates is usually low but the estimate of prevalence will be affected. Källén (2003) made a quality report on the MBR. The author found that data reported on gestational duration is reasonable reliable and that stillbirth is annually underestimated by 1-2%, with the majority in preterm births (Källen, 2003). The start of digital transmission after 2008 has further improved reliability in reported data. In studies with information gathered prospectively, as maternal smoking or first trimester BMI, the data is not biased by the outcome of the pregnancy.

The MBR, is a high-quality register on nationwide gathered data with possibilities to detect risk factors even if moderate or rare. But when the outcome is a rare event, as stillbirth or maternal mortality, a large study sample is needed to detect such risk factors.

Statistical methods

Hypotheses testing, p-values, and confidence intervals

Karl Popper, the philosopher, describes science as a process of disproving hypotheses. Each time a hypothesis has fail to be rejected the stronger evidence that the events studied are correlated (Kirkwood and Stern, 2003). Statistical methods formalize this idea by looking for evidence against a very specific form of hypothesis, the null hypothesis.

Testing hypotheses

- *H0 - Null hypothesis:* The null hypothesis is that there are no differences between groups or no associations between variables.
- *P – value*: P-value (or significance level) is used to consider whether a finding could be by chance. Or the strength of the evidence that is required to reject the null hypothesis of no difference between the outcomes studied. The greater the strength of evidence required (smaller the p-value), the larger sample size needed. A predefined level of significance is decided, usually $p<0.05$ and if reached the null hypothesis can be rejected.
- *Power analyses:* A sample size calculation is performed to justify the proposed study size and demonstrating that the study can answer the question posed. The size of the increased risk that it is desired to demonstrate needs to be states as a larger study group is needed if the increased risk is small. The study power is often, and in our studies set to 80%. Interpreted as 80% probability to reject the H0 hypothesis given that the H0 is truly false.

Type of outcome measures for a variable

The raw data of an investigation consist of observations made on individuals. The number of individuals is called the sample size and any aspect of the individual studied is called a variable. The main division for classification is between numerical (quantitative) and categorical (qualitative) variables.

- *Numerical or quantitative variable:* A numerical variable that is either continuous or discrete. A continuous numerical variable is a measure on a continuous scale. A discrete variable can only take a limited numbers of discreet values, usually hole numbers. Analyses performed for numerical variables are mean, median, and standard deviation.
- *Categorial or qualitative variable:* If the categorial variable only has two possible values (e.g., dead, or alive) it is a binary (dichotomous) variable.

Some non-numerical categories can be considered to have a natural ordering and are then distinguished as ordered categorical or ordinal (e.g., educational level, years, ≤9, 10-12, 13-14 and ≥15). Ordinal variables can be used as continuous variables in statistical models if regression analysis indicate that this is appropriate. For categorical variables which are not ordinal, or if a linear model does not seem appropriate, the class variables can be 'dummy coded' before entering the analyses. Analyses for binary variables uses the proportion of individuals who experience the event of interest and is then used to estimate the probability or the risk.

- *Prevalence*: the presence of a certain condition in a population.
- *Incidence*: the proportion of events in a certain population.
- *Risk:* the number of cases divided by the total population.

In our studies because of the use of one measure point, the definitions for prevalence, incidence and risk will be the same.

- *Odds:* the number of cases divided by the number of non-cases. Odds can be used in case-control studies and if the outcome measure is rare, it will approach the outcome variable 'risk'.
- *Confidence interval (CI):* 95% confidence interval is the range within which the investigated parameter is likely to be with 95% certainty.

Methods to describe data

In our studies we have used descriptive analyses to describe demographic data and maternal and foetal characteristics. We used proportions of data by groups or classes (strata), (e.g., women who are overweight or obese). The strata are compared with Chi2 -test, used to get p-values that summarizes the evidence of different proportions along investigated variables across study groups. Normal approximation is used to calculate the binominal distribution for the statistical uncertainty of the incidence with CI 95%, using number of events (x), probability of success (p) and standard error (SE).

Normal approximation

If p=x/n where x=number of events and n=total population and

Then, the Standard Error (SE(p)) =$\sqrt{p * (1-p)/n}$

And the 95% Confidence interval can be calculated: p+/- 1.96*SE(p)

A normal approximation is appropriate when n*p*(1-p)>10.

Methods to compare risks or odds between exposure groups

Tabel 1. Four field table for explanation of statistical calculations.

	Exposed	**Non-exposed**	**Total**
Cases	*a*	*b*	(a+b)
Non-cases	*c*	*d*	(c+d)
Total	(a+c)	(b+d)	

Risk ratio -RR, relative (the probability) risk – used in STUDY II, III, and IV.

$$RR = \frac{\mathrm{a}/(\mathrm{a}+\mathrm{c})}{\mathrm{b}/(\mathrm{b}+\mathrm{d})}$$

Odds Ratio-OR: comperes two variables exposure and risk of disease - used in STUDY I.

$$OR = \frac{\mathrm{a}/\mathrm{b}}{\mathrm{c}/\mathrm{d}} = \frac{a/c}{b/d}$$

In cases of rare events (a+c)≈c and (b+d)≈ d, thus RR≈OR.

For RR both OR:

- =1 no differences between the study groups are detected
- <1 the outcome studied is less probable in the exposed than in the non-exposed group.
- >1 the outcome studied is more probable in the exposed than in the non-exposed group.

Confidence interval for RRs and OR's:

When a p-value answers the question of how compatible the results are with the null-hypothesis, the OR's (or RR´s respectively) together with CI gives information about the uncertainty of the estimate showing a range in which 95% of the values of the studied parameter would be with 95% certainty. The width of CI is a measure of the precision of the obtained result.

A *confounder* is a variable that is associated with the exposure as well as with the outcome variable studied. The confounder must not be directly caused by the exposure in question. If so, it is considered a modifier instead. Confounders are normally controlled for using different types of regression models. For binary outcomes, the most common statistical methods to control for confounders are multiple logistic regression, or modified Poisson regression models.

Logistic regression-, and Poisson regression model:

- Logistic regressions models are used to estimate odds ratios and risk ratios when the outcome variable is binary - as often in case-control studies.
- Poisson regression analyses are also used for binary outcome variables and for discrete outcome variables such as incidence and mortality rates in cohort analyses (McNamee 2005).

When investigating interactions in regression models, a heterogenicity test can be used to identify the interaction or effect modification on the regression line.

Number Needed to Treat

Number Needed to Treat (NNT) is a measure of the impact of the number of patients who must be treated to prevent one adverse outcome that is caused by the exposure/intervention.

$$NNT = \frac{1}{\text{risk difference}}$$

Number Needed to Harm (NNH) is the measure of a harmful treatment used when the impact of a treatment has known adverse side effects. The NNH=1-NNT.

Outcome measures

- *Apgar score <7 at five minutes*: As described in the introduction Apgar at five minutes is, even with the possible error from being an assessed value of individual judgment, considered a valid parameter for wellbeing of the neonate. Apgar <7 at five minutes is commonly used and has the advantage that it can be compared with results on Apgar score <7 at five minutes in other studies.
- *Caesarean section:* A CS was considered elective if performed before attempt of vaginal labour and as emergency whenever following Trial of Labour (TOL).
- *Forceps/vacuum extraction:* identified by checkbox in the data source.
- *Induction:* All cases with a checkbox for induction in the data source.
- *Meconium aspiration*: when the amniotic fluid is stained by meconium and the neonate has inhaled it, diagnosed by neonatal checkbox in the register.
- *Stillbirth*: Intrauterine death, dead before start of delivery or death during labour.

- *Neonatal death:* Born alive, death within 28 days.
- *Perinatal death*; intrauterine, intrapartum, or postpartum death within 7 days.
- *Stillbirth or neonatal death before 45 post-menstrual weeks*: The outcome measure includes all deaths (stillbirths or neonatal deaths) occurring before 45 (ultrasound adjusted) post-menstrual weeks. This outcome was defined with the aim that all children would be 'at risk' for an equal period, avoiding systematic bias since when a child is born, it is out of risk of stillbirth. For example: if we compare stillbirth rate among children born at 39 weeks with those born at 41 weeks, the child born at 41 weeks would be 'at risk' for a longer period. By extending the time of observation until 45 post-menstrual weeks for both children, we avoid this source of bias. Following the children to 45 postmenstrual weeks (and not shorter) ensures that all children has at least 14 days of follow up after a delivery where the child survives but has a poor outcome.

Study specific material and methods

Singletons in cephalic presentations were included in all four studies. Excluded were singleton in breech and multiple pregnancies because of higher risks for CS, maternal complications, and adverse neonatal outcome (Ghai, 1988, Kiely, 1990, Behran et al., 2016, Dobhit et al., 2017, Macharey et al., 2017, Swanson et al., 2017**)** and thus would bias the material. In the studies, adjustments were made for year of delivery (continues linear), BMI (continues), and smoking (semi-continuous: 1= no smoke, 2= smoking <10 cigarettes/day and 3 = smoking ≥10 cigarettes/day). In study I we also adjusted for hospital level (I – local, II – regional and III - university) and maternal age (continuous and entered as class variables- 5-year classes, respectively). In stud III and IV, additional adjustments were made for country of birth (classes: 1 = Nordic countries, 2 = Europe/USA/Canada/Australia/New Zealand, 3 = other), and for highest achieved educational level (ordinal: 9 years, 10-12, 13-14, ≥15). Missing data was imputed with the overall mean, except in study IV where women with unknown BMI were excluded. The data on BMI used in our studies are first trimester BMI registered at the first antenatal visit. The index pregnancy in study nr II is birth number two.

In 1998, the version ICD-10 was introduced in the region Skåne and in 1997 in the rest of Sweden (ICD-10). That is the reason to why the first delivery in study II had to be 1999 or later, exceptional birth from 1998 can be in the material.

In study I and II, pregnancies $\geq 41^{+3}$ weeks are definition as prolonged pregnancies. The reason for choosing 41 weeks and three days as the time of entry was that no

pregnant women with any pregnancy complications would have been allowed to proceed this far, leaving only assumed healthy pregnancies in the study sample. No healthy pregnancy would have been in question of induction because of gestational age unless it was the routine management at the individual maternity unit or region. For the time studied recommended management of post-term pregnancies was an examination at 42^{+0} and if everything normal induction at latest at 42^{+6}. The discussion back then was to move the induction point forward towards 42 completed weeks. As our studies are retrospective, they will reflect the management routine at the time studied.

Statistics were calculated using SPSS in study II, III and IV and in study I Gauss (GaussTM, Aptech Systems Inc. Maple Valley USA).

Study I

Pseudorandomised retrospective register study

Study period 2001-2013

Study population N = 199 770

Included were women with singletons in cephalic presentation with pregnancies $\geq 41^{+3}$– 42^{+6} delivering at a maternity unit with more than 500 deliveries per year.

No exclusions due to maternal diagnosis were made as this would bias the results.

For every maternity unit, with more than 500 deliveries per year, an active management rate of pregnancies lasting $>42^{+3}$ weeks among all becoming 41^{+3} was computed. The maternity unit rates were sorted in tertials, the units with the lowest ratio of pregnancies becoming 42^{+3} (<12.6%) were defined as units with more active management and correspondingly units with the highest ratio of 42^{+3} among all 41^{+3} pregnancies (>17.6%) as the least active management (most expectant) units. The study period was divided in to three time periods, tertials, to identify shifts regarding activity during the study period. Analyses on OR were obtained from analyses of the least against the more active management unit. Maternal outcomes were vaginal, elective CS, emergency CS, and forceps/vacuum extraction. Neonatal outcomes were perinatal death, meconium aspiration, Apgar score <7 at five minutes and finally a composite of the three outcomes.

OR and AOR for primiparous and multiparous women, respectively, on the start of delivery, neonatal outcomes and 'neonatal outcome as a composite' were calculated using simple and multiple logistic regression analysis. Information on adjustments and missing data as described in general information. Model adequacy was tested using the Hosmer-Lemeshow procedure to assess the goodness of fit.

Study II

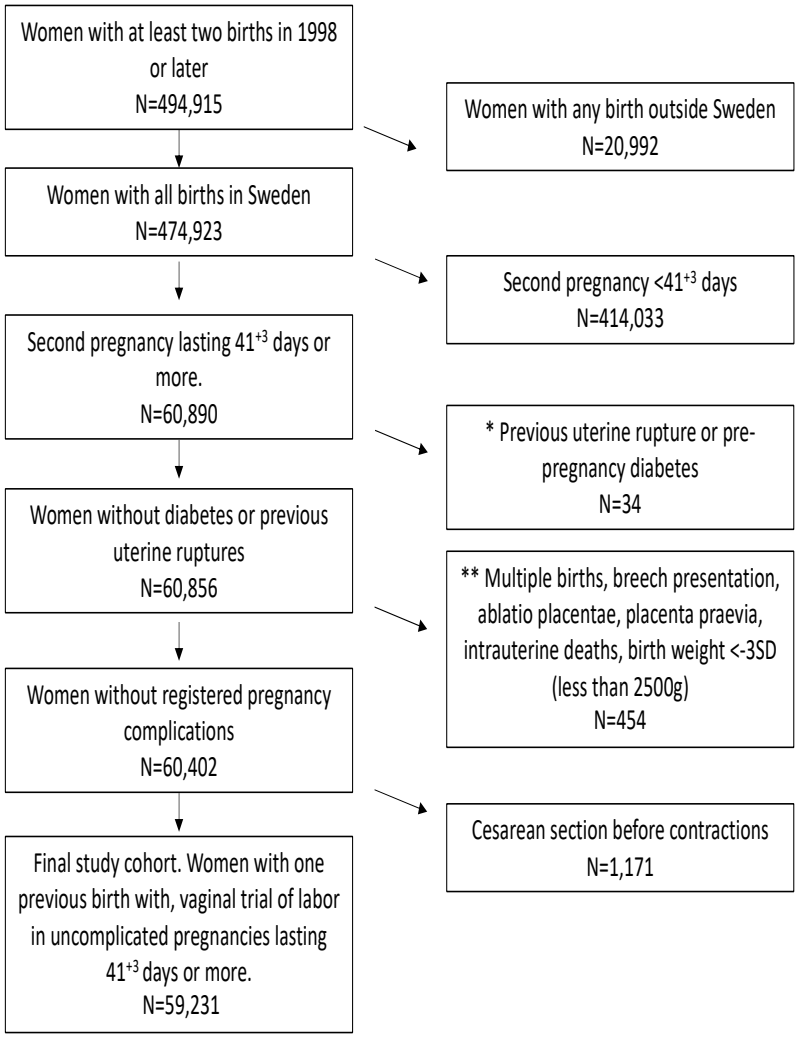
Retrospective study

Study period 1998-2014

Study population, figure 5

Included were second parous women with a singleton in cephalic presentation at gestational duration $\geq 41^{+3}$- 42^{+6}. Maternal exclusion criteria for second birth (index) were pregestational diabetes, gestational diabetes, gestational hypertension, pre-eclampsia or eclampsia, placenta previa, ablatio placenta, intrauterine death, multiple birth, other presentations than cephalic or severe growth restriction. First delivery conditions were grouped by start of delivery (spontaneous, elective CS or induction), mode of delivery (elective CS, emergency CS or vaginal) and if appropriate by indication for first labour CS, (pre-eclampsia, multiple birth, non-cephalic presentation, placenta previa, pre-term birth, small for gestational length, polyhydramnios, large for gestational age, post-term, failed induction, dystocia, foetal asphyxia, and none of these indications). Main outcomes considered were mode of delivery (second labour) vaginal or emergency CS and neonatal outcome measured one by one and as a composite of Apgar score <7 at five minutes, meconium aspiration and neonatal death.

RRs were obtained using modified Poisson regression. Adjustments and missing data handled as described in general information and valid for the index (second) delivery. Homogeneity test of the RRs across first delivery start and delivery mode were based on weighted sums of the squared deviation of the stratum specific log-RRs from their weighted means.



Figur 5: Flowchart on the study II population:

Study III

Retrospective cohort study

Study period 2005-2016

Study population N= 892 339

Included were singletons in cephalic presentation from gestational week 39^{+0} to 42^{+2}. Cohorts of nulliparous and multiparous, respectively and from BMI classes, BMI <25, 25-29.9, and ≥30 were established.

Primary outcome measure was 'stillbirth or neonatal death before 45 post-menstrual weeks' as described in 'outcome measures', secondary outcome was stillbirth. For the primary outcome gestational duration was classified as 39^{+0}-40^{+2}, 40^{+3}-40^{+6}, 41^{+0}-41^{+2} and 41^{+3}-42^{+2}. The classification is set narrower around 41^{+0} as this is the gestational length of interested with new international recommendation for late term pregnancies. For the stillbirth analyses, gestational duration was divided into 3- and 4 days intervals (39^{+0}-39^{+2}, 39^{+3}-39^{+6}, 40^{+0}-40^{+2}, 40^{+3}-40^{+6}, 41^{+0}-41^{+2}, 41^{+3}-41^{+6} and 42^{+0}-42^{+2}). Primiparous was defined as no previous birth, multiparous as at least one previous birth before the study. Adjustment was made as described in general methods above.

For parity and BMI strata specific RR in relation to gestational duration class were calculated using modified Poisson regression analyses. To estimate the rate of stillbirth for each certain gestational duration class, the number of stillbirths occurring during that certain period was divided by the total number of still ongoing pregnancies. The number of ongoing pregnancies at a certain gestational age class was calculated from the sum of all births occurring at a more advanced duration class, plus half of the births occurring during the certain period.

Study IV

Retrospective study

Study period 2005-2017

Study population N=352 567

Included were nulliparous women with singletons in cephalic presentation born from 39^{+0} to 41^{+6}.

BMI-class were constructed as BMI <25, 25-29.9, and ≥30, pregnancies with unknown BMI were excluded. In the demographic table BMI ≥35 is presented, but for statistical calculations this BMI class is combined with BMI 30-34.9 as the subgroup was too small for valid calculations. Gestational duration was classified as: 39^{+0}-39^{+2}, 39^{+3}-39^{+6}, 40^{+0}-40^{+2}, 40^{+3}-40^{+6}, 41^{+0}-41^{+6}.

The primary outcome measure was neonatal morbidity defined as stillbirth or perinatal death before 45 post-menstrual weeks (ultrasound adjusted). The secondary outcome measure was Apgar score <7 at five minutes.

To compare descriptive data Chi2 test was used. Modified Poisson regression analyses were used to obtain coefficients used to visualize the association between gestational duration for Apgar score <7 at 5 minutes, and stillbirth or death <45 post-menstrual weeks, respectively, by maternal BMI classes. For Apgar <7 a linear model was used, while for the mortality estimates, a third-degree polynomial model was fitted. The construction of 'baseline incidence' for Apgar <7 at five minutes, and for stillbirth or neonatal death before 45 post-menstrual weeks, were made from calculating the incidence for women over all at 41^{+0} (in the study population*).* The baseline incidence illustrates the impact from BMI-classes in addition to increasing gestational duration in pregnancies 39^{+0}-41^{+6}.

Ethical approval

Paper I, II, III and IV was approved at the Research Ethics committee at Lund University (2015/ 397, 2015-06-25). The committee saw no ethical problems with the studies being carried out. With the size of the register and that data has been deidentified the risk of individual recognition is very low.

Results

General results

During the time studied the management of post-term pregnancies has shifted towards earlier and more active management. The management has differed in-between regions because of a lack of national guidelines. These regional differences gave us the possibility to perform the studies included in this thesis.

In study I and II the impact of parity on gestational duration of 41^{+3} and after is studied from its effects on maternal and neonatal outcome.

Study I showed that infants of primiparous, but not multiparous, women delivered at units with the most expectant management of pregnancies $\geq 41^{+3}$, compared to women delivered at units with more active management, were at higher risk for Apgar scores <7 at 5 minutes and meconium aspiration. The risk for any adverse neonatal outcome was approximately 30% higher among primiparous women giving birth at the expectant delivery unit versus giving birth at delivery unit with more active management. For primiparous women, the elevated activity level among units in the more active management group corresponds to a Number Needed to Treat of 180 to prevent one case of 'poor neonatal outcome' (composite outcome: Apgar score <7 at 5 minutes, or meconium aspiration, or perinatal death).

For multiparous women, at the same gestational duration no improvement from active management on either Apgar score, meconium aspiration or perinatal death could be identified. Instead, an increased CS risk resulted in a Number Needed to Harm (NNH) = 76. Interpreted as one of 76 women handled at a more active maternity unit will have an emergency CS without any detectable benefit for the child.

In study II, the index pregnancy was delivery number two and singletons in cephalic presentation were included. The study was undertaken to investigate if any sub-group of multiparous women could be identified that would gain from active management in pregnancies $\geq 41^{+3}$. The results showed that infants of women who were induced were at higher risk of poor neonatal outcome than were infants of women with spontaneous start of labour. But no increased risk for poor neonatal outcome after induction at 41^{+3}-41^{+6} compared to, regardless of start of labour, at $\geq 42^{+0}$ weeks was detected.

The results indicate a huge variation of vaginal success rate after second delivery induction, depending on first labour delivery mode, and the indication for CS when applicable. For women attempting a second labour with a prior CS the maternal risk for an emergency CS is 52% after induction and 38% after spontaneous start.

In study III, women with a known first trimester BMI and gestational duration from 39^{+0} to 42^{+2} were included. The results showed that children to primiparous women born at $\geq 41^{+3}$ were at significantly increased risk of stillbirth or neonatal death before 45 post-menstrual weeks compare to children born at 39^{+0}-40^{+2}. Overweight and obesity further amplified the risk increase. Among children of multiparous women, no increased risk of mortality with increasing gestational duration after 40^{+2} was detected.

The risk for stillbirth (secondary outcome) in pregnancies 39^{+0} and beyond was more than doubled among primiparous compared to multiparous women.

In study IV, the absolute risk for a primiparous woman to have a child with Apgar score <7 at five minutes increased with BMI classes and gestational duration. The calculated, baseline incidence for primiparous woman at 41^{+0} to have a child with Apgar score <7 at five minutes was 1.5% and was reached at different gestational durations depending on maternal weight (i.e., BMI class). For obese primiparous women, the baseline incidence was reached already at 39^{+3}, a gestational duration at which non-medical induction isn´t considered with today's management.

For the outcome stillbirth or neonatal death before 45 post-menstrual weeks women who are overweight or obese were at increased risk throughout the entire study period, but without a significant risk increase from prolonging gestational duration.

Our results indicate that for multiparous women a thorough medical history should be gathered before deciding on non-medical IOL. Women specific information on parity and BMI must be considered when counselling women in term to late-term pregnancies about action points for labour induction. Primiparous women who are overweight or obese are at amplified risk for poor neonatal outcome in term pregnancies, and at an earlier gestational age than when induction usually is recommended.

Study specific results

Study I

During the study period a shift of the management of post-term pregnancies is evident. In 2001- 2004, most Swedish maternity units used a more expectant management of pregnancies $\geq 41^{+3}$, 6.0% of the pregnant women were handled with a more active management. In 2010-2013, 54.3% were handled at more active management units. It is also evident that regions within Sweden have had different management routines, Stockholm being more active and northern, western, and south of Sweden being more expectant. The maternal characteristics did not differ between the more active and the least active management units. More active management units had higher induction rates (38.1% of primiparous and 30.2% of multiparous women) compared to the least active maternity units (25.5% and 19.0%, respectively). As a composite of elective and emergency CS, figure 6 shows the increased risk for any CS for primiparous and multiparous women, irrespectively of delivery start and by activity level. The risk estimates for 'any CS' were almost identical to the one for emergency CS, which reflects that after 41^{+3}, the vast majority of CS consists of emergency CS. For primiparous women, emergency CS rates after induction were for more and least active management units 34.1% and 35.0% and correspondingly for multiparous women 12.6% and 12.9%. Analyses indicate a 15% increased risk of CS after induction vs spontaneous start for primiparous women (OR least vs more active = 0.85 (95%CI: 0.82-0.88)). Also, for multiparous women, induction was associated with an 18% increased CS rate (OR (least versus more active management) = 0.82 (95%CI: 0.77-0.87))). Analyses on term pregnancies (39^{+0}-41^{+2}) were performed to evaluate if benefits for primiparous women at more active units could result from a more efficient obstetric management, no such association was indicated.

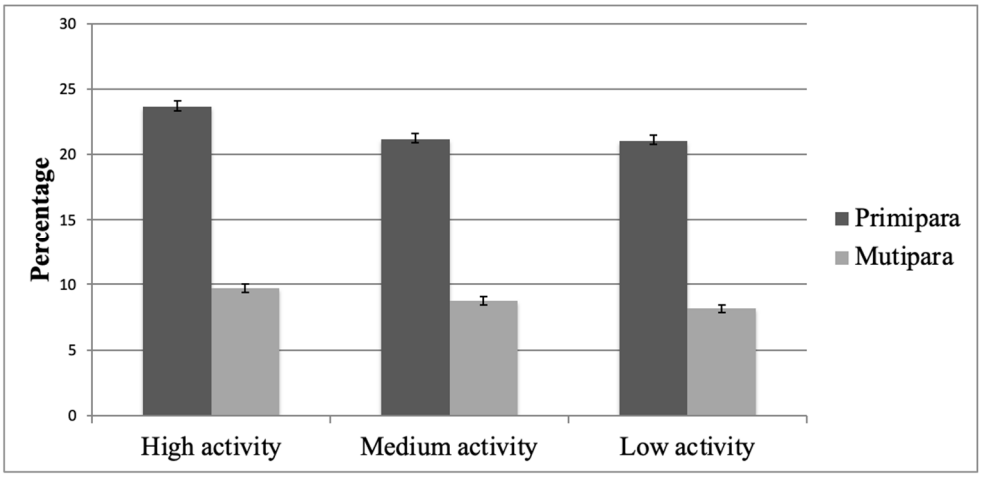


Figure 6: Any caesarean section irrespective of start of delivery for primiparous and multiparous women at high, medium, and low active management units. Bars indicate 95% confidences intervals (data from study I, previously unpublished).

Significant improved results for children to primiparous women with reduced risk of Apgar score <7 at 5 minutes and meconium aspiration when delivered at a maternity unit with more active management AOR (least versus more active management) =1.27 (95%CI: 1.12-1.44) and AOR=1.49 (95%CI: 1.14-1.95), respectively (figure7). For multiparous women, no significant improvement of any of the perinatal outcomes was detected between least versus more active maternity units. This strengthens the casualty from the degree of active management on improved outcome for children of primiparous women after 41^{+3}.

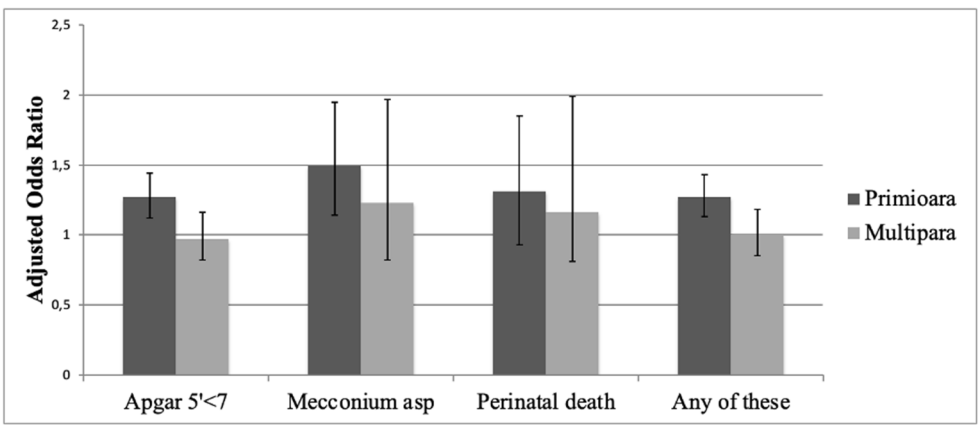


Figure 7: Adjusted Odds Ratios (most expectant versus more active management units) for poor perinatal outcome in deliveries at $\geq 41^{+3}$. Adjusted for year of birth, hospital level, maternal age, body mass index, and smoking. Bars indicate 95% confidences intervals (data from study I, previously unpublished).

Study II

For multiparous women $\geq 41^{+3}$, regardless of first labour delivery mode the emergency CS rate after induction was 13.6% and after spontaneous start of labour 6.1% resulting in an ARR=2.11 (95%CI: 2.00-2.23). The increased risk of emergency CS after induction was evident independently of first labour delivery mode (vaginal, emergency, or elective CS). The most pronounced increased emergency CS risk was detected for women with a second labour induction with a history of a prior CS, 52.1% versus 37.7% after spontaneous start of labour (ARR= 1.36 (95%CI: 1.28-1.44)). For adverse neonatal outcome as a composite and for Apgar score <7 at five minutes an increased incidence after second labour induction was indicated ARR=1.37(95%CI: 1.13-1.66) and ARR=1.44 (95%CI: 1.18-1.77) respectively.

Children to women with a previous vaginal delivery were at lower risk of poor neonatal outcome than were children of women with one previous CS, independent of induction or spontaneous start of second labour.

Subgroup analysis of women with one previous CS shows a great variety in the risk of an emergency CS from induction or spontaneous start of second delivery, and from conditions or diagnosis present at first CS, table 2. As shown in table , women with a first CS condition present or diagnose of gestational diabetes, multiple birth, or placenta previa have no significant increased CS risk from induction. All other diagnoses or indications have an increased emergency CS risk after induction, with the most pronounced risks following a first CS due to post-term pregnancy, failed induction, or foetal asphyxia. The results suggest that a woman with one previous CS should not be managed with the same guidelines as pregnant ‘women over all’ as the maternal risks are considerably increased from elective IOL.

Table 2: Risk of emergency CS in women with trial of second labour among uncomplicated pregnancies ≥41^{+3} in relation to start of second labour among women with a previous CS by conditions or diagnosis present at first delivery CS. Adjusted for year of birth (index pregnancy), maternal age, BMI, and smoking (data from study 2, published as a figure).

	Start of second labour						OR for emergency CS second labour, induction vs spontaneous start			
	Induction			Spontaneous start						
First delivery CS	Cesarean		Total	Cesarean		Total	Univariate models		Multivariable	
	n	(%)	N	n	(%)	N	OR	95%CI	AOR	95%CI
Conditions present at 1st delivery CS:										
Gestational diabetes	9	(47.4)	19	15	(42.9)	35	1.2	0.4-3.4	1.2	0.4-3.7
Pre-eclampsia	65	(43.6)	149	51	(21.5)	237	2.8	1.8-4.4	2.7	1.7-4.2
Mulltiple birth	23	(30.7)	75	32	(19.9)	161	1.8	0.9-3.3	1.7	0.9-3.2
Non-cephalic presentation	238	(34.0)	699	265	(16.7)	1583	2.6	2.1-3.2	2.5	2.0-3.1
Placenta Praevia	14	(35.9)	39	29	(27.6)	105	1.5	0.7-3.2	1.3	0.6-3.0
Preterm delivery	73	(31.5)	232	90	(19.5)	461	1.9	1.3-2.7	1.8	1.2-2.6
SGA	113	(45.4)	249	92	(22.8)	403	2.8	2.0-4.0	2.8	1.9-4.0
Polyhydramn	118	(51.5)	229	116	(34.0)	341	2.1	1.5-2.9	2.0	1.4-2.8
LGA	106	(48.0)	221	208	(36.6)	568	1.6	1.2-2.2	1.6	1.1-2.2
Post term	398	(54.5)	730	525	(39.6)	1326	1.8	1.5-2.2	1.8	1.5-2.1
Failed induction	513	(55.8)	920	611	(40.0)	1526	1.9	1.6-2.2	1.9	1.6-2.2
Dystocia	537	(58.5)	918	985	(42.8)	2299	1.9	1.6-2.2	1.8	1.6-2.1
Fetal asfyxia	404	(51.7)	782	552	(34.3)	1610	2.0	1.7-2.4	2.0	1.7-2.4

Study III

The risk for stillbirth or neonatal death before 45 post-menstrual weeks compared to surviving neonate by parity and BMI was studied. Maternal characteristics from multivariable analyses revealed that having a child that survives 45 weeks decreases, with increasing maternal age (ARR for one-year-increase = 1.05, (95%CI: 1.04-1.06)), primiparity (ARR vs multiparity = 2.50, (95%CI: 2.25-2.79)), BMI (ARR for one-BMI unit increase = 1.08, (95%CI: 1.07-1.09)), maternal smoking (ARR versus non-smoking = 1.35, (95%CI: 1.18-1.54)) and from maternal country of birth (ARR non-Europe/USA/Canada/Australia/New Zealand vs Nordic countries = 1.67, (95%CI: 1.47-1.90)). For primiparous women, the relationship between neonatal survival in relation to gestational age is confirmed in statistical calculation with an indicated increased risk from 41^{+0} and with a statistically significant increase from 41^{+3}- 41^{+6} regardless of BMI classes (ARR=1.29 (95%CI: 1.10-1.52), and for women with BMI ≥30 (ARR=1.52 (95%CI: 1.10-2.10)). Among children to multiparous women, a weak u-shaped association between gestational length beyond 39^{+0} and stillbirth or neonatal death before 45 weeks was indicated, with the lowest estimates among pregnancies lasting 40^{+3} to 40^{+6} weeks, regardless of BMI-class. No increased risk for mortality before 45 post-menstrual weeks in pregnancies lasting 41^{+0} compared to pregnancies 39^{+0} to 40^{+2} was found among children to multiparous women.

The risk of stillbirth among children of primiparous women, all weight classes together, increased from 0.2 per thousand ongoing pregnancies at 39^{+0}- 39^{+2} weeks to 1.45 per thousand at 42^{+0}-42^{+2}. The corresponding stillbirth risks for children of multiparous women were 0.2 and 0.53, respectively. Figure 8 shows that in early term there was no apparent impact of BMI or parity on stillbirth risk. At more advanced gestational weeks, there were distinctly increased risks of stillbirth among children of primiparous women, especially among children of overweight or obese women. Regarding children of multiparous women with BMI ≥30, the stillbirth rate increased with advancing gestational duration (from 0.23 per thousand ongoing pregnancies at 39^{+0}-39^{+2} weeks to 1.44 at 42^{+0}-42^{+2} weeks). But for multiparous women with BMI <30, no distinct association between stillbirth and advancing gestational age was noted.

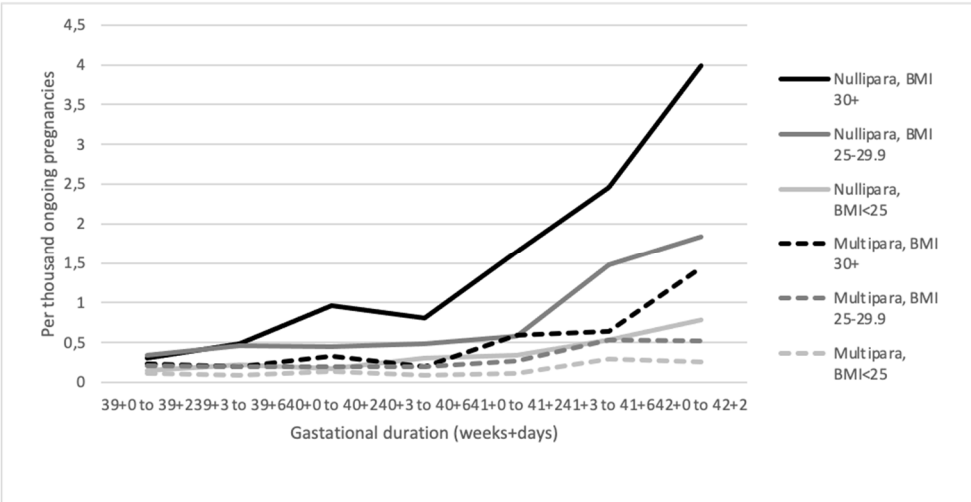


Figure 8: Risk of stillbirth per thousand ongoing pregnancies in relation to gestational length by parity and BMI classes (published in study III).

Study IV

The results of study IV indicate that for primiparous women, the risk of a child with Apgar score <7 at five minutes, stillbirth, and stillbirth or neonatal death <45 post-menstrual weeks increases with BMI classes.

Women who were overweight or obese were more likely to have gestational diabetes and preeclampsia, more often pregnancies that procced to $<41^{+0}$, and a lower rate of vaginal non-instrumental deliveries. They were also more likely to have labour induction and a higher rate of CS, both elective and emergency. Low educational level (≤12 years), was strongly associated with overweight or obesity. Children to

women who were overweight or obese were at increased risk of low Apgar score, birthweight >4500g, and stillbirth or neonatal death before 45 postmenstrual weeks.

For all BMI classes, together and fractionated, the risk of a child with Apgar score <7 at five minutes decreases with birth at gestational duration <40 weeks (AOR=0.8 (95%CI: 0.74-0.86)) and increases after 41^{+0} weeks (AOR =1.36 (95%CI: 1.27-1.45)) compared to delivery at 40^{+0}-40^{+6}.

A linear regression line for each BMI class was obtained from the coefficients retrieved from Poisson regression analyses (figure 9). In the linear model, the crude RR for one day increase of gestational duration within the interval was RR=1.040 for normal weight, RR=1.039 for overweight, and RR=1.047 for women who were obese. For women overall the baseline incidence of having a child with Apgar score <7 at five minutes at 41^{+0} =1.5%. Gestational duration of 41^{+0} was used based on the international guidelines of elective induction at 41^{+0} weeks. The general incidence of 1.5% risk for neonatal low Apgar occurs at different gestational durations for individual BMI classes (figure 9).

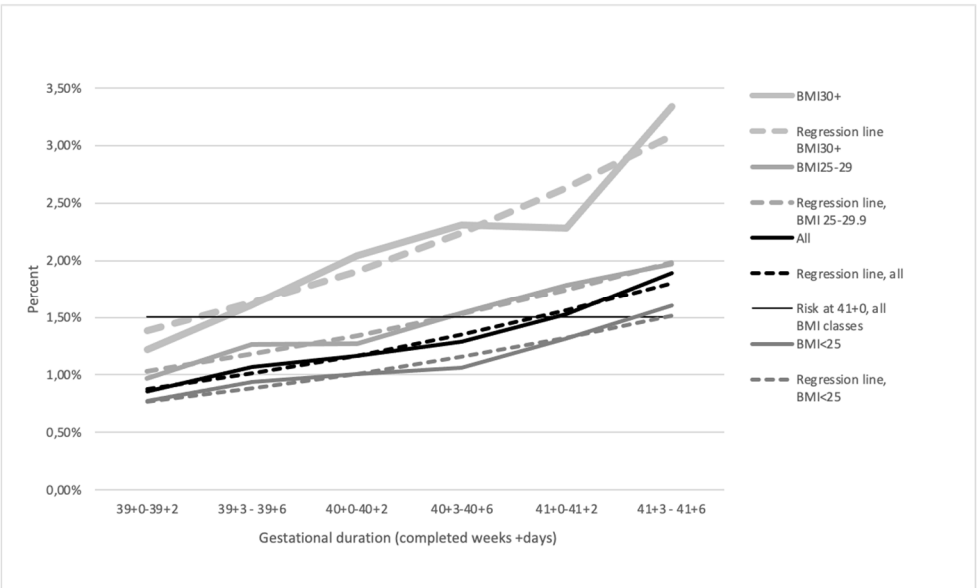


Figure 9: Absolute risk of Apgar score <7 at five minutes combined with BMI classes and gestational duration (figure from study IV).

Children to primiparous women had, regardless of BMI class, no positive effect of delivery <40 weeks (compared to delivery at 40^{+0}-40^{+6}) on the risk for stillbirth and stillbirth or neonatal death before 45 post-menstrual weeks. For all BMI classes (but not for the divided classes) deliveries after >41^{+0}, compared to at 40^{+0}-40^{+6},

indicated an increased risk for stillbirth or death before 45 post-menstrual weeks (ARR=1.26 (95%CI: 1.07-1.48).

Even if no increased risk for stillbirth or neonatal death before 45 post-menstrual weeks in relation to advancing gestational duration was detected it is evident that for women who are overweight or obese, the risk for neonatal mortality increases throughout the study period (39^{+0}-41^{+6}) compared to women with BMI <25 (figure 10). Using the same procedure as for Apgar score, the baseline incidence of stillbirth or neonatal death before 45 post-menstrual weeks at 41^{+0} was = 0.22%.

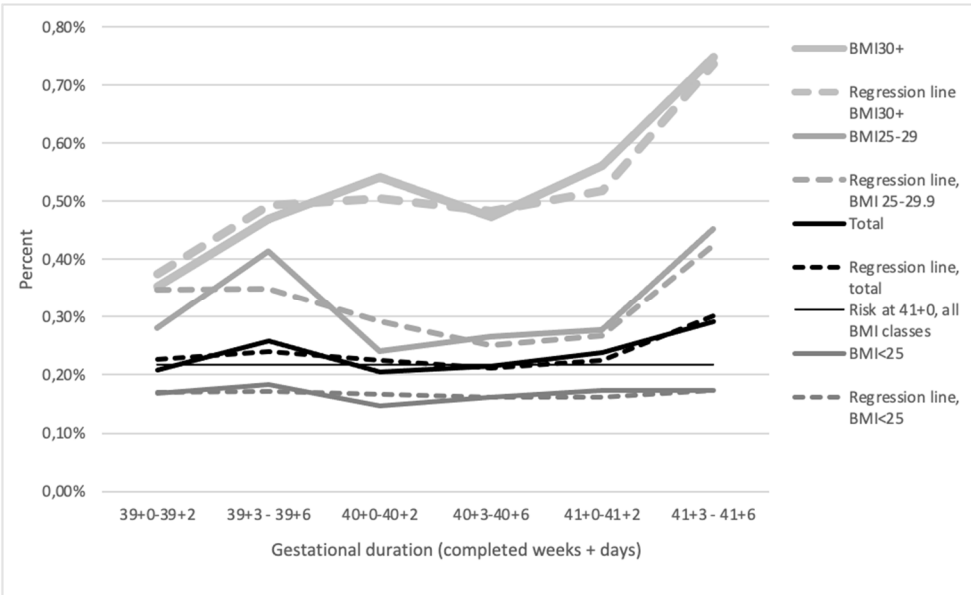


Figure 10: Stillbirth or neonatal death before 45 post-menstrual weeks combined with BMI classes and gestational duration (figure from study IV).

For primiparous women with BMI <25, no association between gestational duration and increased risk of stillbirth or neonatal death before 45 weeks were found.

Discussion

The studies are retrospective register studies from a large data source with high degree of reported values, providing good reliable results. Contrary to our significantly results of increased CS rates after induction - for all variables studied - the results from Randomized Controlled Trials (RCT) states that CS rates are not increased after induction in late term (or term) pregnancies.

The argument is that the results from retrospective studies are distorted by inclusion bias because of comparing induced with spontaneously started labours. This is a valid criticism. It will always be some observation during an assessment, even if small and not recorded, that indicates induction for one but not the other of two pregnancies that appear to be alike. This is the reason for adjustments in retrospective studies. The randomized controlled trial on outcome after induction is designed to compare induction versus expectant management. Even if the best outcome for the individual women and the child would be a spontaneous start of labour this is not a possible choice, but induction or expectant management is. Still, an RCT needs sufficient power from the number of included women to draw conclusions on moderately increased risks of rare conditions (neonatal or perinatal death). Even in our study I, where 199 770 women were included, the power was limited to detect association between perinatal death and delivery unit in terms of least and most active management. A pronounced strength of study I is that maternity units were not compared by how they report on management, but by their actual management of all pregnancies being 41^{+3} becoming 42^{+3}, i.e., comparing two groups rather than induction versus spontaneous start of labour.

When comparing maternal characteristics from study I and the Swedish RCT it is evident that the RCT reports a proportion of women with higher maternal educational level and a lower prevalence of BMI >30 compared to our MBR data. This difference in proportion raises the question of which pregnant women that agree to participate in experimental studies. The methodological approaches have their pro and cons. They are complementary in the endeavour to improve management in term pregnancies.

In study I, the results for pregnancies 39^{+0} to 41^{+2} were further analysed to evaluate whether the improved perinatal outcome in the most active maternity units could be a result of overall more efficient obstetric management. No such associations were indicated, which in turn suggests that the differences between the least and more

active managed units were not due to an overall more efficient obstetric management, but to different handling among prolonged ($\geq 41^{+3}$) and post term pregnancies (expectant versus more active management).

Maternal age and parity are related variables, but with opposite effects (Haavaldsen et al., 2010, Kortekaas et al., 2020). In study I, maternal age is handled as a continuous independent variable in the logistic regression analysis. To investigate the impact from maternal age, analyses with maternal age entered as a class variable (5-year-classes) were performed and resulted in AOR that was identical to those previously retrieved. This indicates that our results on added risk from primiparous women is not because of a lower maternal age for primiparous than multiparous women.

The objective of study II was to investigate if there was a possibility to select women who would benefit from induction, based on information from the first pregnancy and labour. We did not aim to evaluate type of management, just to analyse induction in its relation to available information regarding first delivery. The results indicate an increased risk for CS after induction, independent of spontaneous start or IOL.

Even if effort was made to adjust for pre-labour complications, it can´t be ruled out that to some extent the high CS rates in the induction group are because of an over-representation of complicated pregnancies.

Independent of first delivery mode, 145 children were in the 'composite neonatal outcome' resulting in an almost 99% chance of a healthy child for multiparous women at their second labour. The composite for neonatal outcome consists, to a vast majority, of Apgar score <7 at five minutes which is far less severe than neonatal death. The result indicates that information regarding conditions present at the first delivery can be used to estimate the chance of a second delivery induction resulting in a vaginal delivery of a healthy child.

Unlike in RCT, where all pregnancies should be included, an observational retrospective study suffers from the risk of increased confounding by indication. If conditions that are known to be indicators for inductions were included, the results for the induction group would have appeared worse than they really are.

Our results for multiparous women without any medical indications suggest a move towards 41^{+6} (rather than 41^{+0}) as an action point for IOL without endangering the health of the neonate. This result should have implications when discussing alteration of the guideline of induction in late term pregnancies.

The results from observation on women with prior CS are of interest, as these women are often excluded from investigations on obstetrical management in late term pregnancies. There are other studies with the aim to explore ways to predict the vaginal success rate with TOLAC. The best practice for maternal and neonatal outcomes for women with a prior CS in a second pregnancy without medical

complications, from induction or expectant management in late term pregnancies, needs to be studied further and to be managed considering that the 'accepted vaginal success rate' is individual for every woman.

An important question, but one not covered in this thesis, is that of maternal experience from induction versus expectant management. A positive delivery experience has been reported as having involvement in the birth process, and having midwife support. Negative delivery experience is reported as having anxiety, pain, and having a first baby (Waldenström, 1999, Larsson et al., 2010). A recent study on maternal experience from a self-assessment scale (VAS) indicates no differences between induction at 41^{+0} or expectant management; both groups rate their experience high (Nilvér et al., 2021). This is important as many studies, including the latest Cochrane review on the subject, states that women should be informed on the risk, so they are able to make an 'informed choice of IOL'. This implies not only to recommend the best medical management but also to have a woman centred management.

For obstetric care follow up, caesarean section is used as an outcome for the evaluation of obstetric care regarding different categories of women, (WHO-Robson classification., 2017). Primiparous with a singleton in cephalic presentation $\geq 37^{+0}$ (Robson 1) is the group of greatest interest to keep CS rates low. But perhaps the most interesting group is women with a previous scar in uterus (a prior CS). For maternal experience, could a second labour elective CS on maternal request, after a first vaginal delivery be a measure of first delivery low experience? To study this, women with the most negative experiences from their first labour should be included, as they without an elective CS have the potential benefits from being multiparous whiteout the disadvantages related to a CS. To induce labour or not in women without medical indications but with a prior CS as an informed choice needs further investigation. Or, as concluded in a Cochrane review from 2017, no RCTs studying elective repeat caesarean delivery with IOL in women with previous caesarean delivery were found (Dodd et al., 2017). Are such trials possible to conduct, because of the large numbers needed to investigate the risk of rare but serious adverse outcomes (e.g., uterine rupture)? To gather further data on the best management to induce women with a prior CS, observational (cohort) studies including different methods of cervical ripening, are suggested to be the best alternative (West et al., 2017).

In Study III, parity and BMI in relation to gestational duration with the outcomes stillbirth per se, and stillbirth or neonatal death taken together were studied. To investigate if the increased risk associated with maternal BMI was related to actual BMI rather than the dichotomy of 'obese or not', we intended to study the outcome among obese women with BMI ≥35. The proportion of women in Sweden with a BMI ≥35 during the studied time-period was too low to calculate any risk estimates with adequate precision.

When considering stillbirth rates only, the mortality among neonates is disregarded, introducing a systematic bias as children who are born in early term gestation have a shorter time 'at risk' of death compared to those born later. With the primary outcome chosen in the current study (stillbirth or neonatal death before 45 post-menstrual weeks), we eliminated the risk of confounding due to the aforementioned censoring. The impact from being overweight or obese on stillbirth or neonatal death before 45 post-menstrual weeks was increased for women who were older, primiparous, smoking in early pregnancy, born outside Europe/USA/Canada/Australia/New Zealand, and had a lower level of education. These are known risk factors that have to be addressed to reduce the number of stillbirths or neonatal deaths even more and in turn make the management of term pregnancies more individualized but also more complex.

The studies indicates that primiparity is a risk factor for perinatal death independent of maternal BMI. From our results there appears to be little justification to treat primiparous and multiparous women the same. Although the data doesn´t reach statistical significance, should an earlier point of action for IOL be considered for primiparous women with BMI ≥30 and possibly even for those who are overweight (BMI 25-29.9)? It could also be argued that for those with a normal BMI <25, induction of labour to prevent stillbirth is not easily justified, even for primiparous women. According to our results, both parity and BMI should be considered when creating guidelines, and when consulting women without medical reasons for induction, to make an informed choice of induction versus expectant management in term pregnancies.

In study IV, primiparous women in BMI classes are studied in relation to gestational duration with Apgar score, stillbirth, and stillbirth or neonatal death as outcomes. Because of the non-linear association between BMI and gestational duration it was impossible to identify a certain gestational duration at which the risk for children of women who were overweight or obese were at increased risk.

The duration of the gestational age is not as specific as it may appear in our manuscripts. A pregnancy considered to be 41^{+3} could be between 40^{+6} and 42^{+0} if dating was done in weeks 12-14 and between 40^{+0} and 42^{+2} if dated in gestational weeks 15-20 (Saltvedt et al., 2004). Systematic bias of ultrasound-based gestational duration estimations has been reported due to foetal sex (male), intrauterine growth restriction, and maternal BMI (Källén 2002, Simic et al., 2010). If the foetus is female, the risk from ultrasound dating is an underestimation of gestational age and with large differences - 1 to 2 weeks - on the EDD between LMP and the ultrasound, the foetus would be at enhanced risk for entering the post-term period.

However, on group-level, the timing of gestational duration mention is nevertheless meaningful as the guidelines will consider not only gestational weeks, but also consider the days within each week. Thus, it is of utmost importance that maternity staff are aware of individual differences to avoid adverse outcomes due to

undetected late to post-term pregnancies, and it is feasible that this timing should depend not only on parity, but also on maternal BMI.

Even though Apgar score is a subjective assessment it is often used in epidemiological studies in the absence of objective measures of delivery outcomes other than mortality. Apgar score <7 at five minutes has proven to be a reliable marker of new-born's health (Thorngren-Jerneck and Herbst., 2001, Razaz et al., 2019). It has also been reported to be associated with child health (Iliodromitis et al., 2014., Li et at., 2013) school grades and academic achievements at 16 years of age (Stuart et al., 2011).

Even if the most high-risk pregnancies, in early term would have been eligible for intervention, the design of study IV would still have been bias by inclusion. This is because pregnancies will, at certain observation points, be evaluated with evolving risk factors identified and managed by induction or CS (inclusion bias). This would potentially lead to an over-estimation on the considered outcomes in the 39^{+0}-39^{+6} group, resulting in a lower negative effect of advancing gestational duration on pregnancy outcome than if no intervention had been done.

The results suggest that to reduce adverse outcomes manifested by low Apgar scores (perinatal asphyxia) in children of primiparous women, action points may have to be individualized, taking maternal BMI into account. The same conclusion could be drawn when making decisions to reduce perinatal death, even if it was harder to define the optimal timing of offering induction by maternal risk profile.

Clinical implications

The new guidance from international recommendation on the management of late term pregnancies has already improved the stillbirth rates in late term pregnancies in Sweden (figure 11). But with increasing induction rate for women at 41 weeks or longer, the stillbirth rate must be interpreted carefully, the child born is out of risk but the child in the uterus is still at risk of stillbirth.

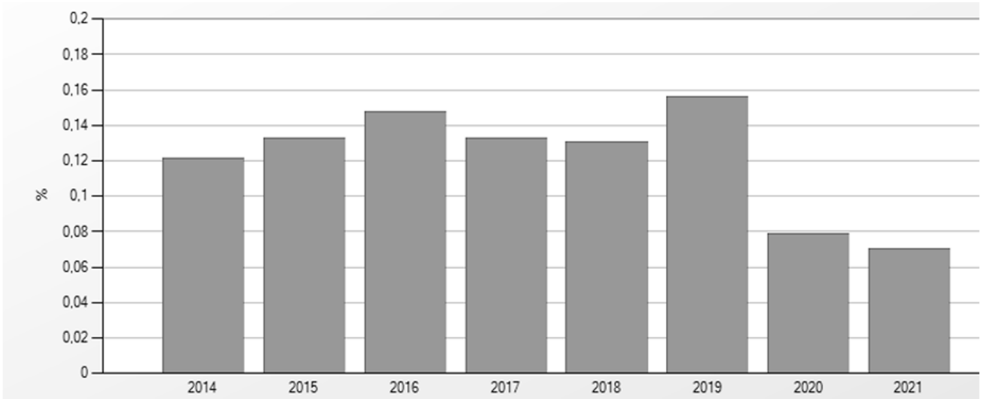


Figure 11: Annual stillbirth rates among all women with pregnancies from 41^{+0} and onwards in Sweden (Graviditetsregistret).

To decrease the incidence even further, new approaches other than general guidelines identifying children to subgroups of women with increased risk are needed. The results of this thesis suggest that there appears to be little justification to use the same induction guidelines for primiparous and multiparous women in pregnancies lasting 39 gestational weeks or more, especially for women who are obese. During the gestational weeks of interest (41^{+0} to 41^{+6}), our results would suggest IOL in the beginning of the week for primiparous women, and at the end of the week for multiparous women without medical indication.

Conclusions

In term to post-term pregnancies, the risk of adverse neonatal outcome is affected by both parity and BMI.

Neonates to primiparous women benefit from a more active management in late term pregnancies. Regardless of gestational duration, primiparous women who are overweight or obese are at increased risk of having a child who die perinatally compared to women of normal weight. For obese primiparous women, the risk of a child with Apgar score <7 at five minutes is increased from 39^{+3}, compared to the baseline incidence.

For multiparous women, the risk of having a child with adverse neonatal outcomes in term pregnancies is low, regardless of BMI. After a prior CS, diagnoses and/or conditions present at the first CS should be considered when advising on induction.

The result from our analyses emphasises parity and BMI as risk factors to be considered in term pregnancies. Individualized management of risk factors in association with gestational duration could be a way to lower the numbers of adverse neonatal outcomes even further.

The following conclusions are based on the findings from the original studies included in this thesis:

I. Children of primiparous women benefit (measured as a composite of Apgar score <7 at five minutes, meconium aspiration and perinatal death) from active management, whereas no such improvement of neonatal outcome was indicated among children of multiparous women.

II. For multiparous women, increased risk for CS and poor neonatal outcome after second labour induction in pregnancies $\geq 41^{+3}$ were found. The results indicate a large variation of vaginal delivery success rate after second delivery induction and spontaneous start, dependent on first labour delivery mode, and the indications for a prior CS when applicable.

III. Pregnancy duration of 41^{+3} to 42^{+2} was associated with increased risk for stillbirth or neonatal death before 45 post-menstrual weeks among primiparous women, especially among women with obesity. For

multiparous women, no significant association between gestational duration and mortality was found.

IV. Women who were overweight or obese were, regardless of gestational duration, at increased risk of having a child who died perinatally or had low Apgar score <7 at five minutes compared to women of a normal weight. The results indicate that it is important to study the combined association of BMI and gestational duration on pregnancy outcome.

Reflections for future work

Future topic of interest will be how to improve the individualized care and action points for other risk factors in term to late term pregnancies, such as maternal country of birth and maternal age in primiparous women. With improving numbers on adverse outcomes and new guidelines in process, my guess is that the focus will be shifted toward the antenatal period and identifying high risk pregnancies earlier, possibly by new markers? Interesting subgroups of women are, from my point of view, women with type I Diabetes, mental illness and of course women who are overweight or obese. How are these women best managed during pregnancy to prevent adverse maternal and neonatal outcomes in term pregnancies?

In the light of our strong evidence for the negative effects of pregnant women being overweight or obese, this is an area of great interest with pregestational advice and weight loss after delivery.

The suggested management for late term pregnancies in Sweden (elective induction between 41^{+0}-41^{+6}) are, from our results, appropriate for primiparous women, but not for women who are overweight or obese. Another group that demands more knowledge on how to manage it, is women with a prior CS. Could a spontaneous start of labour be awaited until $41^{+6}/42^{+0}$, if nothing deviating is found at 41^{+0} examination, with neonatal benefits from being multipara? Then, at $41^{+6}/42^{+0}$ perform IOL or repeated CS depending on first CS condition, cervical ripening, and maternal wish. It would be interesting to follow up the management in relation to maternal satisfaction and from numbers on IOL and elective CS entering the post-term period.

A randomized controlled study on obese primiparous women with induction from 39^{+0} versus 40^{+0} and or even 41^{+0} would be of great interest to confirm or challenge our results from studies III and IV. But to reach power, the size of such an RCT could be a problem, as stillbirth and perinatal death are rare events.

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Individualized management in term pregnancies

Lina Lindegren is a consultant physician in Obstetrics and Gynecology at Helsingborg Hospital and a PhD student in the Department of Clinical Science, Lund University.

The purpose with this thesis is to investigate the impact of maternal BMI and parity in term pregnancies in relation to gestational duration on adverse maternal and neonatal outcome among women with singletons in cephalic presentation.

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