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# Labour dystocia: Risk factors and consequences for mother and infant

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# Labour dystocia: Risk factors and consequences for mother and infant

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To be publicly defended in Skandiasalen, Astrid Lindgrens Children's Hospital, Karolinska University Hospital, Solna

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*To my family*

# Abstract

***Background:*** Labour dystocia (prolonged labour) occurs in the active first stage or in the second stage of labour. Dystocia affects approximately 21-37% of nulliparous, and 2-10% of parous women. The condition is associated with increased risks of maternal morbidities, instrumental vaginal deliveries and is the most common indication for a primary caesarean section. The effects of the duration of second stage on neonatal outcomes are still unclear. Dystocia primarily affects nulliparous women, but the risk of recurrence in following labour has not previously been investigated. The aim of this thesis was to elucidate factors influencing the risk of dystocia and the effects of prolonged second stage of labour on neonatal outcomes.

***Material and Methods:*** Studies I-IV are population-based cohort studies. The first two are nation-wide, based on the Swedish Medical Birth Register (MBR). In study I, births between 1992 and 2006 were covered and in study II, the corresponding period was 2006 to 2011. The Stockholm-Gotland Obstetric Cohort was used in the third and fourth studies, from 2008 to 2012 in study III and 2008 to 2013 in study IV. Term and post-term singleton pregnancies with infants in cephalic presentation, were studied in all four papers. In study I, 239 953 women who gave birth to their first and second infants, were assessed regarding the risk of recurrence of labour dystocia and mode of second delivery. In study II, the association between use of low-molecular-weight heparin (LMWH) during pregnancy and risk of labour dystocia was examined in 514 875 nulliparous and parous women. Study III and IV included 32 796 and 42 539 nulliparous women, respectively. The associations between duration of second stage (study III and IV), and adverse neonatal outcomes such as low 5-minute Apgar score (Study III), umbilical cord acidosis, birth-asphyxia-related complications and admission to neonatal intensive care unit (NICU) (study IV) were assessed. In addition, the effect of duration of pushing on adverse neonatal outcomes were examined in study IV.

***Results:*** The overall risk of recurrence of labour dystocia in second labour was not very high, but there was a substantial risk of recurrence of labour dystocia in women with previous caesarean section. Instrumental vaginal delivery and caesarean section in second labour were not only associated with previous dystocia and mode of delivery but also with fetal and maternal characteristics. LMWH use during pregnancy was not associated with risk of labour dystocia after adjustments for potential confounders. Increasing duration of second stage was associated with increased risk of low 5-minute Apgar score, birth-asphyxia-related complications, and admission to NICU for the infant. Umbilical artery acidosis increased with duration of pushing, but not with duration of second stage. However, the absolute risk differences of most of the adverse neonatal outcomes, were low.

***Conclusions:*** Taking individual obstetric and demographic information into account is important in the risk assessments for dystocia and instrumental delivery in second labour. Use of LMWH during pregnancy does not seem to influence the risk of labour dystocia. With increasing duration of second stage and pushing, fetal surveillance is of outmost importance.



***Key words:*** Labour dystocia, mode of delivery, recurrence, low-molecular-weight heparin, pushing, second stage of labour, duration, neonatal outcomes, asphyxia

# LIST OF SCIENTIFIC PAPERS

I. **Labour dystocia - risk of recurrence and instrumental delivery in following labour - A population-based cohort study**
Anna Sandström, Sven Cnattingius, Anna-Karin Wikström and Olof Stephansson
*BJOG 2012, 119(13):1648-1656*

II. **Does use of low-molecular-weight heparin during pregnancy influence the risk of prolonged labor: A population-based cohort study**
Anna Sandström, Sven Cnattingius, Anna-Karin Wikström, Olof Stephansson and Anastasia N. Iliadou
*PLoS ONE 2015, 10(10) e0140422*

III. **Prolonged second stage of labor is associated with low Apgar score**
Maria Altman, Anna Sandström, Gunnar Petersson, Thomas Frisell, Sven Cnattingius and Olof Stephansson
*European Journal of Epidemiology 2015, 30:1209-1215*

IV. **Durations of second stage of labour and pushing, and adverse neonatal outcomes - A population-based cohort study**
Anna Sandström, Maria Altman, Sven Cnattingius, Stefan Johansson, Mia Ahlberg and Olof Stephansson
*Manuscript submitted for publication*

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# List of abbreviations

| | |
|---|---|
| ACOG | American College of Obstetricians and Gynecologists |
| aOR | Adjusted odds ratio |
| BMI | Body Mass Index |
| BE | Base excess |
| CI | Confidence Interval |
| CPD | Cephalopelvic disproportion |
| CS | Caesarean section |
| DAG | Directed acyclic graph |
| GEE | Generalized estimating equation |
| HIE | Hypoxic ischemic encephalopathy |
| ICD-9 and -10 | International Classification of Diseases, 9:th and 10:th revisions |
| LMWH | Low-molecular weight heparin |
| MAS | Meconium aspiration syndrome |
| MBR | Swedish Medical Birth Register |
| MVU | Montevideo units |
| NICE | National Institute for Health and Clinical Excellence |
| NICU | Neonatal intensive care unit |
| pH | Power of hydrogen |
| RCT | Randomised Controlled Trial |
| OR | Odds ratio |
| PROM | Premature rupture of the membranes |
| RR | Relative risk |
| SNQ | The Swedish Neonatal Quality Register |
| TOLAC | Trial of labour after caesarean |
| VBAC | Vaginal birt after caesaren |
| WHO | The World Health Organisation |

| | |
|---|---|
| Acidosis | Umbilical artery pH <7.05 and BE <-12 mmol/L |
| Birth-asphyxia related complications | HIE, hypthermia tratment of the neonate, neonatal seizures, MAS, and/or recussitation in delivery room with heart compressions and/or intubation |

# 1 INTRODUCTION

Labour dystocia is the leading cause of interventions during delivery. Other terms used equally for labour dystocia are prolonged labour, difficult labour, dysfunctional labour, failure to progress, cephalopelvic disproportion (CPD) and obstructed labour. Dystocia can be diagnosed during the active phase of first stage of labour or in the second stage of labour including the descending (also called passive phase) and expulsive phases (also called bearing down or pushing) (Figure 1.1).

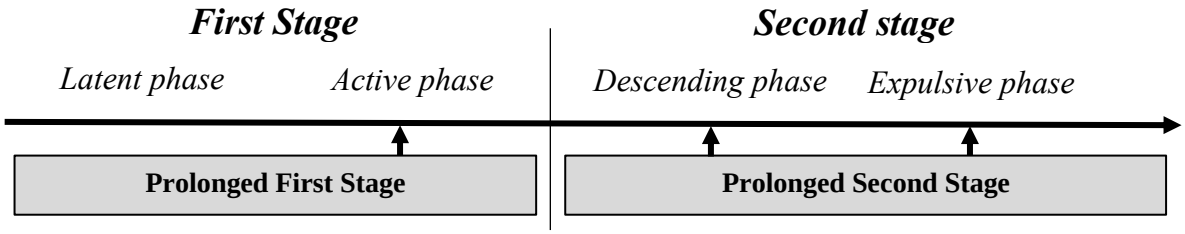



**Figure 1.1: Stages and phases of the delivery process.**

The World Health Organisation (WHO) estimates 303 000 global maternal deaths in 2015, where 99% occur in low-income countries. Obstructed labour contribute to an estimated 2.8% of the maternal causes of death worldwide.[1, 2] An estimated 3.1 million deaths occurred in the neonatal period (0-27 days) globally in 2010, where intrapartum–related complications accounted for 23% (0.7 millions).[3]

In a high-income setting, it is uncommon with extensive durations of delivery and obstructed labour by abnormal presentation of the fetus, with subsequent maternal and neonatal mortality or severe morbidity. Challenges in these settings include increasing incidence of labour dystocia and high caesarean section rates, partly due to dystocia. The objectives are to reduce non-medically indicated caesarean sections and instrumental vaginal deliveries, and to avoid adverse maternal and neonatal outcomes. The absence of consensus about the definitions of the beginning of active labour, of normal labour and dystocia in first and second stages, makes this field difficult to explore.

The four studies in this thesis aim to investigate factors influencing the risk of dystocia and consequences of dystocia for the mother and the neonate. These associations were studied in term and postterm pregnancies (≥ gestational week 37), which is the gestational age period when dystocia primarily occurs. In addition, the majority of all serious complications affect term infants because of their large number. Hopefully, the results of these studies may contribute to an improved and safer delivery care for the woman and the infant, with as few interventions as possible.

# 2 BACKGROUND

## 2.1 THE SWEDISH HEALTH CARE SYSTEM FOR PREGNANT WOMEN

All women in Sweden are offered free health care during pregnancy. About 98% of pregnant women adhere to the routine antenatal program and 99% are delivered in hospitals. Uncomplicated pregnancies and deliveries are supervised by nurse-midwives with little involvement from obstetricians, whereas complicated pregnancies and deliveries are managed together with obstetricians.[4] Since the beginning of the 1990s, all pregnant women are offered at least one ultrasound scan during pregnancy; the average is slightly more than two ultrasounds.[5] If only one routine ultrasound scan is offered, this is usually around gestational week 18, and is accepted by more than 95% of all pregnant women.[6] According to Swedish recommendations from 2010, if an ultrasound scan is performed at 12-14 gestational weeks this is to be preferred for dating the pregnancy rather than a scan at 15-22 weeks.[7]

## 2.2 SWEDISH DELIVERY STATISTICS

The Swedish delivery statistics were retrieved from the National Board of Health and Welfare's report in 2015. During the 21st Century the number of deliveries in Sweden has increased, and in 2014 the number reached almost 114 000. Among mothers with a personal identity number, 99% of the infants were found in both the Swedish Medical Birth Register (MBR) and in Statistics Sweden. Slightly more infants were registered in the MBR since mothers without personal identity numbers, such as asylum-seeking women and women without documents, are more frequently reported in the MBR.[8]

Compared to 1973, women giving birth in Sweden in 2014 were older (mean age 23.7 and 28.5 years, respectively) and are more often born in other countries than Sweden (10.3% and 26.7%, respectively). The proportion of women being over-weight or obese (BMI 25 or more) at the first antenatal visit has increased over time (25.4% in 1992 compared to 38.1% in 2014) (Figure 2.1). While daily smoking during pregnancy decreased drastically during the same time period (from 22.9% to 5.5%). Compared to women with upper secondary and post-secondary education, women with only compulsory education, are more often smokers and over-weight during pregnancy.

In 2014, about 88% of all pregnancies were delivered at full-term (from 37+0 to 41+6 gestational weeks) and 17% of these were induced. About 76% were delivered by a vaginal non-instrumental delivery. The rates for caesarean section among singleton deliveries were 5.3% in 1973 and 17.7% in 2014. The frequency of caesareans differed between the Swedish Counties, from the lowest rate of 11.6% to the highest of 21.6% in the Stockholm County. The proportion of caesarean sections was somewhat lower in groups with higher education than for other groups.

Of all childbirths in 2014, vaginal instrumental deliveries with vacuum extraction was performed in 7.6%, and with forceps in 0.1 % (Figure 2.2). Among nulliparous women with vaginal deliveries in Sweden, 52.7% used epidural analgesia. This varied from hospital to hospital, however, and ranged from 21.7% to 72.4%.[8] The number of stillbirths was 4.0 per 1 000 born infants and the neonatal mortality within 0-27 days after birth was 1.5 per 1000 live-born in 2014.[8] According to the Swedish Neonatal Quality Register (SNQ) the proportion of neonates admitted to neonatal wards within 0-28 days after birth in 2014 was on average 10.0% in Sweden, and 9.8% in the Stockholm County.[9]

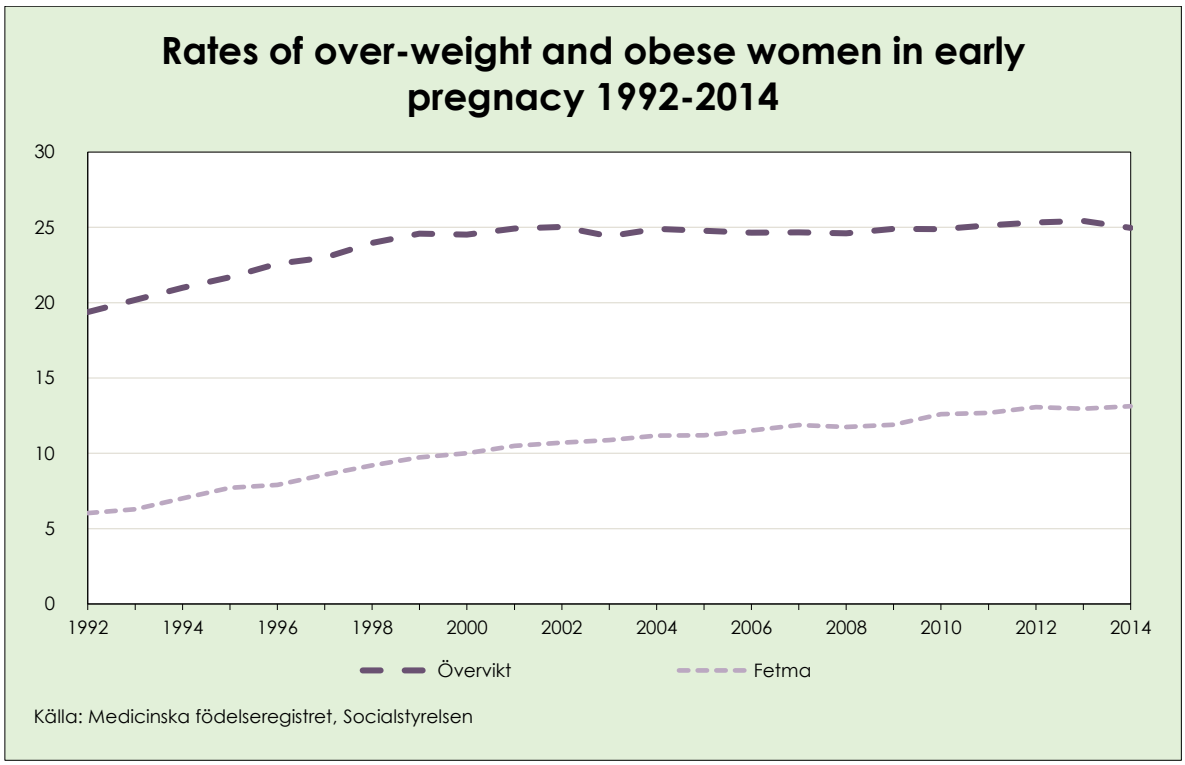



**Figure 2.1: Rates of over-weight and obese women in early pregnancy in Sweden 1992 to 2014.**
Dark purple line: Over-weight women (BMI 25.0-29.9) Light purple line: Obese women (BMI ≥30)
Source: The Swedish Medical Birth Register, National Board of Health and Welfare

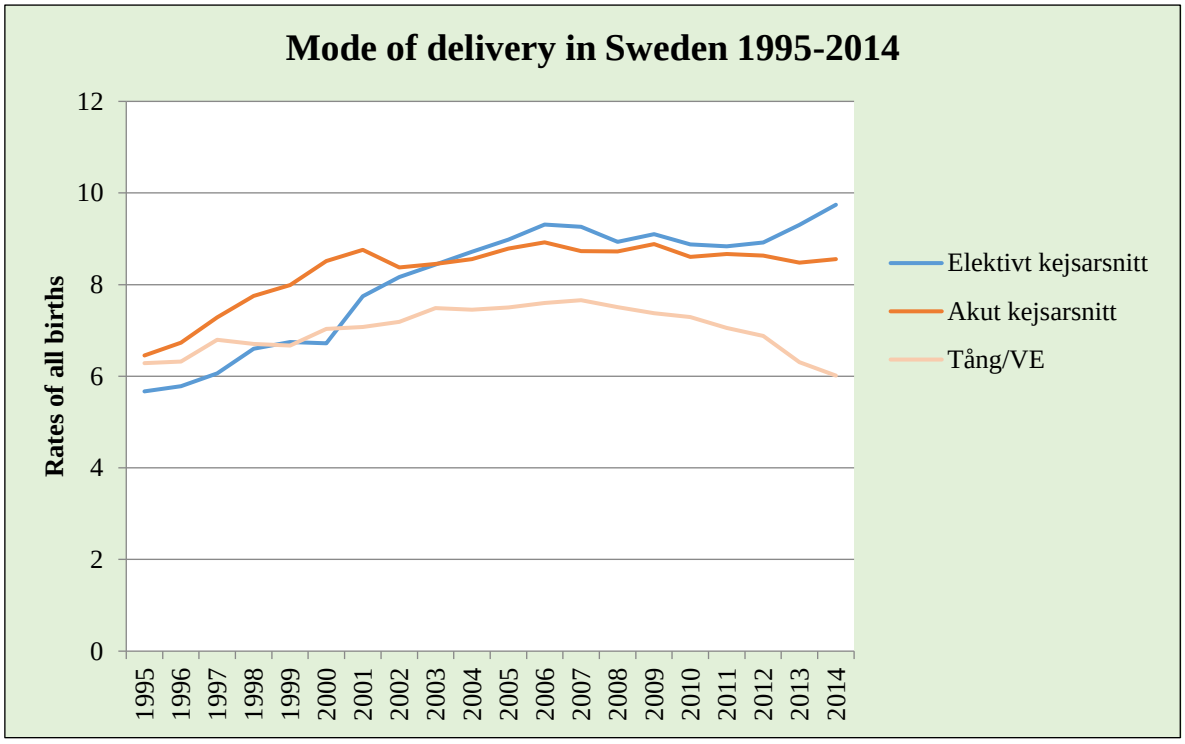



**Figure 2:2: Mode of delivery among women giving birth in Sweden 1995 to 2014.**
Blue line: Elective caesarean sections Red line: Emergency caesarean sections
Pink line: Instrumental vaginal deliveries (vacuum extractions and forceps)
Source: K Källén, National Board of Health and Welfare

## 2.3 THE LABOUR PROCESS

Labour is a continuous process, yet it is divided into different stages and phases. Friedman's work in the 1950s and thereafter has been the foundation for assessing normal labour progression.[10-13] Statistical observations of 500 nulliparous women at term were studied by graphing cervical dilation against time and was then synthesised into the characteristic sigmoid curve (Figure 2.3).[11] Labour was divided into the first and second stages. The first stage was further divided into the latent phase and the active phase. By defining the thresholds of normal labour, Friedman's work has had a profound impact on labour management world-wide for more than six decades.

### Latent phase

The latent phase starts with the onset of labour, i.e. the perception of contractions followed by cervical effacement and initial dilation and continuous until the active phase begins. The duration of the latent phase varies greatly and it is commonly ill-defined. According to Friedman's work, based on the 95$^{th}$ percentile threshold, a prolonged latent phase is defined as more than 20 hours for nulliparous and 14 hours for parous women.[13] According to the Swedish Society for Obstetrics and Gynecology's definition of the International Classification of Diseases, 10$^{th}$ revision (ICD-10), prolonged latent phase is defined as more than 18 hours. Labour dystocia cannot be diagnosed during the latent phase.

### Active phase of first stage of labour

The active phase of first stage of labour (also referred to as the active phase) is demonstrated by an increased rate of cervical dilation and ultimately fetal descent. It usually starts at cervical dilation of 3-5 cm and continues until the cervix is fully dilated (in Sweden fully dilated is defined as retracted, i.e. the cervix can no longer be reached around the presenting part when dilated ten centimetres) (Table 2.1). The active phase was subdivided into the acceleration, maximum slope and deceleration phases in Friedman's curve, which describes the pace of cervical dilation (Figure 2.3).

According to Friedman's studies in the 1950s, the rates of cervical dilation was 1.2 to 6.8 cm/h in nulliparous women.[11] More recent studies have found longer durations of the active phase than previously described by Friedman.[14-16] In a study where a historical cohort (1959-1966) was compared to a contemporary cohort (2002-2008), the median duration from 5 cm to 10 cm was 1.2 hours (95$^{th}$ percentile 7.9) compared to 3.0 hours (95$^{th}$ percentile 15.0), respectively.[16] In addition, Zhang and co-workers in 2002, found that an absence of dilation change for 2 hours before 7 cm was common.[15] Other studies have also found that the transition from the latent to the active phase takes place later than previously described.[17, 18]

The historical definitions of labour progression have been reassessed in studies on contemporary populations. The study from the Consortium on Safe Labor includes singleton deliveries at term in vertex presentation with vaginal deliveries and normal perinatal outcomes. The study population reflects current obstetric management, in which almost half the women received oxytocin and about 80% received epidural analgesia. The median duration for nulliparous women admitted at 4 cm was 5.3 hours and the 95$^{th}$ percentile 16.4 hours. The standard dilation rate for nulliparous women was 0.5-0.7 cm/h and for parous women 0.5-1.3 cm/hours.[19] This was substantially slower than the rates derived from Friedman's work. According to this study, labour may take longer than 6 hours between 4 and 5 cm and longer than 3 hours to progress from 5 to 6 cm dilation for both nulliparous and parous women. Thereafter, labour accelerates much faster in parous women (Figure 2.4).[19] The authors suggest that dilation of 6 cm seems to be a better transition point between latent and active phase and that there is a non-linear relationship where absence of dilation for 4 hours may be normal in early labour but is prolonged after a dilation of 6 centimetres.[18, 19]

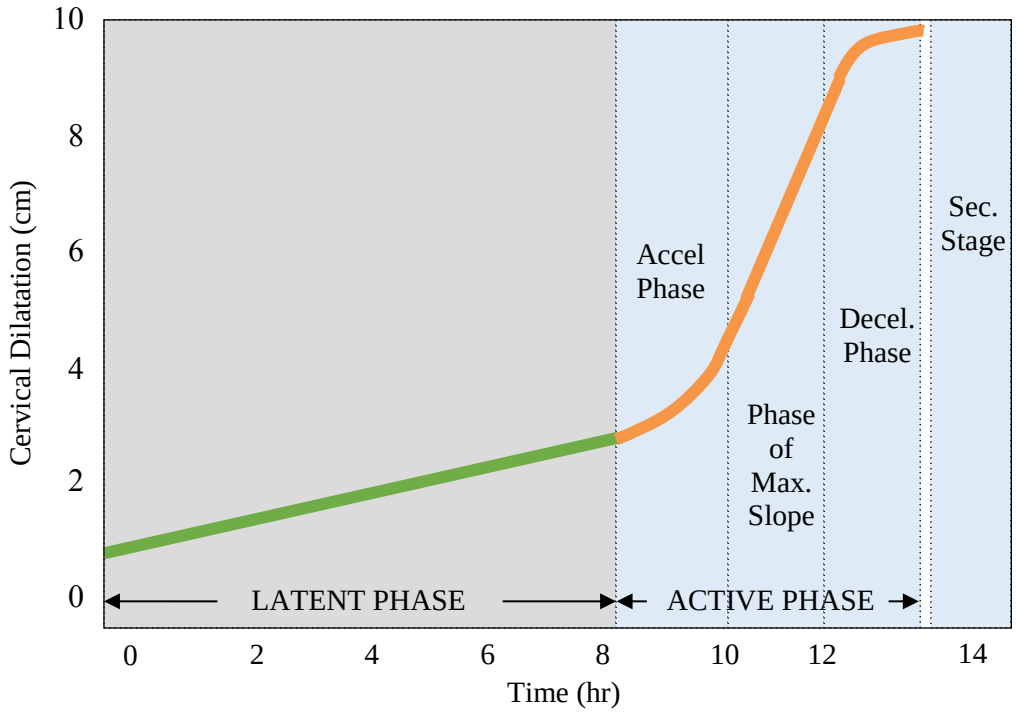



**Figure 2.3 Friedman's labour curve.** The mean labour curve, cervical dilation versus time, based on the study of 500 primigravidas at term.
*Friedman. Primigravid Labour, A graphicostatistical analysis. Obstet and Gynecol 1955.*

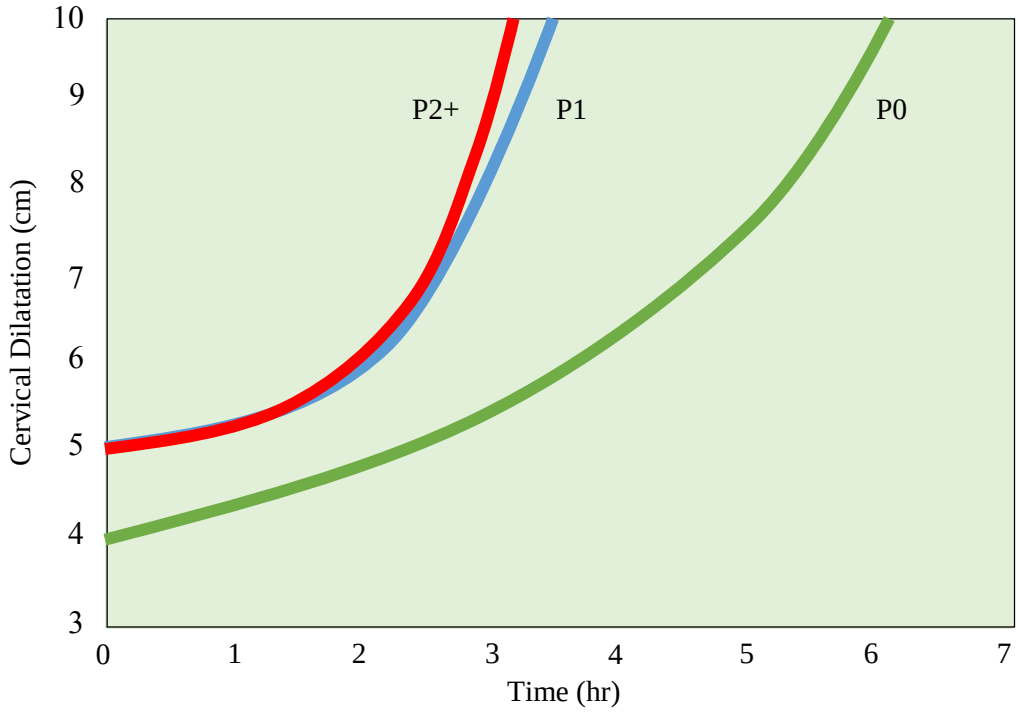



**Figure 2.4: Zhang's labour curve.** Average labour curves by parity in singleton term pregnancies with spontaneous onset of labour, vaginal delivery and normal neonatal outcomes. P0, nulliparous women, P1, women of parity 1, P2+, women of parity 2 or higher.
*Zhang. Contemporary Labour Patterns. Obstet Gynecol 2010.*

**Table 2.1: Definitions of the start of the active phase of first stage of labour according to British, Swedish and American guidelines.**

| Definitions of the start of the active phase of first stage of labour |
|---|
| ***U.K., NICE guidelines, 2014:***[20]<br>Regular painful contractions and progressive cervical dilation from 4 cm. |
| ***Swedish guidelines, National Board of Health and Welfare, 2001*:***[21]<br>Two out of three criteria's:<br>Cervical dilation of 3-4 cm<br>Three or more regular contractions every ten minutes<br>Rupture of the amniotic membranes |
| ***American College of Obstetricians and Gynecologists, 2003***:[22]<br>Cervical dilation of 3-4 cm |
| ***American College of Obstetricians and Gynecologists, 2014:***[23]<br>Cervical dilation of 6 cm (for most women, with reassuring fetal and maternal status) |

* A revised recommendation by the Swedish Association of Midwifes and Swedish Society of Obstetrics and Gynecology was made in 2015:[24] Two out of three criteria: Dilation of the cervix of 4 cm *or* complete effacement of the cervix and dilation of more than 1 cm, at least 2-3 spontaneous regular, painful contractions or spontaneous rupture of the membranes. Together with these criteria's, progress of the delivery must be documented within the following two hours.

**Second stage of labour**

The second stage of labour is defined as the duration from complete cervical dilation until birth of the infant. It starts with the descending phase, also called the passive phase, with passive descent of the fetal head. The passive phase is followed by the active phase, also known as expulsive phase, bearing down or pushing. The active phase of second stage of labour begins either when contractions become expulsive or by voluntary active pushing by the woman.[25] The clinical routine in Sweden is "delayed pushing", i.e. to start active maternal expulsive efforts when the woman either feels a strong urge to push or, when the fetal vertex is by or close to the pelvic floor.[26]

In the work performed by Friedman, the mean duration of the second stage of labour was 57 minutes in nulliparous and 18 minutes in parous women.[11] When excluding caesareans, the mean duration in nulliparous was 103 minutes, and 33 minutes in parous women in another report.[27] Longer durations have been described with the use of epidural. In a study in 1989, the mean duration for nulliparous women without and with epidural analgesia was about 50 minutes (95$^{th}$ percentile: slightly more than 2 hours) and about 1 hour and 20 minutes (95$^{th}$ percentile about 3 hours), respectively. For parous women without epidural about 20 minutes (95$^{th}$ percentile about 1 hour) and with epidural, 45 minutes (95$^{th}$ percentile slightly more than 2 hours).[28, 29] In the study by Consortium on Safe Labour, the median duration of second stage for nulliparous women without epidural analgesia was 36 minutes (95$^{th}$ percentile 2 hours and 48 minutes). The corresponding median duration for nulliparous women with epidural was 1 hour and 6 minutes (95$^{th}$ percentile 3 hours and 36 minutes).[19]

The normal upper limit for duration of second stage of labour in nulliparous women has historically been 2 hours. This limit was established already at the beginning of the 20$^{th}$ century. In a landmark

study from 1952, an increased infant mortality was reported after 2.5 hours and the 2-hour rule became the standard.[30] The decision to increase the thresholds of duration of second stage by an additional hour with the use of epidural analgesia, was influenced by a study by Cohen et al in 1977.[31] Until recently, the normal duration of second stage of labour for nulliparous has commonly been defined as 2 hours and 3 hours, the upper limit with epidural analgesia. The corresponding limits for parous women have been 1 and 2 hours, respectively (Table 2.3).[29]

## Biological changes during pregnancy and parturition

The parturition is a multifactorial physiologic process, a culmination of series of integrated biochemical events, leading to gradual changes in myometrium, decidua and the uterine cervix. The timing of labour is based on a complex interaction between the mother, fetus and the placenta. The uterus consists mainly of muscular tissue, and the myometrium enables growth of the fetus and the placenta. Meanwhile, there is a myometrial unresponsive state through the action of various inhibiting substances and hormones.[32] To enable parturition, the myometrium must be converted from this quiescent state and become a highly coordinated, contractile organ. The fetus probably influences this conversion in myometrial activity by affecting placental steroid hormone production, by mechanical distention of the uterus and by the secretion of hormones and other stimulators of prostaglandin synthesis.[33]

The non-pregnant cervix consists mostly of extracellular matrix while muscle fibres only constitute a small part. The ripening process mainly involves changes in the extracellular matrix. This partly inflammatory process, starts already in the first trimester, with a gradual decrease in extracellular matrix proteoglycans and collagen.[34] Just before or at the start of labour, an inflammatory reaction, which is characterised by the presence of pro-inflammatory cytokines and leukocytes takes place.[35] This remodelling leads to softening, effacement and dilation of the cervix and allows the passage of the fetus into the birth canal.

Additional changes involve a shift from progesterone dominance in favour of estrogen, increased responsiveness to oxytocin, and actions of prostaglandins and relaxin. Increased formation of gap-junctions between myometrial cells allows transmission of the contractile signal.[32, 33]

The composition of proteoglycans in the extracellular matrix alters during pregnancy and delivery. Levels of heparin sulphate proteoglycans increase during labour[36, 37] and could play a role in myometrial contractility.[37] Compared to normal labour, the heparin sulphate proteoglycan syndecan 3 decreases in protracted labour.[38]

Low-molecular weight heparin (LMWH) is a form of antithrombotic drugs. These are used during pregnancy as prophylaxis for or treatment of venous thromboembolism as well as for some clinically practiced indications during pregnancy. The effects of LMWH on myometrial contractility and interleukin secretion from cervical cells as a part of the cervical remodelling has been described in an in vitro study.[39]

### Montevideo Units

To evaluate the uterine contraction pattern, Montevideo units (MVU) are used. MVUs are calculated by subtracting the baseline uterine pressure (mmHg) from the peak contraction pressure and summarising the intensity of each contraction in a 10-minute period. To record the baseline intrauterine pressure in the uterus, an intrauterine pressure catheter is used. Generally more than 200 Montevideo Units during a 10-minute period are considered necessary for adequate labour during the active phase.

## 2.4 LABOUR DYSTOCIA

### 2.4.1 Definition

**Dystocia** - abnormal or difficult labour
*Dys* (greek) - a combining form signifying difficult, painful, bad, disordered, abnormal; the opposite of eu-
*Tokos* (greek) - birth

*Dorland's Illustrated Medical Dictionary, 28th Edition, 1994*[40]

"Dystocia literally means difficult labour and is characterized by abnormally slow labour progress".

*Williams Obstetrics 24th Edition, 2014*[41]

Other terms used equally for labour dystocia are prolonged labour, difficult labour, dysfunctional labour, failure to progress, cephalopelvic disproportion (CPD) and obstructed labour. The definition of dystocia is debated and there is no consensus. Dystocia can be diagnosed during the active phase of first stage or in second stage of labour including the descending and expulsive phases.

**Dystocia in the active phase of first stage of labour**

Dystocia in the active phase has been divided into protraction disorder: slower-than-normal progress and arrest disorder: complete cessation of progress. Based on Friedman's studies, the definition of protracted active phase with the 95th percentile has been cervical dilation of less than 1.2 cm/h for nulliparous and less than 1.5 cm/h for parous women.[11-13] Active phase *arrest* has traditionally been defined as the absence of cervical change for 2 hours or more in the presence of adequate uterine contractions (Table 2.2). These time limits have been the paradigm for labour management for more than half a century.

**Table 2.2: Traditional definitions of labour dystocia in active phase of first stage of labour.**

| Labour patterns during active first stage of labour | Nulliparous | Parous |
|---|---|---|
| <u>Protraction disorder</u> | | |
| Dilatation | <1.2 cm/h | <1.5 cm/h |
| Descent | <1.0 cm/h | < 2.0 cm/h |
| <u>Arrest disorder</u> | | |
| No dilation | >2 h | >2 h |
| No descent | >1 h | >1 h |

**Table 2.3: Definitions and recommended interventions for labour dystocia in Sweden, U.K. and the U.S.**

| **Swedish Society of Obstetrics and Gynecology's definition of ICD-10 codes for dystocia, 2014** |
|---|
| ***Primary dystocia:*** slow progress, dilation of the cervix less than 1 cm/hour during the active phase, cervical dilation ≥ 3-4 cm.<br>***Secondary dystocia:*** no progress for at least 2 hours after initially normal progress; down-bearing of the head is also progress.<br>***Prolonged first stage of labour:*** first stage (from 3-4 cm) of more than 15 hours in nulliparous and 11 hours in parous women.<br>***Prolonged second stage of labour:*** (for example >3 hours in nulliparous women) |

| **National Swedish guidelines: Indication for augmentation with oxytocin during active labour, 2011[26]** |
|---|
| Initiation of augmentation of labour with oxytocin is recommended if:*<br>***Active phase of first stage progress:*** less than 1 cm per hour for 3 hours<br>***Second stage progress:*** has ceased during descending phase for 1 hour, expulsive phase for 30 min<br>*Following conditions must be fulfilled: At most, 5 contractions in 10 minutes, no signs of fetal asphyxia, low probability of fetopelvic disproportion, ruptured membranes (spontaneous or by amniotomy), progress of the delivery is monitored, continuous cardiotocography (CTG) and information given to the woman |

| **U.K. NICE-guidelines[25]** |
|---|
| ***Second stage of labour:*** Nulliparous: delay should be diagnosed when the active second stage has lasted 2 hours, and most women are expected to be delivered within 3 hours. Corresponding duration for parous women are 1 hour, and 2 hours respectively. Suspect delay for nulliparous and parous women if inadequate rotation and/or descent of the presenting part after 1 hour and after 30 minutes of pushing, respectively. |

| **American College of Obstetricians and Gynecologist (ACOG) Practice Bulletin, 2003[29]** |
|---|
| "Before an arrest disorder can be diagnosed in the first stage of labour, the following two criteria should be met: 1) the latent phase is completed 2) a uterine contraction pattern exceeds 200 Montevideo units for 2 hours without cervical change"<br>The diagnosis of a prolonged second stage should be considered when the second stage exceeds 3 hours if regional anesthesia has been administrated or 2 hours if no regional anesthesia is used. In parous women, the diagnosis can be made when the second stage exceeds 2 hours with regional anaesthesia or 1 hour without:" |

**Table 2.3: Definitions and recommended interventions for labour dystocia in Sweden, U.K. and the U.S.**

| **Recommendations for the Safe Prevention of the Primary Caesarean Delivery**<br><br>American College of Obstetricians and Gynecologist (ACOG) and Society for Maternal, Fetal Medicine. Obstetric Care Consensus, 2014.[42] | |
|---|---|
| ***First stage of labor*** | |
| "A prolonged latent phase (e.g. greater than 20 hours in nulliparous women and greater than 14 hours in parous women) should not be an indicator for caesarean delivery". | 1B. Strong recommendation, moderate-quality evidence |
| "Slow but progressive labor in the first stage of labor should not be an indication for caesarean delivery". | 1B. Strong recommendation, moderate-quality evidence |
| "Cervical dilation of 6 cm should be considered the threshold for the active phase of most women in labor. Thus, before 6 cm of dilation is achieved, standards of active phase progress should not be applied". | 1B. Strong recommendation, moderate-quality evidence |
| "Caesarean delivery for active phase arrest in the first stage of labor should be reserved for women at or beyond 6 cm of dilation with ruptured membranes who fail to progress despite 4 hours of adequate uterine activity*, or at least 6 hours of oxytocin administration with inadequate uterine activity and no cervical change". | 1B. Strong recommendation, moderate-quality evidence |
| ***Second stage of labor*** | |
| "A specific absolute maximum length of time spent in the second stage of labor beyond which all women should undergo operative delivery has not been identified". | 1C. Strong recommendation, low-quality evidence |
| "Before diagnosing arrest of labor in the second stage, if the maternal and fetal conditions permit, allow for the following:<br>At least 2 hours of pushing in parous women<br>At least 3 hours of pushing in nulliparous women<br><br>Longer durations may be appropriate on an individualized basis (e.g., with the use of epidural analgesia or with fetal malposition) as long as progress is being documented". | 1B. Strong recommendation, moderate-quality evidence |

* More than 200 Montevideo Units

When diagnosing labour dystocia in the active phase, augmentation with oxytocin is usually recommended. According to the ACOGs recommendations from 2003, diagnosis of active phase arrest should only be made in the active phase and when there is no cervical change for a minimum of two hours with adequate uterine contractions (≥200 Montevideo units in a 10 minute period)(Table 2.3).[29] In studies of prolonged oxytocin augmentation in active phase from 2 hours to 4 hours, the vaginal delivery rates increased and seemed to be safe.[29, 43, 44] In their study, Zhang and co-workers found a non-linear relationship, where the absence of dilation for 4 hours may be normal in early labour but being prolonged after dilation of 6 centimetres.[19] This propose that there is not "one rule" for the whole active phase. The recommendations for safe prevention of primary caesarean, replacing previous ACOG guidelines for dystocia and augmentation of labour in 2003, are partly based on this study (Table 2.3).[29, 42] Oxytocin is indicated when cervical dilation rate is less than 1 cm/h for 3 hours, according to the Swedish national recommendations for augmentation with oxytocin (Table 2.3). Re-evaluation is recommended after at least 4 hours of optimal augmentation with oxytocin (i.e. 4-5 contractions every 10 minutes)[26]

**Dystocia in second stage of labour**

The following definition of prolonged second stage of labour has been widely used:
more than 2-3 hours for nulliparous and 1-2 hours for parous women; the upper limit is modified by the use of epidural analgesia.[29] Interventions only based on time are disputed, since this could lead to non-medically indicated instrumental vaginal and caesarean deliveries (Table 2.3). Women with epidural analgesia, delayed compared to immediate pushing is associated with a longer duration of the second stage of labour. Delayed pushing, however, is associated with a shorter duration of pushing and an increase in spontaneous vaginal delivery, compared to immediate pushing.[45, 46] According to Swedish recommendations, augmentation with oxytocin is recommended if there is absence of progress during the descending phase for 1 hour or for 30 minutes in the expulsive phase (Table 2.3).[26]

### 2.4.2 Prevention and treatment of labour dystocia

**The partogram**

A partogram, also known as partograph, is used to assess the progression of labour as well as to gather information about the maternal and fetal status during the parturition. Originally, the partogram was implemented to prevent prolonged and obstructed labour, to increase the safety for labouring women and their infants, especially in developing countries. Friedman introduced the first graphically presented tool for labour progress.[10] This eventually became a partogram with two diagonal parallel straight lines.[47] The alert line was evolved and represented the modified mean rate of cervical dilation of the slowest 10% of nulliparous women in the active phase.[48] This corresponds to a cervical dilation of 1 cm per hour. The action line is usually placed two to four hours after the alert line to notice slow labour progress (Figure 2.3). The partogram is now a part of routine labour care in most parts of the world.

In a study by the World Health Organization (WHO), the introduction of the partogram reduced prolonged labour and the proportion of labours requiring augmentation, rates of emergency caesarean section and stillbirths and was therefore recommended.[49] In the partogram by WHO, less than 1 cm/h for a minimum of 4 hours demands action.

The use, benefits and potential risks of unnecessary interventions of a partogram is likely to be influenced by health care providers, socioeconomic settings as well as cultural differences. The

benefits and harms of partogram use has been assessed in a Cochrane review in 2014. Use versus no use of a partogram was compared as well as different action line designs. Use compared to non-use of partogram did not demonstrate any differences in caesarean section rates, instrumental vaginal deliveries or infant Apgar score <7 at 5 minutes.

Compared to women in the four-hour action line group, women in the two-hour action line group were more likely to receive oxytocin augmentation. When the three- and four-hour action line groups were compared, the caesarean section rates was lowest in the four-hour action line group. No explicit recommendation regarding the use of the partogram was made.[50]

Other trials have concluded potential benefits of the partogram.[51, 52] The partogram is a simple and objective tool, well implemented in obstetric practice. The discussion instead concerns how it should be designed to optimize the safety of the mother and the infant as well as not increase unnecessary interventions.

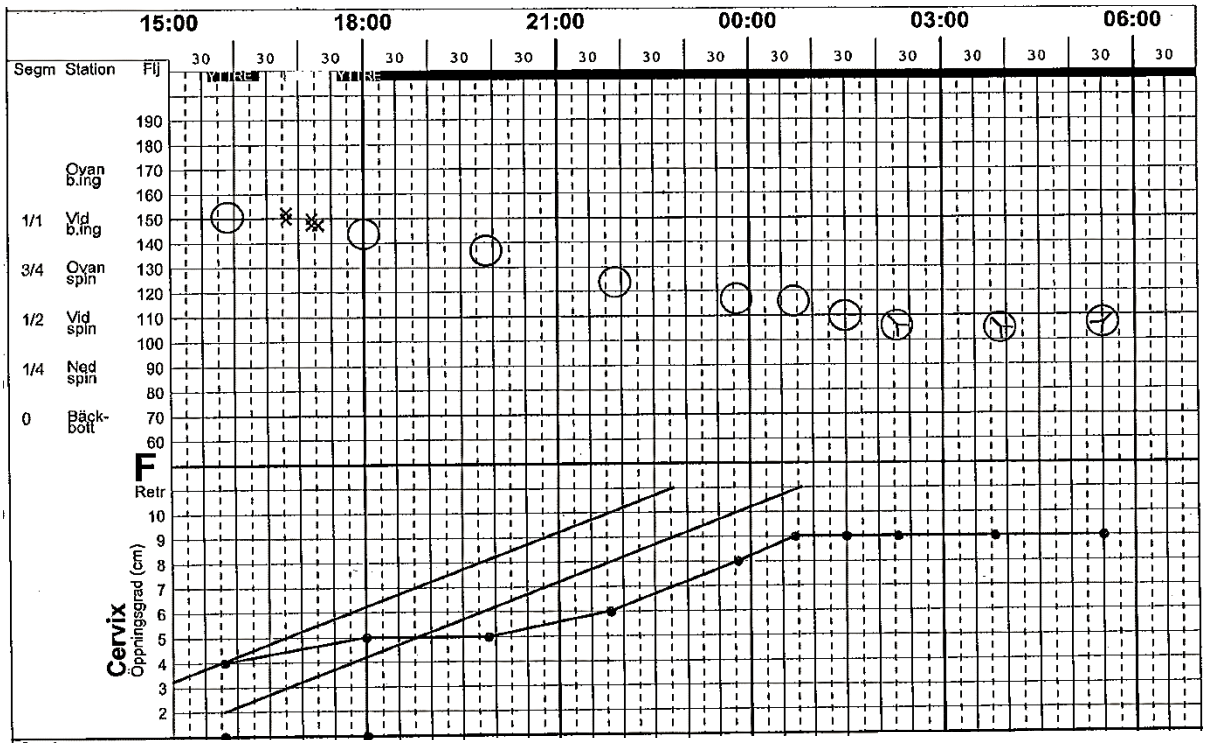



**Figure 2.3: A partogram with prolonged first stage of labour.** The fetal head station and cervical dilation plotted against time.

### Amniotomy

Amniotomy is an intentional artificial rupture of the amniotic membranes. It is one of the most commonly performed interventions during labour. The procedure can be used for induction of labour. In active labour, amniotomy can be performed either to prevent prolonged duration or therapeutically when slow progress is already established. A possible explanation for the effects of amniotomy is a release of endogenous prostaglandins and oxytocin, influencing the cervix and the uterus. This intervention has been recommended as a routine procedure during labour under the concept of active management of labour.[53]

A meta-analysis of spontaneous labours, comparing routine amniotomy with keeping membranes intact for as long as possible, showed no significant difference in the duration of first stage between the groups. When restricted to nulliparous women, a non-significantly shorter duration of 58 minutes

(95% CI -153 to 37 minutes) was found in the amniotomy group.[54] When analysing only the three largest studies that included nulliparous women, a significantly shorter duration was observed.[55-57] Additional outcomes, including caesarean section, 5-minute Apgar score <7, use of pain relief and the childbirth experience did not vary between the groups. In women with spontaneous labours with normal progress, there was a significant reduction of oxytocin augmentation in the amniotomy group.[54]

The effect of amniotomy, compared to preserved membranes in spontaneous labours with slow progress during the active stage was assessed in a small study. In the amniotomy group, a non-significantly decreased duration of labour by 57 minutes was found. Any differences in risks of caesarean section for fetal distress or prolonged labour was not demonstrated.[58] Rouse and co-workers randomised women with prolonged first stage to oxytocin with intact membranes or oxytocin following amniotomy and found a non-significantly shorter duration of labour until birth (-44 minutes, p=0.11)[59]

With a mild delay in progress, preventively early amniotomy together with oxytocin is associated with a shorter duration of labour (average mean difference -1.28 hours [95% CI -1.97 to -0.59]) and a reduction of caesarean section rates compared to expectant management.[60] Early amniotomy increases severe variable fetal heart rate decelerations without any adverse effects on neonatal outcomes.[61]

**Oxytocin**

Endogenous oxytocin is a neuropeptide hormone and plays an important role in a wide range of human functions including the labour process, milk ejection during lactation, and the facilitation of social interaction. The hormone is mainly produced in the hypothalamus and pulsatile released into circulating blood via the pituitary gland.

Intravenous oxytocin is commonly used during labour and can be applied in all stages. Oxytocin can be administrated for induction in the latent phase, for augmentation in the first and second stages and for prophylaxis or treatment of bleedings in the third stage of labour (i.e. after the birth of the infant until the delivery of the placenta). During the active phase of labour, the aim of using oxytocin is to produce sufficient uterine activity for cervical change and fetal descent while avoiding uterine hyper-stimulation (more than 5 contractions in 10 minutes, contractions lasting 2 minutes or more, or contractions within one minute of each other with normal duration) and fetal compromise.[29]

The half-life of oxytocin is 10-15 minutes. After an increase in the infusion rate, the steady-state dose is reached after about 40 minutes. To perform effective contractions, the required dose of oxytocin varies widely.[62] Oxytocin is administrated during labour for 33-75% of nulliparous and 14-38% of parous women in Sweden according to studies before the national recommendations of augmentation with oxytocin were implemented.[26, 63-65]

Augmentation with oxytocin and hyper-stimulation are associated with fetal distress.[66, 67] Hyperactive labour, most commonly with oxytocin augmentation, and the misuse of oxytocin are strongly associated to academia at birth.[68, 69] In a study of women seeking financial compensation because of suspected malpractice in relation to childbirth, the most common events of malpractice were neglecting to supervise fetal wellbeing including signs of asphyxia, and incautious use of oxytocin.[70]

A literature review was made for the "Swedish National Recommendations for Oxytocin during active labour". The following conclusions were drawn:

- When cervix dilation is <1 cm/hour for two hours in the active phase, administration of oxytocin significantly decrease the labour duration and a doubles the risk of hyper-stimulation compared to administration of oxytocin after 3-8 hours.[26]

**Active management of labour**

The concept of "active management of labour" was first advocated in Ireland by O'Driscoll and colleagues in the 1970ies.[53] The purpose of this labour ward protocol for low-risk nulliparous women, was to reduce the length of labour and later on, additionally the caesarean section rates.[71] Since then, the concept has been adopted in modified forms world-wide. A prolonged labour was defined as more than 12 hours, a maximum duration of 10 hours for the first stage and 2 hours for the second stage.

The original concept included:

- One-to-one support in labour (continual support by nurse/midwife during labour)
- Routinely amniotomy early
- Use of oxytocin, early if slow progress
- Strict criteria for the diagnosis of labour
- Strict criteria for identifying progress in labour (using the partogram)
- Strict criteria for identifying slow progress and fetal compromise
- Peer review of assited deliveries

A meta-analysis of studies comparing "active management of labour" with routine care found a non-significant reduction in caesarean section rates in the active management group (RR 0.88 95% CI 0.77-1.01). After the exclusion of one study with a large proportion of post-randomisation exclusions, this effect was statistically significant (RR 0.77 [95% CI 0.63-0.94]). The risk of prolonged labour was decreased by 50% and the duration of first stage of labour was 1.5 hours shorter in the active management group. Second stage duration was not significantly influenced. Neonatal outcomes were not affected.[72] In another meta-analysis, continuous support alone compared to routine care, significantly reduced the duration of labour and the risk of having a caesarean section.[73]

### 2.4.3 Pathophysiology

Historically, the causes of dystocia has been attributed and described as the four "P's":

Power: Abnormal expulsive forces of the uterus. Uterine contractions may be *hypothonic:* the contractions are synchronous but the pressure during a contraction is insufficiently strong, or *hypertonic:* either the basal tonus is elevated or the contractions are inappropriately coordinated to efface and dilate the cervix. Voluntary maternal effort during the pushing phase can also be ineffective.

Passenger: Abnormalities of the fetal presentation, position, or development. This includes macrosomia, malposition and congenital malformations.

Passage: The pelvis. Soft tissue abnormalities of the reproductive tract. Abnormalities of the bony pelvis may create a contracted pelvis.

Psyche: The psychological state of the mother.

Cephalopelvic disporportion: the term was introduced before the 20$^{th}$ century to describe obstructed labour resulting from divergence between the measurements of the fetal head and the maternal pelvis. By then, the main indication for caesarean section was rackets. Nowadays, the bony pelvis rarely limits vaginal deliveries. Today, most cases of cephalopelvic disporportion, results from malposition such as asynclitism, macrosomic fetus or from ineffective uterine contractions. The descent of the fetus occurs mainly after the cervix is fully dilated. Thus, disporportion is usually diagnosed in the second stage.

### 2.4.4 Incidence proportion

The cumulative incidence (incidence proportion) of dystocia during delivery is inherently difficult to assess due to different definitions, study populations and clinical practices related to the condition. According to recent studies, about 21-37% of nulliparous, and 2-10% of parous women are affected by dystocia.[63, 74-77]

In a population of low-risk women, 20% experienced a prolonged active phase of the *first stage* based on Friedman's criteria.[14] According to a Danish study of nulliparous women, the cumulative incidence of dystocia was 37%, and 61% of the cases were diagnosed in the *second stage* of labour.[75] Other recent studies have demonstrated an incidence of prolonged *second stage* of labour in 7-15% in nulliparous and 3-6% in parous women reaching *second stage*.[78-81] In nulliparous women stratified by use of epidural, 16.2% with and 31.1% without epidural were affected. The corresponding numbers for parous women were 7.7% and 18.9%, respectively.[82]

Studies on contemporary populations report longer durations of *first* and *second stages* for nulliparous women than earlier reports.[14, 16, 19, 78, 82, 83] This could be due to several factors. Delivering women of today are older and have higher BMI. Obstetric practice has changed considerably over the last half a century. Use of oxytocin and epidural analgesia has become far more common. Contemporary practice implies lower rates of breech vaginal deliveries, instrumental vaginal deliveries, especially mid forceps, and higher rates of caesarean sections. In addition, fetal heart rate monitoring is part of the common practice nowadays.[16]

### 2.4.5 Risk factors

Most of the studies referred to in this thesis are derived from populations of term and postterm pregnancies (some from gestational weeks 35 and 36).

**Parity**

It is well known that labour dystocia is more common among nulliparous than among parous women.[74, 77, 84, 85] Accordingly, parous women without previous vaginal delivery, have an increased risk of dystocia than other parous women.[74, 86] Failure to progress in *first stage* leading to caesarean as well as prolonged *second stage*, primarily affects nulliparous women.[87, 88] Nulliparity is also associated with an increased risk of interventions due to arrest during the pushing phase of *second stage*.[89] The proportion of secondary arrest, compared to primary dysfunctional labour, is greater among parous than among nulliparous women with labour dystocia.[90]

**Maternal age**

Advancing maternal age is associated with labour dystocia.[87, 91, 92] One study found that older nulliparous women had longer durations and higher rates of dystocia in both *first* and *second stages*, compared to younger women. For parous women, there were no relation between *first stage* and maternal age after adjustments. Yet, an increased risk of prolonged *second stage* was seen among older parous women.[84] Some studies have not found any association between maternal age and labour duration.[27, 93] In a recent study, however, duration of *first stage* of labour decreased with advancing maternal age in both nulliparous and parous women. The *second stage* of labour increased with age in nulliparous women with and without epidural. For parous women, age did not influence the duration of *second stage*.[94]

**Maternal Body Mass Index**

In a study by Kominiarek and co-workers, women with high Body Mass Index (BMI) displayed a longer *first stage*, especially among nulliparous women. For parous women, the entry to the active phase of 6 cm was found to be delayed among obese women.[95] These results are supported by other studies of nulliparous and mixed parities, demonstrating slower labour progression in *first stage* in overweight and obese women.[96-98] Nevertheless, obese and normal-weight women are equally able to reach ≥200 Montevideo units.[97] Caesarean delivery rates due to prolonged *first stage* of labour in addition to dystocia overall, increases with BMI.[99-101]

The duration of *second stage* does not seem to vary for different BMI categories in nulliparous women.[95, 102] In one study, the duration of second stage for parous women even decreased as BMI increased.[95]

**Additional maternal factors**

Ethnicity seems to influence the duration of the *second stage* and the risk of dystocia in *second stage* in contrast to the duration of *first stage*.[103] When adjusted for potential confounders, fertility treatment, hypertensive disorders, gestational diabetes, polyhydramnios and premature rupture of membranes (PROM) were all associated with failure to progress in *first stage* of labour leading to caesarean delivery, in one study.[87] In addition, polyhydramnios, hypertensive disease, gestational diabetes and PROM have also been associated with prolonged *second stage*.[88] Inter-pregnancy interval and short maternal stature are associated with labour dystocia in a dose-response fashion.[85, 92] Maternal fear of childbirth has also been associated with increased duration of labour.[104]

**Delivery characteristics**

Clinical characteristics present at admission to the delivery ward, such as being in latent phase (<4 cm), having a tense cervix, a high fetal head station, and poor fetal-to-head cervix contact are associated with dystocia.[105] Occiput posterior position and high fetal head station at complete dilation of the cerivix are related to prolonged *second stage* of labour.[27, 106-108] A prolonged latent phase increases the risk of labour dystocia, including prolonged *first* and *second stages*.[109, 110] Increasing gestational length and post-term pregnancy are associated with labour dystocia in both *first* and *second stages* of labour.[74, 78, 111] Studies regarding induction of labour and the association with labour dystocia demonstrate different results. Induction of labour has been described associated with labour dystocia.[87, 88] However, in women with vaginal deliveries, active phase arrest was less common in induced labours in one study.[86] Electively induced labour with cervical ripening has been associated with slower early active phase and increased risk of caesarean during first stage. Elective induction without cervical ripening, was however associated with a shorter duration of first stage of labour and no increased risk of caesarean delivery compared to spontaneous delivery.[112] The duration of second stage did not differ according to induction status in one study.[113] When comparing induced labours with deliveries at a greater gestational age, women induced at 39 weeks had a lower risk of labour dystocia.[114]

**Fetal characteristics**

Mothers of macrosomic infants (birth weight >4000 g or >4500 g) have increased rates of prolonged labour[115] and risk of labour dystocia.[74, 75, 116] Compared to normal weight infants, birth weight of >4000 g is associated with duration of *first stage* of labour greater than the 95$^{th}$ percentile.[111] Moreover, the risk of failure to progress in the *first stage* leading to a caesarean section, is increased.[87] Rates and risks of a prolonged *second stage* of labour are significantly associated with birthweight >4000 g.[81, 88]

**First and second stages of labour**

The length of the *second stage* is associated with the duration of *first stage*, regardless of potential confounders. In one study, 16% of women with a *first stage* duration greater than that of the 95$^{th}$ percentile had a *second stage* exceeding 95$^{th}$ percentile, compared to 4% in deliveries with a *first stage* of less than 95$^{th}$ percentile.[117] These results are supported by another study with a corresponding 2.5-fold increased risk.[118]

Women with prolonged *first stage* of labour had more commonly high-risk pregnancies in a study comparing risk of failure to progress in the *first* versus the *second stage* of labour. Compared to women with prolonged *second stage* of labour, women with prolonged *first stage* were older, parous, had postterm pregnancies and macrosomic infants. They were also more likely to have a history of perinatal death, habitual abortion, and infertility treatment than women with a prolonged *second stage*. Inductions and complications such as hypertensive disease, diabetes, PROM, meconium-stained amniotic fluid, poly- and oligohydramnios and non-reassuring monitoring were also more common among women with prolonged *first stage* compared to women with prolonged *second stage* of labour.[119]

Delayed pushing, compared to immediate pushing, has been associated with an increased overall duration of second stage. With delayed pushing, however, the total duration of pushing decrease and spontaneous vaginal delivery rates increase.[45]

### 2.4.6 Epidural analgesia

Epidural analgesia is a central nervous blockade where local anaesthetics are injected into the distal part of the spinal epidural space. When crossing the epidural space, the anaesthesia inhibits painful nerve impulses. The local anesthetics have a dose-response effect on the sensory and motor functions. A lower dose selectively blocks painful stimuli partially, while higher doses also affect motor functions. Blocking of the sympathetic nerves results in vasodilatation and hypotension. Previously, higher concentrations of anesthesia were used with a dense motor block that led to a reduced mobility, decreased pelvic tone and influence on the *second stage* of labour. Nowadays, a lower concentration of local anesthesia combined with different opiates is used, which has no influence on motoric functions.[120]

In a Cochrane review from 2011, including 38 randomized controlled trials, epidural analgesia was compared to opiates in all studies but five, with regard to obstetric outcomes. Women treated with epidurals experienced better pain relief, a reduction in need for additional pain relief and a reduced risk of naloxone administration. The mothers in the epidural group had a significantly increased risk of fever and urinary retention. The use of epidural analgesia did not significantly affect the duration of *first stage* but was associated with a prolonged duration of *second stage* of labour. The mean difference was 13.7 minutes (95% CI 6.7-20.7) and there were also increased risks of instrumental vaginal delivery (1.42 [95% CI 1.28-1.57]) and oxytocin administration. The overall risk of caesarean section or caesarean due to dystocia did not increase significantly in the epidural group. Although, there was an increased risk for caesarean section for fetal distress (RR 1.43 [95% CI 1.03-1.97]). Epidural analgesia was not found to be associated with adverse neonatal outcomes, and the risk of acidosis was even significantly reduced. A substantial heterogeneity for the length of *first* and *second stages* of labour and for oxytocin augmentation in the studies, was reported in the review.[121]

In other studies and reviews, including both randomized controlled trials (RCT) and observational studies, the association between epidural analgesia and a prolonged *second stage* is similar to the

Cochrane analysis. The influence of epidural analgesia on the duration of *first stage* of labour, however, remains unclear. It seems as though RCTs tend to underestimate the true differences while observational studies overestimate the differences in labour duration.[122-124]

There is no evidence of an increased risk of caesarean section or instrumental vaginal birth with early verses late initiation of epidural. The duration of *second stage* of labour is not affected by the timing of epidural analgesia. There is no consensus about the effects on the *first stage* of labour. Adverse neonatal outcomes, such as low Apgar scores and acidosis, did not differ with the time of epidural.[125, 126] In the study by Consortium on Safe Labour, the median duration of *second stage* for nulliparous women without epidural analgesia was 36 minutes (95$^{th}$ percentile: 2 hours and 48 minutes). The corresponding median duration for nulliparous women with epidural was about 1 hour (95$^{th}$ percentile: 3 hours and 36 minutes).[19]

### 2.4.7 Mode of delivery

Dystocia is the most common indication for a primary caesarean section. Since many repeat caesareans are the result of previous caesarean for dystocia, prolonged labour leads to a great number of caesareans.[127 29, 128] The increase in emergency caesarean section rates in Sweden during the past few decades, is partly due to dystocia.[129]

In women who experience active phase arrest in the *first stage*, 67% were delivered by caesarean section using the 2-hour augmentation rule.[86] In another study with oxytocin augmentation for two hours after the diagnosis of active phase arrest, the vaginal delivery rates were 74% and 91% for nulliparous and parous women, respectively. After 4 hours of augmentation with oxytocin, the corresponding rates were 56% and 88%, respectively.[43, 44] The caesarean section rates during *first stage* of labour are largely dependent on the definition of and clinical guidelines for dystocia in *first stage*.

As the duration of the *second stage* of labour and pushing increases, the proportion of spontaneous vaginal deliveries progressively decreases.[79, 130, 131] In nulliparous women reaching the *second stage*, spontaneous vaginal delivery rates were about 60% with a *second stage* of 2-3 hours, and 25% with a *second stage* of 3-<5 hours. The corresponding rate for a duration of 5 hours or longer was 9%.[80] According to another study of nulliparous women with prolonged *second stage*, 80% of those women with epidural and 87% of those without delivered vaginally. Corresponding rates for parous women were 89% and 96%, respectively.[79] In a study of parous women, about 60% had a spontaneous vaginal delivery after a *second stage* of 2-3 hours.[132]

With active pushing in nulliparous women with labour analgesia, the chances of spontaneous vaginal delivery of an infant without signs of asphyxia were about 20% after 2 hours and after 3 hours or more about 10%.[131] Corresponding rates for spontaneous vaginal delivery in another study were 40% after 3-4 hours of active pushing.[130]

### 2.4.8 Maternal consequences

A prolonged *first stage* of labour is associated with maternal fever, chorioamnionitis and endometritis, also when restricted to vaginal deliveries.[43, 44, 86, 111, 118] With active phase arrest, compared to vaginal deliveries, caesarean deliveries are strongly associated with increased risk of chorioamnionitis, endometritis and postpartum haemorrhage.[86] In one study of vaginal deliveries with prolonged *first stage* of labour, rates of 3$^{rd}$ and 4$^{th}$-degree perineal lacerations, postpartum haemorrhage and

endometritis increased, but were no longer statistically significant after adjustments.[86] These results are supported by other studies.[111]

A prolonged *second stage* of labour is associated with adverse maternal outcomes such as postpartum haemorrhage, fever and infection, including chorioamnionitis, urinary retention, third-and fourth degree lacerations, instrumental vaginal deliveries and episiotomy in both nulliparous and parous women.[75, 78-80, 131-136] Since a prolonged *second stage* is associated with instrumental deliveries, and associated maternal complications, the causality between the actual prolonged *second stage* and maternal morbidity is still unclear.[31, 137-139] In a study of nulliparous women by Allen and co-workers, the risk of composite maternal morbidity increased with duration of *second stage*, in spontaneous and instrumental vaginal deliveries. The risks were, however, considerably higher among instrumental deliveries compared to spontaneous vaginal deliveries.[78]

In the study by Allen and co-workers, there was no association in spontaneous vaginal deliveries between duration of *second stage* and chorioamnionitis. In caesarean deliveries, however, an increased risk of chorioamnionitis was found for all durations compared to duration of 2 hour or less in vaginal deliveries.[78] Longer labour may lead to an increased risk of choriomnionitis, but on the other hand, having chorioamnionitis may increase the risk of dysfunctional contractions and lead to a prolonged labour.[111]

Additional but rare complications that are associated with prolonged labour are uterine rupture, especially among parous women with previous caesarean section.[140] In low income countries, fistulas can be seen as a secondary effect of pressure necrosis after a very prolonged *second stage*.[141] Lumbosacral spine and lower extremity nerve injury, usually involving the common fibular nerve, is more common in women with prolonged *second stage* of labour.[142] A prolonged labour is also associated with worse labour pain than expected and a negative labour experience compared to a normal labour duration.[143, 144]

### 2.4.9 Neonatal consequences

**First stage of labour**

Compared to a *first stage* shorter than the 95$^{th}$ percentile, a duration exceeding the 95$^{th}$ percentile was in one study associated with an almost double increased adjusted risk of a composite neonatal outcome (shoulder dystocia, admission to level 2-3 nursery, 5-minute Apgar score <3, arterial cord pH <7.0, cord base excess -12 or less). Shoulder dystocia, admission to NICU and 5-minute Apgar score <3 (with 97$^{th}$ percentile cut off) were also increased in unadjusted analyses.[118] In another study, the adjusted risk of admission to NICU was increased when the duration exceeded the 95$^{th}$ percentile.[111]

Other reports of adverse neonatal outcomes and labour dystocia in the *first stage* are based on Friedman's definitions. In a study stratified by vaginal or caesarean deliveries, prolonged *first stage* was associated with a significantly increased risk of shoulder dystocia in vaginal deliveries. Irrespective of mode of delivery, association with other neonatal complications was not found.[86] This was supported by another study[44], while the rate of *first stage* of labour was not associated with shoulder dystocia in a case-control study.[145] Increased incidence of 1-minute, but not 5-minute Apgar score of <8 in nulliparous women and 1-minute and 5-minute Apgar score <7 in mixed parities have been reported.[75, 87] In studies of prolonged oxytocin augmentation (more than 2 hours) for active phase arrest, no adverse neonatal outcomes were found compared to standard practice, although these findings were based on few observations.[43, 90]

**Second stage of labour**

Associations between prolonged duration of *second stage* and adverse neonatal outcomes have been investigated in numerous papers, but results remains unclear. In the setting of available fetal monitoring, a number of studies have not found any association between prolonged *second stage* and adverse neonatal outcomes in nulliparous and mixed parities.[133-135, 146, 147]

Other studies demonstrate an association between prolonged *second stage* and adverse neonatal outcomes among nulliparous women. Increased risk of neonatal complications including admission to NICU, birth asphyxia, birth trauma, low 5-minute Apgar score, sepsis, seizures and perinatal mortality have been demonstrated.[78, 79, 81] Rouse and co-workers, found an increased need for admission to NICU, but not for other adverse outcomes.[80] Risk of birth trauma was found in the study by Cheng and co-workers, but no other neonatal outcomes were reported.[82]

In parous women, low 5-minute Apgar score, birth depression, minor trauma, NICU admission and overall perinatal morbidity have been reported increased to follow *second stage* durations of 1 hour or longer.[78] These results are supported by another study where a duration of *second stage* of 3 hours or more was associated with most of these adverse outcomes.[132] In a study stratified by epidural analgesia, parous women with epidurals had an increased risk of low 5-minue Apgar score with prolonged second *stage*. In the non-epidural group, risks of shoulder dystocia and perinatal mortality increased.[79] In parous women, composite adverse outcome has been reported to increase after only one hour of active pushing.[130]

Composite adverse neonatal outcomes and neonatal acidosis are associated with longer duration of pushing in two studies.[130, 148] While no such relation was found in another study.[131] According to a Cochrane review, there are no differences between immediate and delayed pushing with respect to most neonatal adverse outcomes.[45] One study found, however, an association between delayed pushing and low umbilical arterial pH (<7.10).[46]

# 3 HYPOTHESIS AND OBJECTIVES

## Hypothesis

Maternal characteristics, and interventions during pregnancy and delivery, influence the risk of labour dystocia, including a prolonged second stage of labour. This consequently influences the risk of adverse neonatal outcomes.

## Objective

The overall objective of the thesis was to increase knowledge about factors influencing labour dystocia and consequences of labour dystocia on mother and infant.

## Specific objectives

- To explore the risk of recurrence of labour dystocia according to maternal characteristics and previous delivery outcomes (I).
- To analyse the possible influence of low-molecular-weight heparin during pregnancy on the risk of labour dystocia (II).
- To assess the association between duration of second stage of labour and risk of a low infant Apgar score (III).
- To analyse the association between increasing durations of the second stage of labour and pushing and risk of adverse neonatal outcomes (IV).

# 4 MATERIAL AND METHODS

## 4.1 SETTING

The studies in this thesis were all conducted in Sweden where there are unique possibilities to perform epidemiological research.[149, 150] This is partly due to the structure of the health care system, the national registration numbers and the nationwide registers. As mentioned previously in the background, all pregnant women are offered free health care in Sweden, and the level of insurance does not influence the care provided. As a result of almost complete coverage of the national registers, study populations can be selected in an essentially non-biased manner.

**The Swedish Personal Identity Number**

A unique national registration number is assigned to all inhabitants in Sweden at birth or on immigration. It was introduced in 1947, initially with a nine-digit number, and in 1967 it became a ten-digit number. It includes six digits giving year, month and date of birth and four digits which make it unique for all individuals. Due to this registration number which is used in Swedish health care registers and in medical records, it is possible to establish links between different data sources.[151]

## 4.2 DATA SOURCES

### 4.2.1 The Swedish Medical Birth Register

The primary source of information for studies I and II is the Swedish Medical Birth Register (MBR). The register is population-based and is held by the National Board of Health and Welfare. More than 98% of all births in Sweden from 1973 and onwards are included.[152, 153] Women and their infants are linked in the register. Prospectively collected information during pregnancy, delivery and the neonatal period are continuously entered through structured forms filled out by midwives and physicians. Demographic data, reproductive history, smoking, assisted reproduction, maternal comorbidity and drug treatments are recorded at the first antenatal visit, usually in the first trimester. Throughout pregnancy information is continuously added. Delivery characteristics such as time of birth, maternal age, parity, onset and mode of delivery, labour analgesia, fetal presentation, medical diagnoses and diagnoses of procedures are recorded during delivery or at discharge from the delivery hospital. Diagnoses are classified according to the Swedish version of the International Classification of Diseases (ICD), revisions 8-10. Information regarding the infant as a single or multiple birth, stillborn or born alive, gestational age, birth weight, length and head circumference, sex, Apgar score, malformations and other diagnoses (classified according to ICD) during the neonatal period are recorded.

The MBR has been evaluated three times and the first two were summarised in a study from 1990.[152] The results of the third evaluation were reviewed in a summary by the Centre for Epidemiology at the National Board of Health and Welfare in 2003.[153] They concluded that there are errors in the data recorded and that some data is missing, as with all large registers. However, only 1.4% of all infants born in Sweden were not recorded during the time-period examined (1973-1998). Regarding specific variables, there were differences in data loss, but for most variables, information was lacking for only a few percent. The most substantial information loss was observed for infant diagnoses, particularly for infants who were admitted to neonatal wards. For variables such as gestational duration, systems based on hierarchy were used to find the most accurate information

derived from the medical records.[153] The national mean of data loss on variables from the antenatal care records in 2014 was about 3%.[8]

### 4.2.2 The Swedish Register of Education

The Swedish Register of Education was used in studies I and II. The register is kept by Statistics Sweden and was established in 1985. It contains information about the highest level of education from elementary to post-graduate level, of all citizens registered as resident in Sweden from the age of 16 to at least 74. The register is updated annually.[154]

### 4.2.3 The Swedish Patient Register

The Swedish Patient Register, kept by the National Board of Health and Welfare, was used in study II. It includes information about dates of hospital admissions, discharges, and main and secondary diagnoses classified according to the international classification of diseases (ICD codes, 7-10th revisions) as well as surgical treatments. The register was established in 1964 and became nationwide in 1987. Since 2001, the register has also included information about out-patient hospital visits from both public and private caregivers. Primary care is not covered.[155]

### 4.2.4 The Swedish Prescribed Drug Register

In study II the Swedish Prescribed Drug Register, which is also kept by the National Board of Health and Welfare, was used. Since July 1st 2005, the personal registration number has been included. The register includes information about all dispensed drugs for the outpatient population prescribed from primary or specialist care. Information includes the prescribed substances, brand name and package, ATC-code (all drugs are classified according to the World Health Organization Anatomical Therapeutic Chemical Classification) and date of dispensing. [156]

### 4.2.5 The Stockholm-Gotland Obstetric Cohort

Since 2008, all pregnant women in the Counties of Stockholm (SLL) and Gotland who attend maternal care units, are recorded in the electronic medical record system Obstetrix (Cerner Inc). The journal system contains detailed prospectively registered information for each pregnancy from the first visit until the mother and infant are discharged from the delivery hospital. The data includes complications, laboratory tests, and examinations such as ultrasound during pregnancy as well as detailed data on the delivery process including longitudinal information from the partogram, like time-specific cervix dilation examinations. In addition, detailed information on operative interventions, umbilical cord blood tests, information from the postpartum period and examination of the new-born infant is included in the journal system. About one fourth of all deliveries in Sweden take place in the Counties of Stockholm and Gotland, which implies an annual number of 25 000 to 30 000 deliveries.

Professor Sven Cnattingius received a 3-year grant to establish a database at the Unit of Clinical Epidemiology, KI, for medical registers concerning pregnancy. This was funded by the Swedish Research Council Program for establishing large data bases for health care research. Trough cooperation with the IT department at Stockholm County Council (SLL-IT), we have established the Stockholm-Gotland Obstetric Cohort database which includes most of the variables in the record

system. (Figure 4.1) This provides unique, detailed material of clinically relevant variables during pregnancy, delivery and after birth. The database enables studies of more specific (especially clinically oriented) outcomes with control for more potential confounders compared with the MBR.

Since 2013, the database is in use and includes information on pregnancies from January 1st, 2008 until October 31st, 2014. Information is electronically transferred directly from the electronic medical record system to the database. Thus, it is difficult to perform a validation of the register. To date, three additional studies based on the Stockholm-Gotland Obstetric Database have been published.[136, 157, 158]

**Figure 4.1:** Photograph of the variables in the electronic medical record system Obstetrix, from where the variables in the Stockholm-Gotland Obstetric Cohort Database are derived from, during the working process at SLL-IT in 2011.

### 4.2.6 The Swedish Neonatal Quality Register

We used the Swedish Neonatal Quality Register (SNQ) in study IV. This register contains data on infants admitted for any level of neonatal care within the first 28 days after birth. The SNQ includes information about the mother, pregnancy complications and delivery characteristics as well as detailed information about admission, diagnoses and interventions during neonatal care. The register was started in 2001, and cover all neonatal units in Stockholm since 2002, and in Gotland since 2007. The register is now nationwide and covers all neonatal units in Sweden since 2012.[9]

### 4.2.7 Term infants

One third of all neonatal deaths and the majority of all registered serious complications, including asphyxia, affect term infants (between 37 and 41 complete weeks). In a report from SNQ in 2014, term infants represent the majority of infants admitted to neonatal wards.[9] Even if the absolute risk for adverse neonatal outcome is small among infants delivered at term, they constitute a large proportion of the neonatal morbidity and mortality because of their large number. It is likely that complications could have been avoided for a large proportion of these infants.

**Table 4.1: Overview of study characteristics**

| | Study I | Study II | Study III | Study IV |
|---|---|---|---|---|
| **Design** | Cohort | Cohort | Cohort | Cohort |
| **Years** | 1992-2006 | April 2006-2011 | 2008-2012 | 2008-2013 |
| **Setting/ Data sources** | Swedish Medical Birth Register<br>Register of Education | Swedish Medical Birth Register<br>Prescribed drug Register<br>Patient Register<br>Register of Education | Stockholm-Gotland Obstetric Cohort | Stockholm-Gotland Obstetric Cohort<br>Neonatal Quality Register |
| **Gestational length** | Term or post-term (≥ 37 weeks) | Term or post-term (≥ 37 weeks) | Term or post-term (≥ 37 weeks) | Term or post-term (≥ 37 weeks) |
| **Subjects** | 239 953 | 514 875 | 32 796 | 42 539 |
| **Exposure variables** | Labour dystocia and mode of delivery in first labour | Use of low-molecular-weight heparins during pregnancy | Duration of second stage of labour | Duration of second stage of labour and pushing |
| **Outcome measures** | Labour dystocia and mode of delivery in second labour | Labour dystocia | Apgar score at 5 min <7 and <4 | Umbilical cord acidosis, birth asphyxia-related complications, admission to NICU |
| **Covariates** | Maternal age (2nd labour)<br>Height<br>BMI (2nd)<br>Smoking (2nd)<br>Education<br>Family situat. (2nd)<br>Country of birth<br><br>Inter-pregnancy interval<br>Birth-weight (1st)<br>Gestational age (2nd)<br>Epidural analgesia | Maternal age<br>Height<br>BMI<br>Smoking<br>Education<br>Assisted reproduction<br>Diabetes<br>Hypertensive disease<br><br>Gestational age<br>Onset of delivery<br>Birth weight<br>Epidural analgesia | Maternal age<br>Height<br>BMI<br>Smoking<br><br>Infant gender<br>Gestational age<br>Sex-specific birth-weight for gest age<br>Head circumference<br>Epidural analgesia<br>Mode of delivery | Maternal age<br>Height<br>BMI<br>Smoking<br>Diabetes<br>Hypertensive disease<br><br>Onset of delivery<br>Use of oxytocin<br>Gestational age<br><br>Epidural analgesia<br>Mode of delivery |

## 4.3 STUDY POPULATIONS AND STUDY DESIGNS

### 4.3.1 Study I and study II

**Study populations**

Studies I and II are population-based cohort studies based on the MBR. We included women giving birth to singleton, live-born infants in cephalic presentation at term or post-term. In study I, we used information about women giving birth to their first and second infant between 1992 and 2006. The women with induction of labour in their first or second delivery or caesarean delivery before onset of first or second labour, and women without information on these variables were excluded. The final study population consisted of 371,086 women with two consecutive deliveries. In study II nulliparous and parous women were included. The study period began April 1st 2006 as the drug register started July 1st 2005, enabling the mothers to be exposed to low-molecular-weight heparins (LMWH) throughout the entire pregnancy. We had access to the MBR until December 31st 2011, when the study period therefore ended. Elective caesarean deliveries were excluded and the final study population consisted of 514 875 deliveries with 408 013 unique mothers.

**Exposures**

Through the personal identity number it was possible to link information on successive births recorded in the MBR in study I. The exposure was labour dystocia along with mode of delivery in first labour including mode of delivery (vaginal non-instrumental delivery, vaginal instrumental delivery and caesarean section) with or without dystocia. Dystocia was defined as any of the following diagnoses of dystocia, classified according to the Swedish versions of the International Classification of Diseases, ninth (ICD-9; 1987-96) and tenth (ICD-10; used since 1997 and onwards) revisions (Table 4.2). The definitions of the diagnoses are specified in the background chapter (Table 2.3). In further analyses, a risk score based on the adjusted odds ratios for dystocia in second labour was created.

**Table 4.2: Diagnoses of labour dystocia according to the Swedish version of ICD-9 and -10**

| | ICD-9 | ICD-10 |
|---|---|---|
| Primary dystocia | 661A | O62.0 |
| Secondary dystocia | 661B | O62.1 |
| Prolonged first stage of labour | 662A | O63.0 |
| Prolonged second stage of labour | 662C | O63.1 |
| Unspecified dystocia | 662B<br>661C | O62.2*<br>O62.9<br>O63.9 |

*The diagnosis O62.2 includes both unspecified dystocia and a prolonged latent phase according to the Swedish version of ICD-10.

Use of LMWH during pregnancy was the exposure in study II. We linked MBR to the Prescribed Drug Register to find information on dispensed LMWHs (dalteparin [Fragmin®], enoxaparin [Klexane®], tinzaparin [Innohep®] and warfarin [Waran®]). Use of any of the LMWH drugs was based on date of dispense, categorized into before pregnancy (30-1 days before last menstrual period),

and during pregnancy: first trimester, second trimester or third trimester. Information about use of warfarin during the period before pregnancy was also collected because this is an indication for LMWH replacement during pregnancy.

The main exposure was use of LMWH during the third trimester. Use during first and/or second trimester was analysed as a secondary exposure since we could not a priori exclude that such use may have an effect on labour duration. Underlying diagnoses associated with LMWH treatment were retrieved from the Patient Register based on ICD-9 and ICD-10 codes from 1987 and onwards, and were divided into ten groups (Figure 4.2). We used information about the dates of the diagnoses to group them into before or during pregnancy. In a secondary analysis, LMWH use was divided into a presumed high dose and a presumed prophylactic dose. The presumed high dose was based on underlying diagnoses with indications for treatment dose and high dose prophylaxis. The presumed prophylactic group comprised remaining women who received LMWH treatment during the third trimester.

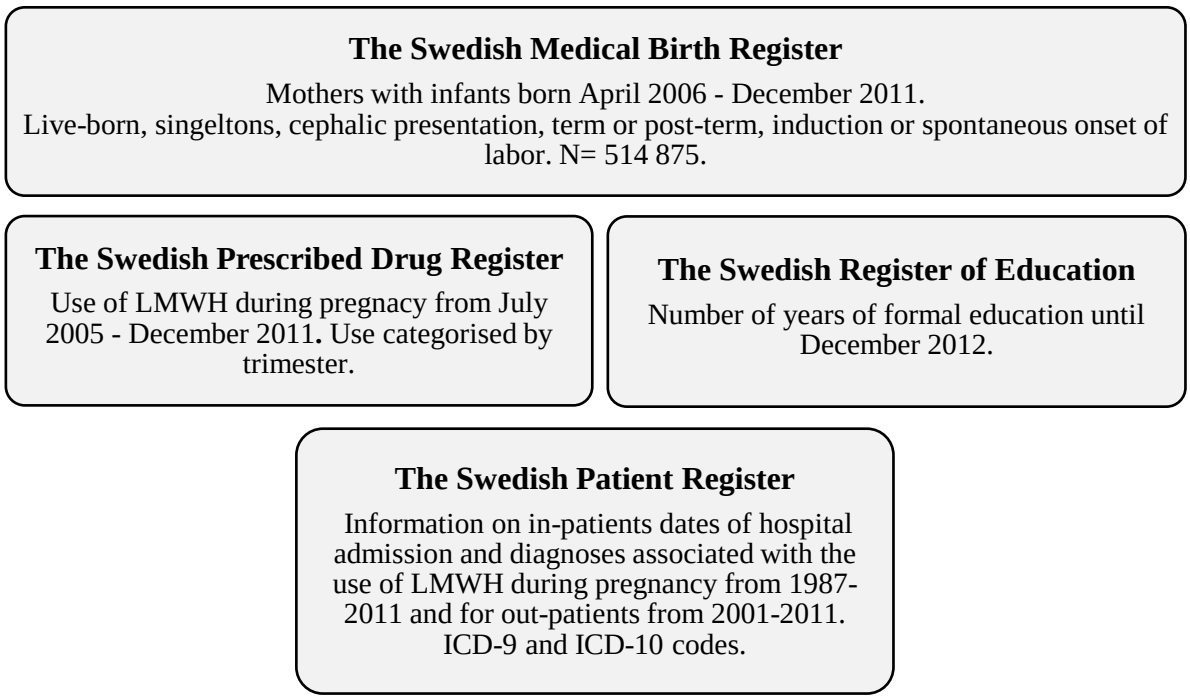



**Figure 4.2:** Registers included in Study II.

**Outcomes**

One of the outcomes observed in study I was diagnosis of labour dystocia in second labour, based on ICD-9 and -10 diagnoses previously described in exposures (Table 4.2). Secondary outcome was mode of delivery in second labour, also stratified by risk score groups. In study II, the outcome was diagnosis of labour dystocia based on the same criteria's as the exposure and outcome of study I (Table 4.2).

**Variables**

Maternal characteristics such as parity, age, height, BMI, assisted reproduction, family situation, and self-reported smoking and inter-pregnancy interval were obtained from the standardised delivery record. The country of birth of the mothers was retrieved from the Register of Total Population (linked at the National Board of Health and Welfare). Information on mother's highest level of formal education was retrieved from the Swedish Education Register. Information on concurrent diseases, such as hypertensive and diabetic diseases, was obtained from the check-boxes in the delivery record or as ICD-10 diagnoses during delivery or at discharge from the delivery hospital. Variables such as infant sex, birth weight and head circumference were registered in the neonatal record. Information on gestational age, onset of delivery, fetal presentation, use of epidural analgesia, infant birth weight, and mode of delivery were obtained from standardised delivery records.

### 4.3.2 Study III and study IV

**Study populations**

In studies III and IV, population-based cohort studies were performed using the Stockholm-Gotland Obstetric Cohort. The database contains information of births from January 1st, 2008 and we used information on births occurring until December 31st, 2012 in study III and until December 31st, 2013 in study IV. Women delivering their first live-born singleton infant in cephalic presentation at 37 completed weeks of gestation and onward, were included in the studies. Elective caesareans, emergency caesareans before fully dilated cervix, and deliveries without labour partogram or a notation of complete dilation of the cervix were excluded from both studies. Additional exclusions of deliveries with inductions and without data on Apgar score were made in study III, and the final study population included 32 796 births. In study IV, out of the 7 delivery units within the Stockholm-Gotland region, one unit did not routinely take umbilical blood samples and deliveries from this unit were therefore excluded. Hence, the study population in study IV comprised 42 539 births.

**Exposures**

The main exposure in studies III and IV was duration of second stage of labour, defined as time in minutes from the first notation of a fully dilated cervix until delivery. Information from the labour partogram was used to measure the duration of the second stage of labour and was categorised into 5 groups: Less than 1 hour (reference); 1 to <2 hours; 2 to <3 hours; 3 to <4 hours; and 4 hours or more. Secondary exposure in study IV was duration of pushing, defined as time in minutes from notation of active pushing in the delivery record until delivery. The duration of pushing was categorised into 5 groups: 0-14 (reference), 15 to 29, 30 to 44, 45 to 59, and ≥ 60 minutes. In addition, analyses of duration of passive phase of second stage, defined as time from notation of a fully dilated cervix until the start of active pushing, were combined with duration of pushing. The passive phase was categorised into 0 to <1 hour, 1-<2 hours, 2-<3 hours and 3 hours or more and pushing was categorised into <45 and 45 minutes or more.

**Outcomes**

The outcomes observed in studies III and IV were different neonatal complications. In study III, the outcome was defined as an Apgar score of <7, or <4 at 5 minutes. This information was retrieved from the delivery record. In order to include detailed information on neonatal complications in study IV, we linked the Stockholm-Gotland Obstetric Cohort to the Swedish Neonatal Quality Register. Here we used information about admitted infants born until December 31st 2013. Adverse neonatal outcomes were defined as: umbilical artery acidosis, birth asphyxia-related complications, and

admission to NICU. Umbilical artery acidosis was defined as a pH-value of less than 7.05 and a base excess (BE) of less than -12 mmol/L. This was retrieved from the delivery record. Birth asphyxia-related complications included any of the following diagnoses or procedures: hypoxic ischemic encephalopathy (HIE), hypothermia treatment, neonatal seizures, meconium aspiration syndrome (MAS) and resuscitation in delivery room with heart compressions and/or intubation. Neonatal diagnoses were coded using the ICD-10 classification at discharge from the delivery hospital and/or the NICU. Some of the diagnoses and procedures were also marked in checkboxes in the NICU record.

**Variables**

Maternal and delivery characteristics were obtained in the same manner as in studies I and II. Additional delivery characteristics such as duration of second stage of labour, use of epidural analgesia, use and notation on start of oxytocin for labour augmentation were obtained from the partogram. Gestational age was hierarchically based on date of conception before embryo transfer, ultrasound examination in second trimester and the date of the last menstrual period. Information on infant sex, birth weight and head circumference were registered in the neonatal record. Birth weight for gestational age was calculated using the sex-specific Swedish reference curve for normal fetal growth.[159]

### 4.3.3 Evaluation of the diagnoses for labour dystocia

We wanted to validate the diagnoses of dystocia classified according to the Swedish version of WHOs ICD-10 codes. We used the Stockholm-Gotland Obstetric Cohort to retrieve the diagnoses of dystocia according to ICD-10: Primary dystocia (O62.0), secondary dystocia (O62.1), prolonged 1st stage (O63.0)**,** prolonged 2nd stage (O63.1**)** and unspecified dystocia (O62.9, O63.9 and O66.9, not O62.2 since it includes the latent phase).

In the same cohort, we could identify prolonged duration of second stage in time according to the following definitions: nulliparous with epidural >3 hours and nulliparous without epidural >2 hours.

Prolonged duration of first stage of labour was not possible to evaluate since the variables for active start of labour was not yet defined in the cohort and information on cervical dilation rate was not possible to retrieve. Therefore, it was only possible to validate the diagnosis of prolonged second stage of labour. In the Swedish Society for Obstetrics and Gynecology's version of ICD-10 diagnoses for dystocia, the recommendation is to primarily use O62 diagnoses. Therefore, the O63 diagnoses could possibly be underreported.

In the evaluation we used the same study population as in study IV. There were 42 539 women giving birth to their first-born, singleton infant in cephalic presentation at 37 gestational weeks or later. Women without fully dilated cervix were excluded (Tables 4.3). In this population, 29.6% had any diagnosis of dystocia. According to duration of time of second stage among nulliparous women, 25.7% had a prolonged second stage. When using the ICD-10 diagnosis O63.1 for prolonged second stage, only 5.4% had received the diagnosis (18.6% of those with prolonged second stage according to time). Therefore, it was not possible to validate the diagnosis of prolonged second stage. What is worth mentioning is that among women receiving the ICD-10 diagnosis of prolonged second stage, 89% had a prolonged second stage according to duration of time (Tables 4.3).

**Tables 4.3: Diagnoses of labour dystocia in second stage of labour.**

| Nulliparous, gestational week ≥ 37, cephalic presentation, fully dilated cervix N total = 42 539 | | |
|---|---|---|
| **Prolonged 2nd stage according to duration of time:** | **N** | **%** |
| Nulliparous with epidural > 3 hours | 7 397 | 17.4 |
| Nulliparous without epidural > 2 hours | 3 529 | 8.3 |
| **Total prolonged 2nd stage according to duration of time:** | 10 926 | **25.7** |
| **Dystocia according to ICD-10 diagnoses of labour dystocia:** | | |
| **Prolonged 2nd stage** (O63.1**)** | 2 289 | **5.4** |
| **Unspecified dystocia** (O62.9, O63.9 and O66.9) | 235 | 0.6 |
| **Prolonged 2nd stage** (O63.1), **secondary dystocia** (O62.1), and **unspecified dystocia** (O62.9, O63.9 and O66.9) | 9 867 | 23.2 |
| **Any diagnoses of dystocia:** Primary dystocia (O62.0), Secondary dystocia (O62.1), Prolonged 1st stage (O63.0) Prolonged 2nd stage (O63.1) and unspecified dystocia (O62.9, O63.9 and O66.9) (not O62.2) | 12 607 | 29.6 |

| | **Prolonged 2nd stage according to ICD-10 diagnosis (N=2 289)** |
|---|---|
| **Prolonged 2nd stage according to duration of time** | 88.9% |
| **No prolonged 2nd stage according to duration of time** | 11.1% |

| | **Prolonged 2nd stage according to duration of time (N=10 926)** |
|---|---|
| **Prolonged 2nd stage according to ICD-10 diagnosis** | 18.6% |
| **No ICD-10 diagnosis of prolonged 2nd stage** | 81.4% |

## 4.4 STATISTICAL ANALYSES

**Logistic regression analysis**: is used to study the statistical relationship between one or more independent (predictor) variables and a dependent (outcome) variable. The dependent variable must be discrete and should be binary (dichotomous) in nature. The independent variables can be dichotomous, categorical or continuous. There should be no high intercorrelations among the independent variables and no outliers in the data. To model a linear relationship, the outcome variable is transformed by the logit function. The results are presented as odds ratios (OR), with an estimated confidence interval (CI). With a rare outcome, the OR approximates the relative risk (RR).

**Polytomous regression analysis**: also called multinomial logistic regression. This method is used to make logistic regression analysis when the outcome variable is categorical and has more than two groups.

**Poisson regression analysis**: Is commonly used for survival analysis to estimate incidence rate ratios. Poisson regression can also be used when the outcome is binary to estimate prevalence ratios (relative risks) with a 95% CI. Compared to logistic regression, this method is preferred to use when possible although not with case-control studies, especially if the outcome is not rare, since the relative risk is usually the parameter of interest in epidemiological studies.[160]

**Generalized estimating equation (GEE)**: is used to account for correlation between dependent observations in a study population. With GEE, weighted combinations of observations is used to extract the adequate amount of information from correlated data.[161]

**Interaction analysis**: is conducted to estimate the possible effect modification of an interaction variable. A significant interaction indicates that the effect of one independent (predictor) variable on the outcome variable varies at different values of the other independent variable. It is tested by adding a term to the regression model in which the two predictor variables are multiplied.

All analyses were conducted using **SAS** software, version **9.2 - 9.4**.

### 4.4.1 Study I and study II

In study I, logistic regression analysis was used to study the association between labour dystocia and mode of delivery in first labour, and labour dystocia in second labour. Polytomous regression analysis was used to analyse the outcome mode of delivery in second labour, with three categorical outcomes: vaginal spontaneous, vaginal instrumental and caesarean deliveries. Adjustments in the regression models were made for dystocia and mode of delivery in first labour, birthweight at first delivery, inter-pregnancy interval and maternal characteristics at second pregnancy/delivery (maternal age, BMI, height, education, family situation, country of birth and cigarette smoking), gestational age and year of second delivery.

To further study the risk of caesarean section or instrumental vaginal delivery in second labour, we applied a risk score system based on the adjusted OR for dystocia in second labour, where ORs in the range 1.25 to 1.49 gave 1 point and 1.50 to 1.74 gave 2 points. Inter-pregnancy interval, maternal age, BMI, height, not co-habiting with the infant's father and post-term pregnancy were associated with increased risks of dystocia in second labour. The maximal sum of the score was 9 points and the population was stratified into three risk score groups of 0, 1-2 and 3 or more risk scores.

In study II, logistic regression analysis to estimate unadjusted and adjusted OR for the risk of labour dystocia in relation to use of LMWH during pregnancy was used. All analyses were stratified by

parity, by treatment period of LMWH. Generalized estimate equations were used to account for the correlation between mothers with more than one child in the study population.

Several adjusted models were used to account for possible confounders. All were adjusted for maternal characteristics (treatment with LMWH, age, height, BMI, smoking, diabetes, hypertensive disease, assisted reproduction and level of education), onset of labour and year of birth. In additional three models, further adjustments for gestational age, epidural analgesia and birth weight were made. A test for interaction was made in the logistic regression model to estimate the possible effect modification by the onset of labour or epidural analgesia on the association between use of LMWH and labour dystocia. A p-value of $<0.05$ was considered statistically significant. Additionally, stratification analyses for epidural analgesia and presumed high dose or prophylactic dose of LMWH were made.

Gestational age may be considered a mediator between LMWH and dystocia since use of LMWH has been associated with preterm birth. This association could be attributed to iatrogenic factors rather than spontaneous preterm deliveries.[162-166] Thus, we analysed the distribution of gestational length at birth among women with and without LMWH. Since this distribution was similar in the two groups in this population of term and post-term births, adjustments for gestational length at birth were made in the regression model.

### 4.4.2 Study III and study IV

In study III, logistic regression was used to calculate crude and adjusted odds ratios with 95% CI. A test for interaction was done in the logistic regression model to estimate the possible effect modification caused by epidural analgesia or mode of delivery, on the association between duration of the second stage of labour and Apgar score. Stratification by mode of vaginal delivery was thereafter made.

In study IV, poisson regression analysis with 95% CI, was used to estimate adjusted relative risks. Poisson regression analysis was the preferred method since some of the outcomes were relatively common, and therefore a relative risk is a more accurate estimation of the associations than odds ratios.[160]

Maternal characteristics, such as age, height, BMI and smoking were considered confounders in studies III and IV. Additionally, in study IV, adjustments were made for hypertensive disease and diabetes. Delivery characteristics such as onset of delivery, use of epidural analgesia, oxytocin for labour augmentation, and mode of delivery were handled in different ways in study III and study IV. In study III, we excluded mothers with induction of labour. In study IV, we adjusted for onset of labour (induction or spontaneous). In study III, there was no interaction between epidural and duration of second stage with respect to the 5-minute Apgar score, and epidural analgesia was considered to be a confounder and was therefore adjusted for in a secondary model. In study IV, stratified analyses for epidural were made. Oxytocin for augmentation was considered a mediator in study III, and was consequently not adjusted for. While in study IV, oxytocin before second stage of labour was considered to be a confounder (Figure 4.3). In the analysis of the duration of pushing (study IV), oxytocin before active pushing was also regarded as a confounder.

Stratified analyses of mode of vaginal delivery were made in studies III and IV. Gestational age was adjusted for in both studies, while infant sex, sex-specific birth-weight for gestational age and head circumference were only considered in study III.

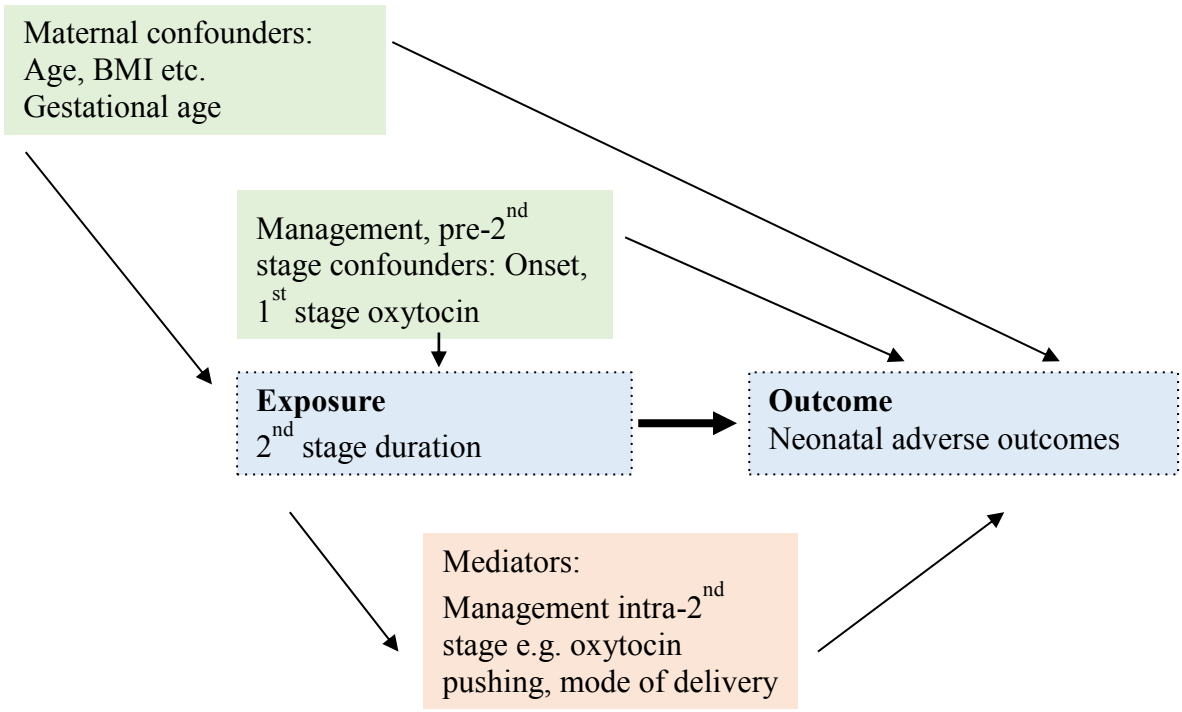



**Figure 4.3: Directed acyclic graph (DAG) in study IV.** The influence of maternal and delivery characteristics on the association between duration of second stage of labour and neonatal complications.

## 4.5 ETHICAL CONSIDERATIONS

The Personal Data Act aims to prevent the violation of personal integrity in the processing of personal data. It specifies that treatment of sensitive individual information in research only can be conducted after ethical permission has been granted by an ethical board. After approval from one of the six regional ethical review boards in Sweden, national register data can be accessed for research. Ethical approval was obtained from regional ethical boards prior to the initiation of all the four studies.

In studies I and II the cohorts were retrieved from the MBR held by the National Board of Health and Welfare. Inclusion of individual data in the MBR does not require consent from the patients. The data was anonymized for the researchers with unidentifiable sequence numbers. The key to the personal identity number is held at the National Board of Health and Welfare and is saved for three years, with the possibility to apply for prolongation. The key can be used by and among different authorities to link different registers. Links to the Prescribed Drug Register, Education Register and Patient Register were made in study II. All data was analysed at an aggregated level in the two studies.

Ethical approval for studies I and II: The Regional Ethical Review board No. 4 in Stockholm, Sweden: 2008/1182-31/4, date of approval September 3rd 2008.

The Stockholm-Gotland Obstetric Cohort was used in studies III and IV. Information in the database was retrieved from the medical record system Obstetrix. The database is kept by the Unit of Clinical epidemiology. All data were anonymized and de-identified prior to analysis. In addition to ethical approval to use the information, we applied for informed consent from the health care givers, who were responsible for the data. In 2012, we obtained informed consent from all but one of the forty-three head of departments for all maternal care units and delivery wards in the Stockholm and Gotland Counties. Information from this maternal care unit has thus been excluded from the cohort. There was no informed consent for the patients prior to their inclusion in the study.

Ethical approval for studies III and IV: The Regional Ethical Review board No. 5 in Stockholm, Sweden: 2009/275-31, date of approval April 2nd 2009 and 2012/365-32, date of approval March 14th 2012.

# 5 RESULTS

## 5.1 RECURRENCE OF LABOUR DYSTOCIA AND INSTRUMENTAL DELIVERY (STUDY I)

### 5.1.1 Summary of main findings

Recurrence of labour dystocia affected 12.3% of women with dystocia in their first labour. Overall, 91% of women with previous dystocia had a non-instrumental vaginal delivery in subsequent pregnancy. The risk of recurrence of dystocia, and also of instrumental vaginal and caesarean deliveries in second labour was increased for women with previous dystocia, especially among women with previous caesarean delivery. In addition, fetal and maternal characteristics were also associated with dystocia in second labour. Thus, it is important to take first labour as well as fetal and maternal characteristics into account in the risk assessments for dystocia and instrumental delivery in second labour.

### 5.1.2 Main findings

The study population consisted of 239 953 women with spontaneous onset of first and second consecutive deliveries, of whom 21.5% were diagnosed with dystocia in their first labour and 5.3% in second labour. The risk of dystocia in second labour increased with increasing inter-pregnancy intervals, maternal age, BMI, decreasing maternal height, among mothers not cohabiting with the father-to-be, as well as in postterm pregnancies. Compared with a non-instrumental vaginal first delivery without dystocia, a previous vaginal delivery (non-instrumental or instrumental) with dystocia was associated with approximately a four-fold increased risk of dystocia in second labour. The corresponding absolute risks, however, were about 10%.

The trial of labour after caesarean (TOLAC), only including women with spontaneous onset of first and second labour, was approximately 60%. For women with a previous caesarean, the incidence of dystocia in second labour was higher among those with previous dystocia than for women without previous dystocia (34 % vs. 21%, respectively).

The risks of instrumental vaginal and caesarean deliveries in second labour were higher among women with previous dystocia than in women without previous dystocia. Compared to women with a previous instrumental vaginal delivery without dystocia, there was only a slightly increased risk of vaginal instrumental delivery and caesarean section in second labour for women with a previous instrumental vaginal delivery with dystocia. Among women with TOLAC without previous dystocia, 15% had a vaginal instrumental delivery and 23% a caesarean section in second labour. Among women with TOLAC with previous dystocia, corresponding risks were 17% and 32%, respectively (Table 5.1).

We used risk score groups to analyse rates of mode of delivery in second labour in more detail. Risk factors were based on the adjusted ORs for dystocia in second labour for inter-pregnancy interval, maternal characteristics, and gestational age in second labour. The rates of vaginal instrumental delivery and caesarean in second labour generally increased with previous dystocia and increasing risk score. Among women with TOLAC with previous dystocia and a risk score of 3 or more, 66% had a

vaginal instrumental or caesarean delivery (17% and 49% respectively). In women with TOLAC without previous dystocia and a risk score of 0, the corresponding risk was 32% (14.0% and 18% respectively).

**Table 5.1. Labour dystocia and mode of delivery in first labour and mode of delivery in second labour among women with spontaneous onset of first and second consecutive deliveries from 1992 to 2006 in Sweden.**

| | | Mode of delivery second labour (n=239 953) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Vaginal instrumental (n=5 827) | | | Caesarean (n=4 659) | | |
| **Mode of delivery first labour** | **Total No.** | **Rate (%)** | **aOR*** | **(95% CI)** | **Rat (%)** | **aOR*** | **(95% CI)** |
| **Vaginal non-instrumental** | | | | | | | |
| No dystocia | 172 136 | 1.1 | **1.00** | (Reference) | 0.8 | **1.00** | (Reference) |
| Dystocia | 29 044 | 2.1 | **1.86** | (1.67-2.1) | 1.2 | **1.41** | (1.22-1.62) |
| **Vaginal instrumental** | | | | | | | |
| No dystocia | 12 249 | 5.5 | **4.81** | (4.33-5.34 ) | 2.0 | **2.35** | (2.00-2.76) |
| Dystocia | 18 527 | 7.2 | **6.54** | (6.01-7.12) | 2.6 | **3.13** | (2.77-3.54) |
| **Caesarean** | | | | | | | |
| No dystocia | 4 042 | 14.6 | **20.07** | (17.85-22.57) | 22.9 | **40.24** | (36.05-44.91) |
| Dystocia | 3 955 | 17.0 | **29.54** | (26.24-33.26) | 32.1 | **63.76** | (57.18-71.10) |

* aOR= adjusted Odds Ratios. Data were adjusted for dystocia and mode of delivery in first labour, birth weight in first labour, inter-pregnancy interval, maternal age, early pregnancy BMI, maternal height, education, family situation, country of birth, cigarette smoking, infant's gestational age in second labour and year of second birth.

## 5.2 USE OF LOW-MOLECULAR-WEIGHT HEPARIN DURING PREGNANCY AND RISK OF PROLONGED LABOUR (STUDY II)

### 5.2.1 Summary of main findings

In total, 5 275 deliveries (1.0%), were exposed to LMWH during pregnancy, 0.9% among nulliparous women and 1.1% among parous women. In nulliparous women, labour dystocia affected 21.2% of women who did not use LMWH, 19.9% of those using LMWH in third trimester, and 23.9% of those using LMWH in the first and/or second trimester. For parous women, the corresponding rates were 4.7%, 4.3%, and 5.5%, respectively. In both unadjusted and a number of adjusted models, the use of LMWH in the third or in the first and/or second trimester was not significantly associated with labour dystocia among nulliparous or parous women. The conclusion is that use of LMWH during pregnancy is not associated with a risk of labour dystocia.

### 5.2.2 Main findings

In the study population comprising 514 875 women with spontaneous or induced onset of labour, labour dystocia affected 21.2% of nulliparous and 4.7% of parous women. The most common underlying diagnosis for LMWH use was deep venous thrombosis. The unadjusted risk of labour dystocia increased with age, short maternal stature, higher BMI, diabetes (gestational and pre-gestational), chronic hypertension, in vitro fertilization, increasing length of gestation and with induction of labour in both nulliparous and parous women. Smokers had a reduced risk of labour dystocia. Dystocia was strongly associated with epidural analgesia and with increasing birth weight. Use of epidural analgesia was more frequent among women without LMWH compared to those with LMWH in their third trimester. Gestational length at birth was not associated with use of LMWH in third trimester.

**Table 5.2: Regression analysis of use of low-molecular-weight heparin (LMWH) during pregnancy and diagnosis of labour dystocia in nulliparous and parous women with singleton infants in cephalic presentation, term or postterm births with induction or spontaneous onset of delivery, in Sweden, April 2006-December 2011.**

| | **Labour dystocia** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Nulliparous women (N=232 104)** | | | | | | | |
| | **Model 1** | | **Model 2** | | **Model 3** | | **Model 4** | |
| **Use of LMWH** | **aOR*** | **(95% CI)** | **aOR*** | **(95% CI)** | **aOR*** | **(95% CI)** | **aOR*** | **(95% CI)** |
| **No use** | **1.00** | (Reference) | **1.00** | (Reference) | **1.00** | (Reference) | **1.00** | (Reference) |
| **Third trimester** | **0.87** | (0.76-1.00) | **0.90** | (0.79-1.04) | **1.00** | (0.87-1.15) | **1.03** | (0.89-1.19) |
| **First and /or second trimester** | **1.01** | (0.84-1.22) | **1.04** | (0.87-1.26) | **1.08** | (0.89-1.31) | **1.09** | (0.89-1.32) |
| | **Parous women (N=282 771)** | | | | | | | |
| **No use** | **1.00** | (Reference) | **1.00** | (Reference) | **1.00** | (Reference) | **1.00** | (Reference) |
| **Third trimester** | **0.85** | (0.69-1.05) | **0.89** | (0.72-1.10) | **0.99** | (0.80-1.22) | **1.03** | (0.83-1.27) |
| **First and /or second trimester** | **0.97** | (0.68-1.37) | **1.03** | (0.73-1.46) | **0.96** | (0.68-1.38) | **0.99** | (0.69-1.42) |

*aOR= adjusted Odds Ratios.
Model 1: Adjustments for maternal characteristics: treatment with LMWH, age, height, BMI, smoking during pregnancy, diabetes, hypertensive disease, assisted reproduction, education, year of birth and onset of labour
Model 2: Adjustment for characteristics in model 1, and gestational length at birth.
Model 3: Adjustment for characteristics in model 1, gestational length at birth and epidural analgesia.
Model 4: Adjustment for characteristics in model 1, gestational length at birth, epidural analgesia and birth weight.

Compared to no use, LMWH use during the third trimester in nulliparous women was not associated with labour dystocia after adjusting for maternal characteristics (Table 5.2, model 1). When gestational length at birth, epidural analgesia and birth weight were taken into account, LMWH was shown not to affect risk of labour dystocia (Table 5.2 models 2-4). Use of LMWH in the first and/or second trimesters in nulliparous women was not associated with risk of labour dystocia. The analyses for parous women treated with LMWH in third trimester compared to no treatment demonstrated the same pattern (Table 5.2).

In additional analyses, use of LMWH in the third trimester was stratified by a presumed high dose or prophylactic dose. Rates of labour dystocia in nulliparous women were 21.2% who had not used LMWH, 19.3% of those with presumed prophylactic dose, and 22.0% with presumed high dose. For parous women corresponding rates were 4.7, 4.7 and 2.7, respectively. Compared to no treatment, nulliparous women with a presumed prophylactic dose had a slightly reduced risk of labour dystocia after adjustments for maternal characteristics, but this was not significant after further adjustments. In nulliparous women, there was no association between a presumed high dose of LMWH and labour dystocia in crude analyses. After adjustments, however, a presumed high dose was associated with an increased risk of labour dystocia (OR 1.48 [95 % CI 1.12-1.97], after adjustments for maternal characteristics, gestational age, epidural analgesia, and birth weight; data not shown in table).

## 5.3 PROLONGED SECOND STAGE OF LABOUR AND RISK OF LOW APGAR SCORE (STUDY III)

### 5.3.1 Summary of main findings

The overall rate of infant Apgar score at 5 minutes <7 and <4 was 0.7% and 0.1%, respectively. Compared to women with duration of second stage of <1 hour, adjusted ORs of 5-minute Apgar score <7 generally increased with duration of second stage, and with a duration ≥4 hours, the OR was 2.71 (95% CI 1.67-4.40). Duration of second stage of labour was associated with a 5-minute Apgar score <7 in spontaneous vaginal deliveries, but not in instrumental vaginal deliveries. The conclusion of the study is that prolonged second stage of labour is associated with an increased risk of a low 5-minute Apgar score.

### 5.3.2 Main findings

The study population consisted of 32 796 nulliparous women with spontaneous onset of labour. The duration of the second stage of labour was less than 1 hour in 32.7% of all deliveries, 1 to 2 hours in 28.9%, 2 to 3 hours in 17.9%, 3 to 4 hours in 11.9%, and 4 hours or more in 8.6%. Adjustments were made for maternal and infant characteristics. In a secondary model, additional adjustments for epidural analgesia was made.

**Duration of second stage and Apgar score <7 at 5 minutes**

Rates of Apgar score <7 at 5 minutes increased gradually with duration of the second stage (Table 5.3). Rates of Apgar scores <7 at 5 minutes were also increased in infants of older mothers (≥35 years), increased with decreasing maternal height, with delivery characteristics such as epidural analgesia, augmentation with oxytocin, and postterm gestational length (≥42 weeks). Male sex, a birthweight for gestational age lower than the 3$^{rd}$ or more than the 97$^{th}$ percentile, and a large head circumference (≥38 cm) were also associated with increased rates of 5 minute Apgar scores <7.

Compared to a second stage of labour of less than 1 hour, odds ratios of Apgar score <7 at 5 minutes generally increased with duration of the second stage in crude and adjusted analyses (Table 5.3).

**Duration of second stage and Apgar score <4 at 5 minutes**

Rates of Apgar score <4 at 5 minutes (per thousand deliveries) increased from 0.7 for a second stage of < 1 hour to 1.1 at 1 to <2 hours, 0.9 at 2 <3 hours, 2.6 at 3 to <4 hours and 2.8 at ≥4 hours. Rates of Apgar scores <4 at 5 minutes also increased among infants of mothers with maternal age of 30 years or more, with decreasing maternal height, epidural analgesia, augmentation with oxytocin and with a birth weight for gestational age lower than the 3rd or more than the 97th percentile.
Compared to a second stage of labour of less than 1 hour, a duration of 3 to <4 hours was associated with an increased risk of an Apgar score <4 at 5 minutes with adjusted OR 4.28 (95% CI 1.52-12.05). The crude OR for the duration of the second stage of 3 to <4 hours was 4.36 (95% CI 1.58-12.03), but after adjusting for maternal and infant characteristics, the risk was no longer significantly increased (OR 2.77 [95% CI 0.82-9.38]).

**Table 5.3: Duration of second stage and risk of Apgar score <7 at 5 minutes. Nulliparous women with term and postterm singleton live births.**

| | | | | Apgar 5 min <7 | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Odds ratio (95% CI) | | | | | |
| **Second stage (hours)** | **Total** **32 796** | **n** | **rate/ 1000** | **Crude** | | **Adjusted[a]** | | **Adjusted[b]** | |
| **<1** | 10 731 | 44 | **4.1** | 1.00 | (Reference) | **1.00** | (Reference) | **1.00** | Reference |
| **1 to <2** | 9 491 | 66 | **7.0** | 1.70 | (1.16-2.49) | **1.78** | (1.19-2.66) | **1.71** | (1.14-2.56) |
| **2 to <3** | 5 856 | 43 | **7.3** | 1.80 | (1.17-2.74) | **1.66** | (1.05-2.62) | **1.55** | (0.98-2.46) |
| **3 to <4** | 3 898 | 35 | **9.0** | 2.20 | (1.41-3.44) | **2.08** | (1.29-3.35) | **1.91** | (1.18-3.09) |
| **≥4** | 2 820 | 39 | **13.8** | 3.41 | (2.21-5.25) | **2.71** | (1.67-4.40) | **2.45** | (1.49-4.02) |

[a]Adjusted for maternal age, height, BMI, smoking, sex, gestational age, sex-specific birth weight for gestational age and head circumference.
[b]Adjusted for the variables in model a above, and epidural analgesia.

## 5.4 DURATIONS OF SECOND STAGE OF LABOUR AND PUSHING, AND RISK OF ADVERSE NEONATAL OUTCOMES (STUDY IV)

### 5.4.1 Summary of main findings

The overall rates of umbilical artery acidosis, birth asphyxia-related complications and admission to NICU were 1.08%, 0.63%, and 6.42%, respectively. Rates and adjusted relative risks of birth asphyxia-related complications and admission to NICU generally increased gradually with the

duration of second stage (Table 5.4). There was no association between the total length of the second stage and the risk of acidosis. The duration of pushing among vaginal deliveries, however, was associated with increased rates and relative risks (RR) of acidosis. Birth asphyxia-related complications and admission to NICU were increased after 45 minutes of pushing.

### 5.4.2 Main findings

The number of all adverse neonatal outcomes generally increased with maternal age and BMI, and with decreasing maternal height. Rates were also increased for infants of non-smokers and mothers with gestational hypertension, preeclampsia and diabetes. Adverse neonatal outcomes were slightly more common after induction of labour and with use of augmentation with oxytocin. Acidosis increased with gestational age from 37 to ≥42 weeks. Being admitted to NICU was most common in the 37$^{th}$ gestational weeks and most uncommon in the 39$^{th}$ gestational week.

There were 360 infants (1.08%) with umbilical artery acidosis, 269 infants (0.63%) with birth asphyxia-related complications (defined as any of the following conditions: hypoxic ischemic encephalopathy [HIE], hypothermia treatment, neonatal seizures, meconium aspiration syndrome [MAS] and resuscitation in delivery room with heart compressions or intubation) and 2 733 infants (6.42%) were admitted to NICU. Adjustments were made for maternal characteristics as well as delivery and fetal characteristics. The relationships between the adverse neonatal outcomes are demonstrated in Figure 5.1.

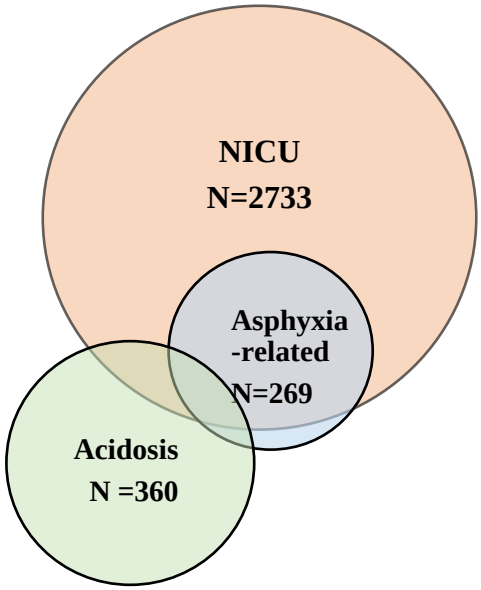



**Figure 5.1: The relationships between the adverse neonatal outcomes.** There were 269 infants with birth-asphyxia-related complications, and 245 of these (91.1%) were admitted to NICU. Among the 360 infants with acidosis, 82 (22.8%) were admitted to NICU and 25 (6.9%) also had at least one birth asphyxia-related complication. Among the 2 733 infants admitted to NICU, 245 (9.0%) had a birth asphyxia-related complication and 82 had acidosis. (531 of infants admitted to NICU had missing value for pH). Twenty-four infants had all three outcomes. Among infants with birth asphyxia-related complications, there were 60 infants with missing pH values.

**Duration of second stage**

The median duration of second stage of labour was 1 hour and 33 minutes and 95% of the infants were delivered within 4 hours and 32 minutes. The number of birth asphyxia-related complications gradually increased with duration of second stage: from 0.42% at <1 hour to 1.29% at ≥4 hours. For admission to NICU, corresponding rates were 4.97% and 9.45%. Risk of acidosis was not associated with duration of the second stage. Adjusted relative risks (RR) of birth asphyxia-related complications and admission to the NICU generally gradually increased with duration of the second stage (Table 5.4). There was no association between duration of second stage and risk of acidosis.

**Table 5.4: Duration of second stage of labour and rates and risks of umbilical artery acidosis, birth asphyxia-related complications and admission to neonatal intensive care unit (NICU).**

| | | **Acidosis[a]** | | | | **Birth asphyxia-related complications [b]** | | | **Admission to NICU** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N total[c]** | **%** | **aRR[d]** | **(95 % CI)** | **N Total** | **%** | **aRR[d]** | **(95 % CI)** | **%** | **aRR[d]** | **(95 % CI)** |
| | 33 429 | **1.08** | | | 42 539 | **0.63** | | | **6.42** | | |
| **Second stage (h)** | | | | | | | | | | | |
| <1 | 10 518 | 0.99 | **1.00** | (Reference) | 13 558 | 0.42 | **1.00** | (Reference) | 4.97 | **1.00** | (Reference) |
| 1 to <2 | 9 690 | 1.12 | **1.10** | (0.84-1.45) | 12 225 | 0.53 | **1.19** | (0.83-1.70) | 6.02 | **1.22** | (1.10-1.35) |
| 2 to <3 | 6 130 | 1.27 | **1.19** | (0.88-1.60) | 7 710 | 0.77 | **1.59** | (1.10-2.31) | 7.11 | **1.41** | (1.26-1.57) |
| 3 to <4 | 4 115 | 0.92 | **0.77** | (0.52-1.14) | 5 238 | 0.74 | **1.56** | (1.04-2.35) | 7.92 | **1.57** | (1.39-1.77) |
| ≥4 | 2 976 | 1.04 | **0.84** | (0.55-1.28) | 3 808 | 1.29 | **2.46** | (1.66-3.66) | 9.45 | **1.80** | (1.58- 2.04) |

aRR: Adjusted relative risk
[a]Acidosis: Umbilical artery acidosis, pH <7.05 and BE <-12.
[b]Birth asphyxia-related complications include any of the following conditions: hypoxic Ischemic encephalopathy (HIE), hypothermia treatment, neonatal seizures, meconium aspiration syndrome (MAS), or advanced resuscitation after birth (heart compressions or intubation).
[c]Data missing for pH and/or BE: N=9 110.
[d]Adjusted for: Maternal characteristics: maternal age, height, BMI, smoking, hypertensive disease and diabetes. Delivery and fetal characteristics: onset of delivery (spontaneous or induction), oxytocin before retracted cervix and gestational length at birth.

**Duration of pushing**

Duration of pushing was analysed for vaginal deliveries. The median duration of pushing was 32 minutes, and 95% of the infants were delivered within 1 hour and 18 minutes. The occurrence of acidosis gradually increased with duration of pushing: from 0.57% at <15 minutes to 1.69% at ≥ 60 minutes with adjusted RR 2.55 (95% CI 1.51- 4.30). Numbers of birth asphyxia-related complications and admissions to the NICU increased after 45 minutes. Compared to <15 minutes, adjusted relative risks of admission to the NICU increased with duration of pushing (45-<60 minutes OR 1.43 [1.22-1.67] and ≥ 60 minutes 1.54 [1.31-1.80]), but the risk of birth asphyxia-related complications was not associated with duration of pushing.

The risk of birth asphyxia-related complications and admissions to NICU generally increased with the duration of the second stage in both the non-epidural and epidural groups in the stratified analyses. In analyses stratified by mode of vaginal delivery, the adjusted relative risks of birth asphyxia-related complications and admission to the NICU increased with duration of the second stage for non-instrumental deliveries but not for instrumental vaginal deliveries.

The length of the passive phase of the second stage and the duration of pushing (<45 minutes or ≥45 minutes) and occurrence of adverse neonatal outcomes in vaginal deliveries were analysed in additional analyses. Rates of acidosis increased in deliveries with long pushing time, while the length of the passive phase did not have a major impact. The number of birth asphyxia-related complications and admission to NICU generally increased both with the length of passive phase of second stage and pushing time, and especially in combination.

# 6 DISCUSSION

## 6.1 METHODOLOGICAL CONSIDERATIONS

### 6.1.1 Study design

The association between an exposure and specific outcomes can be studied in observational cohort studies. The study population is followed over time and individuals are grouped by exposure status and are compared with regard to occurrence of events of interest. The most common disadvantage with prospective observational cohort studies is their long duration and consequently the risks of loss of follow up, selection bias and high costs. To use previously collected data from registers could be an option.

We used the MBR to perform cohort studies in ***study I*** and ***study II***. This gave us the opportunity to use pre-existing, prospectively collected data (i.e. before the occurrence of the outcome) in a systematic manner. The MBR is nation-wide and population-based. Given the large size of the cohort, even rare exposures can be studied. One example is the use of low-molecular-weight heparins during pregnancy in ***study II***. The cohort size also makes it possible to study associations between exposures and outcomes in stratified analyses, such as dystocia together with mode of delivery in first labour and mode of delivery in second labour as performed in ***study I***.

***Studies III-IV*** are cohort studies based on the Stockholm Gotland Obstetric Cohort. The data is population-based from the Stockholm-Gotland area. Similar to the MBR, the information had already been collected in a prospective manner, but this cohort includes more detailed information. This gave us the opportunity to study the exposures of duration of the second stage (***study III***) together with duration of pushing (***study IV***) on several neonatal outcomes.

The major limitation with this type of cohort studies is that information on exposures, outcomes and potential confounders are restricted to information included in the registers. A prospective observational cohort study, where data is collected for the purpose of the study, does not have this limitation. Randomized controlled trials are sometimes, but not always a possible option within the obstetric field, due to ethical considerations and power concerns.

### 6.1.2 Systematic error

Systematic errors are non-random. They occur due to incorrect selection of the study population (selection bias), incorrect classification of the studied variables (information bias) or disregard for other interacting variables that influence the results (confounders). Increased sample size cannot remediate this.

### 6.1.3 Internal validity

Internal validity implies how sound the results of the study are. This can be achieved by avoiding systematic errors such as selection bias, information bias and confounding, together with lack of random errors. Selection bias, information bias and confounding are all present to some degree in observational studies. Therefore, conclusions of causality cannot be drawn. With limited internal

validity follows limited external validity. A homogenous study population, an optimised study design and thorough data collection increases the internal validity.

### 6.1.4 Selection bias

If the association between exposure and outcome differs between the subjects in the study group and those in the source population, i.e. the population from which the study group is recruited, this can lead to an under- or overestimation of the true relative risks. Selection bias in cohort studies is mainly a matter of external validity rather than internal validity.

Since ***studies I*** and ***II*** are population-based, with an almost complete coverage of births in Sweden, the issue of selection bias is limited. In ***study I***, however, elective caesareans in first and second deliveries were excluded. Additionally, induced labours were excluded in order to eliminate the effects of onset of delivery. This results in a selection bias if labours with these onsets are different from labours with spontaneous onset, with regard to the studied associations. Women with an elective caesarean in second pregnancy are more likely to have a history of dystocia, instrumental vaginal delivery and caesarean section. It was shown that these factors increase the risk of both labour dystocia and instrumental delivery in second labour. The strength of the association between previous dystocia and instrumental delivery on mode of delivery in second labour may thus be underestimated. We were also forced to exclude a small group of women with missing information on fetal presentation, gestational age and onset of labour. If the characteristics of women who were excluded due to missing information were different from the characteristics of women having this information, this would introduce a selection bias. In ***study II***, women with elective caesareans were excluded. Those using low-molecular-weight heparin (LMWH) who were delivered by an elective caesarean section may have other indications for the use of LMWH, compared to those with LMWH in the study population. If these indications were associated with the risk of dystocia, a potential selection bias would be introduced.

***Studies III*** and ***IV*** are population-based, covering about one fourth of the Swedish population. In these studies, only nulliparous women were included, limiting the generalisability on parous deliveries. In ***study III***, induced labours, elective caesareans as well as caesareans during first stage of labour were excluded, leading to a potential selection bias. This was also the case when one out of seven delivery hospitals in the region was excluded in ***study IV***. This delivery hospital did not routinely take umbilical cord blood samples, and may differ in other obstetric practices.

### 6.1.5 Information bias

Information bias occurs when information about the exposure or the outcome of study objects is systematically inaccurate, i.e. misclassified. Misclassification can be either differential or non-differential. When misclassification is different in the exposed and non-exposed groups, it is differential and leads to under- or over-estimation of the true association. Non-differential misclassification occurs equally in both exposed and non-exposed groups and usually leads to an underestimation, a dilution, of the true association. In observational studies, it is most likely that some misclassifications of exposures and outcomes exist.

In studies, either based on the MBR (***I and II*****)** or the Stockholm-Gotland Obstetric Cohort (***III and IV*****)**, information was prospectively collected, diminishing the risk of bias due to differential recall or recording of information. In ***studies I*** and ***II,*** examining the diagnosis of labour dystocia instead of the partograms in is a limitation. In ***study I***, diagnosis of labour dystocia constitute both the exposure and outcome together with the outcome of mode of delivery in second labour**.** Dystocia is additionally the

outcome in ***study II***. There is a risk that diagnosis of labour dystocia could be misclassified when subjectively obtained by the obstetrician on the delivery ward, at discharge or by specially trained administrative staff. In a study by Nystedt and co-workers in 2014, based on the MBR in 2007-2008, it seems as though dystocia is generally a somewhat underdiagnosed condition in relation to the Swedish version of the ICD-10 definitions (Table 4.2). Diagnoses of dystocia in first and second stages recorded in the medical records were compared with partograms for 829 women. Overall, 13.6% of women had labour dystocia according to the codes and partograms. An additional 8.1% had labour dystocia without a recorded diagnosis. None of the mothers diagnosed with dystocia were reported having a partogram without dystocia. Overall, there were 35.6% nulliparous and 10.2% parous women diagnosed with dystocia.[77] This could lead to a non-differential misclassification for the outcome of labour dystocia in ***study I***. However, the proportions of women diagnosed with labour dystocia in our studies are quite similar as compared to other recent studies with similar definitions, although ours are in the lower range.[74, 77, 85] It was not possible to validate the diagnoses of labour dystocia in our population (see Table 4.3).

If an instrumental vaginal delivery or caesarean is performed, an indication is needed. Therefore, the diagnosis of dystocia is potentially more commonly provided in these situations compared to when having spontaneous vaginal deliveries, which may lead to misclassification. If a woman has previously had dystocia and/or a caesarean, this could potentially lead to that the obstetrician terminates the delivery with a vaginal instrumental or caesarean delivery earlier than without these exposures. Thus, the exposures in ***study I*** could have affected the classification of the mode of delivery outcome. This could lead to an overestimation of the relative risks of instrumental deliveries.

In ***study II***, there is a potential for a more frequent diagnosis of labour dystocia to be derived from surveillance bias. Women using LMWH are generally more often classified as high risk, and are therefore supervised more intensively. This could lead to an increased probability of the diagnosis of dystocia, and consequently a risk of over-estimation. Information on LMWH use in ***study II*** was retrieved from the Prescribed Drug Register using data on time for the dispensed drugs, without information on compliance or dose. A consequence could therefore be a misclassification of having the exposure or not and having presumed high-dose or prophylactic dose.

In ***studies III*** and ***IV***, we had access to information about the duration of second stage and were thus not dependent on discharge diagnoses. Nevertheless, in complicated pregnancies, a potential surveillance bias could have been introduced. If there were any signs of fetal compromise, additional examinations would be conducted and a fully dilated cervix could be noticed earlier than with fewer examinations.

In ***study IV***, information about umbilical cord blood samples was missing for 21% of the deliveries. The likelihood of no blood samples being taken from the umbilical cord of infants born in a compromised state is more probable. Thus, infants born with asphyxia may be more likely to have missing samples. This could lead to differential misclassification, where the true association between a prolonged second stage and acidosis would have been under-estimated. Other neonatal outcomes in ***study IV*** are likely to be similarly classified for infants of all women, with respect to the duration of the second stage.

### 6.1.6 Confounding

Confounding is a form of bias and a central issue in epidemiological studies. The concept of confounding implies that the effect of the studied exposure is confused with the effects of other variables, called confounders, which leads to distortion of the results. If there is an imbalance between

the non-exposed and exposed groups, the confounder affects the outcome. A confounder is associated with the studied exposure and is also a risk factor for the outcome without actually being a part of the causal pathway as an intermediate step (mediator) between the two. It is of major importance to identify potential confounders. Unidentified or unadjusted confounders may distort the real association between an exposure and an outcome. Confounding may be taken into consideration in the study design by randomisation, restriction or matching. If the study population is large enough, randomisation takes care of known and unknown confounders. Restriction is the selection of subjects who have similar characteristics for variables that might be confounders. This increases the internal validity, but needs to be balanced against selection bias and the external validity of the study. Matching is commonly used in case-control studies. In the analysis of the data, multivariable analysis and stratification can be used to control for confounders, provided that information about confounders is available. The power of a study can be a limitation for both stratification and multivariable analysis.

The quality of the variables in the MBR is generally high, and has previously been discussed in the method section (page 29). In the evaluation of the MBR in 2003, Källén and co-workers commented that lack of data obviously affects the estimates of prevalence, but that there is usually little impact on risk estimates if the missing information is random.[153]

Maternal factors, such as age, height and BMI were considered to be confounders in all four studies. For example, in ***study II***, overweight is a confounder in the association of the use of low-molecular-weight heparin with the risk of labour dystocia. Over-weight is a risk factor for thromboembolism, and consequently the use of low-molecular-weight heparin, and is also associated with labour dystocia.[95, 167] Due to the differences in incidence of dystocia, labour management and potential confounders for nulliparous and parous women, either stratification of parity or a restriction to only nulliparous women were made in ***studies II-IV.***

Unmeasured maternal factors and residual confounding was potentially present in all four studies. It is difficult to decide whether some variables in the delivery process are confounders, part of the causal pathway or influence the associations as effect modifiers. Oxytocin is associated with adverse neonatal outcomes, especially when overstimulation occurs.[68] When a prolonged second stage is established, oxytocin can be administered, and would thus be a mediator of the relationship between prolonged second stage and adverse neonatal outcomes. For this reason, it was not adjusted for in ***study III***. In ***study IV***, however, information about the time of administration of oxytocin was used and was related to the different phases of labour. If the treatment started before the exposure, it was considered a confounder. In ***studies I*** and ***II***, we had no information about the administration of oxytocin. Consequently, we were not able to assess if administration of oxytocin was influenced by the exposures (previous dystocia and use of low-molecular weight heparin) compared to the controls.

### 6.1.7 External validity

External validity is the generalizability of the study. Where there is external validity, results can be applied to individuals and settings other than those in the study population. Since ***studies I*** and ***II*** were population-based and nation-wide, where only 1-2% of births were not included, they are generalizable to the Swedish population. ***Studies III*** and ***IV*** were population-based in the Stockholm Gotland region, and included about one fourth of all births in Sweden. Even though there are national recommendations, the clinical practice of dealing with prolonged labours can vary within and between countries. The risk estimates of the four studies cannot be generalised to other populations or other countries. They can, however, provide information for similar settings in developed countries.

### 6.1.8 Random error

Random error refers to variability in data due to chance, and determines the statistical reliability of the results. Random errors can be reduced by increasing sample size and therefore increasing precision. By using statistical methods, the role of random error can be evaluated and should always be considered in observational studies. A confidence interval of 95% is the standard way to present random error. This indicates that if the data collection and analysis would be repeated a hundred times, the interval would include the correct value in 95 of the cases. A confidence interval of 95% was used in ***studies I-IV***. The role of random error can also be presented as a p-value. The p-value is the probability of congruence of the null hypothesis. A low p-value rejects the null-hypothesis.

Significance testing should be considered as a measure of the role of chance rather than the true association between the studied variables. Besides the sample size and statistical significance, the causality of the results should always be reflected upon against the background of the *a priori* hypothesis, the biological plausibility, the strength of the association, the consistency in sub-analyses and other studies as well as the temporality of exposure and outcome.

Validity together with the precision of a study determines its accuracy. Accuracy is an assessment of the adequacy of the study, i.e. that the study measures what it claims to measure, and of how precise these measurements are.

## 6.2 FINDINGS AND IMPLICATIONS

### 6.2.1 Risk factors for labour dystocia

Differences in the ways in which the study populations were selected, the diagnostic criteria used for dystocia and how confounders were controlled for make it difficult to compare studies of labour dystocia.[137, 168]

**Maternal characteristics**

The incidence of labour dystocia is largely dependent on parity and primarily affects nulliparous women.[74, 137] ***Studies I*** and ***II*** considered dystocia overall, including both first and second stages of labour. Dystocia was more common among nulliparous than among parous women in ***study I*** (21.5% and 5.3%, respectively) and in ***study II*** (21.2% and 4.7%, respectively). These results are congruent with other studies of similar populations.[74-77] Since dystocia differs between nulliparous and parous women and confounding can be associated with parity, the most clinically relevant way is to assess these women separately. ***Studies III*** and ***IV*** were restricted to nulliparous women and the duration of second stage was analysed by the hour. In ***study III***, a duration of second stage of more than 3 hours (irrespective of epidural status) affected 20.5% of the labouring women. In ***study IV***, the corresponding rate was 21.3%. This suggests that diagnosis of labour dystocia could be somewhat under-reported in the MBR.

In ***studies I*** and ***II***, maternal characteristics such as increasing age, BMI and short stature were associated with labour dystocia in nulliparous and parous women. Increasing inter-pregnancy interval was additionally associated with dystocia in ***study I***. These findings are supported by previous studies in nulliparous women or women with mixed parities.[84, 85, 91, 92, 96] It was not possible to assess whether or not the influence of these variables was different in the first and second stages[84, 94, 95] as we examined the diagnosis of dystocia irrespective of stage.

In ***study I***, women not cohabiting with the infant's father-to-be showed an increased risk of dystocia in second labour. Lack of support, during pregnancy and labour may have contribute to these findings since emotional and physical support have been demonstrated to reduce the length of the labour process.[169] Smoking was not found to be associated with labour dystocia in ***study I***. Irrespective of parity in ***study II***, a reduced risk of dystocia in unadjusted analyses was demonstrated in women who smoked. This could possibly be explained by the lower infant birth weight in pregnancies with smoking mothers.[170] In a Danish study, there was no association between smoking and labour dystocia.[92] In ***study II,*** assisted reproduction was associated with an increased rate of labour dystocia in both nulliparous and parous women. This finding is supported by a previous study on the first stage of labour, yet disconfirmed by another study.[87 105]

Previous studies have found a relationship between diabetes and hypertensive disorders and prolonged labour.[87, 88] In ***study I***, no association was found between hypertensive disorders and dystocia. In ***study II,*** however, hypertensive and diabetic diseases were associated with increased unadjusted risks of dystocia. ***Study I*** was restricted to deliveries with spontaneous onset of labour. An association could therefore have been hidden, since women with diabetic and hypertensive diseases more commonly have induced deliveries, and especially those with severe conditions.

**Delivery factors**

During the delivery process, the actual fetal weight is unknown. The assessment of fetal birth-weight by ultrasound in during the third trimester is commonly not very specific.[171] In ***study I***, high birth weight in first labour was associated with increasing rates of dystocia in second labour in a dose-response fashion. After adjustments for potential confounders, this association was no longer significant, suggesting that this finding was due to other factors associated with high birth weight. Increasing birthweight in the concurrent pregnancy in ***study II*** was strongly associated with higher rates of dystocia for nulliparous and parous women. When birthweight was added to the adjusted model, the association between dystocia and LMWH was not substantially affected. According to previous reports, rates as well as adjusted risks of birthweight are associated with labour dystocia in both the first and second stages of labour.[81, 87, 88, 115]

### 6.2.2 Epidural analgesia

Depending on the study period and the selection of the population, the frequency of epidural analgesia during labour differed in the four studies. In ***study I***, 37% used epidural in the first labour and 15% in the second labour. In ***study II***, corresponding rates were 50% of nulliparous and 19% of parous women. In ***study III*** and ***study IV***, 59% and 65% of nulliparous women reaching the second stage, used epidural.

Epidural analgesia is strongly associated with dystocia, but is the relationship is causal? Does epidural analgesia cause the labour dystocia or is it a part of the causal pathway? Can epidural be an effect modifier in the association between the dilation pace and an established dystocia; can an already slow progress be more affected by epidural than a normal pace during labour? A large number of studies, some of which have been discussed in the background section (2.4.6), have tried to elucidate the effects of epidurals. The duration of second stage of labour seems to be significantly associated with the use of epidural, but the effects on first stage remain unclear.[121] Women with epidural differ from women who do not use epidural with respect to other maternal characteristics, but how the use of epidural should be accounted for in observational studies is not clear. Some studies assess associations between prolonged labour and delivery outcomes in analyses stratified by epidural use.[79] In other

studies, epidural was either adjusted for,[86, 130, 132, 133] or not adjusted for[80, 131] in the multivariable analyses.

Compared to women without the use of epidural, the proportion of dystocia in second labour in ***study I*** and in first or following labours in ***study II*** were increased in women with epidural. However, both among women with and without the use of epidural in ***study I***, there was an increased risk of recurrence of dystocia irrespective of mode of first delivery. Thus, we could not explain the risk of dystocia in second labour as being a consequence of the use of epidural. In ***study II***, adjustments and stratified analyses for use of epidural were made, but the association between LMWH and the risk of dystocia was still non-significant among nulliparous and parous women whether an epidural was given or not.

In ***studies III*** and ***IV***, the overall rates of a low 5-minute Apgar score, birth-asphyxia-related complications and admission to NICU among women with epidural was higher than among women who had not had an epidural. In ***study III***, epidural was not found to be an effect-modifier and was therefore treated as a confounder. There is no support in previous studies, however, of an association between epidural analgesia and adverse neonatal outcomes.[121] The effect of an epidural could therefore be due to other confounders associated with their use. In addition, analyses stratified by epidural use were made.

In ***study IV***, the risks of birth-asphyxia related complications and admission to NICU generally increased with duration of second stage in deliveries both with and without epidural. Use of epidural could therefore not explain the association between duration of second stage and adverse neonatal outcomes. Laughon and co-workers even proposed that an increased duration of second stage with epidural analgesia could be less harmful for the infant than a prolonged duration due to other underlying factors.[79]

### 6.2.3 Recurrence of dystocia and mode of delivery in second labour

That labour dystocia primarily affects nulliparous women is well known, but there is little information how previous dystocia influences the subsequent labour. To our knowledge, ***study I*** was the first study to investigate the risk of dystocia recurrence and its relation to the mode of delivery. One in twenty women experienced dystocia in second labour. Among women with previous dystocia, one in ten was also affected in their second labour. However, there were large variations among different groups. Risk of dystocia in second labour was largely influenced by the previous mode of delivery. Further, the risk of having labour dystocia and instrumental vaginal or caesarean delivery in second labour was largely influenced by maternal and delivery characteristics. We therefore created a risk score based on the adjusted odds ratios of labour dystocia.

Compared to women with a normal duration of labour, dystocia is associated with a more negative experience of the delivery and the labour pain.[77, 143, 144] A previous prolonged labour could therefore influence the decision about further pregnancies and a preference for elective caesarean section. Additionally, if having a trial of labour in second childbirth, dystocia in previous delivery can influence the interventions during labour and the spontaneous vaginal delivery rates.

In ***study I***, the results could be applied to create a more individualised antenatal guidance and risk assessment of labour. If a woman has experienced a previous dystocia with a vaginal (non-instrumental or instrumental) delivery, the risk of recurrence of dystocia was only 1 in 10, with low risks of both vaginal instrumental and emergency caesarean deliveries. This could support a woman's

decision to aim for a vaginal delivery in following pregnancy. Our risk score has, however, not been tested in a clinical setting.

### 6.2.4 Caesareans and trial of labour after caesarean

The annual overall incidence of caesarean deliveries in Sweden has increased over time, reaching 17.7% in 2014.[8]. The numbers continue to rise, especially in the elective caesarean group (Figure 2.2). Other western countries like England and the US, have annual incidences of caesareans of 26%, and 33%, respectively.[42, 172] Compared to vaginal delivery, procedure of caesarean section is associated with increased risks of short-term severe maternal morbidity in a low-risk population.[173, 174] Additionally, there are long-term risks of maternal morbidity and mortality following caesareans.[175]

In order to prevent overuse and non-medically indicated caesarean sections, clinically important approaches are prevention of the first caesarean and trial of labour after caesarean (TOLAC). The clinical practise regarding TOLAC differs among countries and even between hospitals. In the US, the most common indication for a caesarean section is an elective repeat caesarean due to previous uterine scare.[176] After one earlier caesarean section, the general Swedish recommendation is to aim for a second vaginal delivery in the absence of medical indications for caesarean. After a second caesarean, an elective caesarean is most commonly recommended.[177] According to recent US studies, less than one in three women had a trial of labour after a previous uterine scar,[176] and 8-16% had a vaginal birth after a caesarean (VBAC).[127, 176, 178] Depending on the selection of women for TOLAC, studies have reported a successful vaginal birth rates of 57-76%.[176, 179, 180] This corresponds to our study on women with spontaneous onset, where almost two out of three with an earlier caesarean had a trial of labour. Among these women, 77% who had not had previous dystocia and 68% with previous dystocia had a successful VBAC.

In deliveries with trial of labour after caesarean with previous dystocia compared to those without, a repeat caesarean is more common.[181-183] Several studies and guidelines for TOLAC stress the importance of identifying demographic and previous obstetric information along with current obstetric characteristics to evaluate the possibility of a successful VBAC.[177, 184-187] An earlier caesarean due to dystocia is commonly noted as a negative predictor[187], although the recurrence rate of dystocia is still unclear. Compared to elective repeat caesareans, rates of maternal complications are higher for failed TOLAC and lower for VBAC.[187] In assessing the risk of adverse outcomes, the probability of a successful VBAC is therefore important to estimate.

### 6.2.5 Low-molecular-weight heparin and labour dystocia

In ***study II***, the use of LMWH during pregnancy and diagnosis of prolonged labour were not associated after adjustments for maternal, delivery and fetal characteristics in our population-based study of more than 500 000 term or post-term nulliparous and parous women with induction or spontaneous onset of labour.

The hypothesis that there is an association between LMWH and labour dystocia was based on the heparin sulphate proteoglycans role in the cervix and uterus during the ripening and delivery processes.[38 36, 37] The LMWH dalteparin increased myometrial smooth muscle contractility in vitro, and this effect was primarily observed together with oxytocin.[39] In ***study II***, we could not study this mediation since we did not have information about the use of oxytocin.

The association between use of LMWH and the duration of labour has previously been assessed in two Swedish investigations.[164, 188] In these studies, 99 and 104 nulliparous women were exposed to the LMWH dalteparin. Exposed women had shorter mean labours and a lower risk of prolonged first stage of labour compared to controls.[164, 188] LMWH had no effect on the second stage duration.[164]

In contrast to these studies, we examined the diagnosis of dystocia rather than the estimated duration of labour. Our study differed to the one by Ekman-Ordeberg since we included women with emergency caesarean deliveries and women with induction of labour. In the study by Ekman-Ordeberg, exposed and unexposed women were matched by age and stratified by use of epidural analgesia, but no adjustments were made for other potential confounders.[188] In the study by Isma and co-workers, there were significant differences of variables such as maternal age, maternal weight, epidural analgesia, gestational length at delivery and frequency of preterm deliveries in the two groups. This was not accounted for in the analysis and may partly explain the shorter duration of labour among women using LMWH.[164]

In the subgroup analyses where LMWH use in third trimester was divided by presumed dose, there was an increased risk of labour dystocia for nulliparous women in the presumed high dose group, compared to no treatment. These results have to be interpreted with caution, but could be due to that these women are a high-risk group, with more frequent surveillance and potentially also interventions during delivery.

In these three studies of the association between LMWH and prolonged labour, all exposed women exposed had an indication for the use of LMWH. These underlying factors could be associated with the duration of labour. The underlying biological effects of LMWH is of great interest since we do not have any drugs other than oxytocin to prevent or treat labour dystocia. The use of LMWH during pregnancy is safe for

the offspring, since LMWH neither cross the placenta nor pass into breastmilk.[189] A randomised controlled trial of the effects of LMWH use on delivery and obstetric outcomes is warranted.

### 6.2.6 Neonatal consequences of prolonged second stage of labour

In our two large population-based cohort studies (***III*** and ***IV***) of nulliparous women in gestational week 37 or more reaching the second stage of labour, we found an increased risk of low 5-minute Apgar score, birth asphyxia-related complications and admission to the neonatal intensive care unit (NICU), even after adjustments had been made for maternal and infant characteristics, and delivery management. Furthermore, the results were also significant when restricted to vaginal non-instrumental deliveries in both studies.

The outcomes were relatively rare and hence, the absolute risk differences for a 5-minute Apgar score of <7 and <4, and birth asphyxia-related complications were small. Still, regarding admission to NICU, the absolute risk difference between second stage duration of less than 1 hour compared to 4 hours or more was 4.5%. The overall rates of adverse neonatal outcomes were similar to those reported in other studies.[80, 81, 131]

Several large studies of contemporary nulliparous populations, with adequate adjustments for confounders support our results in ***studies III*** and ***IV***.[78, 79, 81]In a population-based study by Allen and co-workers, a second stage of less than two hours was compared to durations that was beyond two hours by the hour. An increased adjusted risk of a 5-minute Apgar score <7 was found in the groups with a duration of more than 2 hours to 4 hours. Among spontaneous vaginal deliveries, there was an increased risk of birth depression (delay in initiating and maintaining respiration after birth requiring

resuscitation by mask or endotracheal tube for at least 3 minutes, a 5-minute Apgar score of 3 or less, or neonatal seizures due to HIE), admission to NICU and composite perinatal morbidity with second stages longer than 2 hours.[78] These results are similar to a recent large cohort study stratified by use of epidural analgesia. In nulliparous women, adjusted risks of NICU admission, sepsis, and a 5-minute Apgar score <4 were significantly increased with prolonged duration, regardless of epidural status. With a prolonged second stage, the risk of severe asphyxia increased among women with epidurals and perinatal mortality increased in the non-epidural group.[79] An association between dystocia in second stage and 5-minute Apgar score, seizures, resuscitation at delivery, NICU admission and increased caesarean delivery rates for non-reassuring fetal heart rate was found in another study.[81] Rouse and co-workers found an increased risk of admission to NICU, albeit not for other adverse outcomes.[80]

Still, a number of other studies suggest that a prolonged second stage is not associated with adverse neonatal outcomes in nulliparous and mixed parities, with access to fetal monitoring.[133-135, 146, 147] These contradictory results may be due to different categorisations of the second stage,[134, 147] restriction to vaginal deliveries,[147] or lack or differences in adjustments of confounding factors[80, 133-135, 146, 147] Furthermore, some studies were rather small and probably affected by limited statistical power.[80, 134, 147]

In ***study IV***, pushing time was associated with increased risks of umbilical artery acidosis and admission to NICU. Furthermore, combined analyses showed that rates of birth asphyxia-related complications and admission to NICU also increased with duration of the passive phase of second stage and were even higher when combined with longer pushing. Duration of pushing, but not duration of the passive phase, was associated with increased rates of umbilical artery acidosis.

Fetal pH and base excess (BE) seems to decrease with duration of second stage but is not influenced by the duration of first stage of labour, although the clinical importance is unclear.[190] In contrast to the passive phase of the second stage, acidosis increases during the pushing phase.[191] Some studies have demonstrated a decline in fetal arterial pH and cerebral oxygenation with prolonged pushing time.[192, 193] Fetal lactate levels increase by approximately 1 mmol/L for every 30 minutes of pushing.[194] These results are consistent with the results in ***study IV*** where an association between duration of pushing and umbilical artery acidosis was demonstrated, whereas risk of acidosis was not related to the total duration of second stage. However, in another Swedish study, pushing for 45 minutes or more was not significantly associated with academia after adjustments had been made for hyperactive contractions and augmentation with oxytocin.[68]

Adverse neonatal outcomes have primarily been assessed in relation to the entire second stage of labour. Studies of neonatal consequences related to duration of pushing indicate contradictory results.[130, 131, 148] With continuous fetal surveillance during delivery, Le Ray and co-workers did not find an association between duration of pushing and adverse neonatal outcomes.[131] In a large study by Grobman and co-workers in 2016, seizures and HIE were more common in infants delivered after a long pushing time. With pushing for 2 hours or longer, an increased adjusted risk of neonatal composite adverse outcome was demonstrated.[130] Another study reported an increased risk of neonatal acidosis after only 15 minutes of pushing.[148]

Even though the absolute risk of adverse neonatal outcomes is low, the consequences can be devastating. HIE is a predictor of significant long-term neurodevelopmental sequelae.[195] Severe metabolic acidosis is associated with low 5-minute Apgar score, seizures, HIE, neonatal deaths and long-term sequelae.[196, 197] A low 5-minute Apgar score is associated with neurological disability and low cognitive function[198, 199]

Balancing the risks and benefits of interventions in the second stage is of major importance. Aiming to reduce non-medically indicated caesareans and instrumental vaginal deliveries, and equally important, avoiding adverse maternal and neonatal outcomes, is a challenge. At the same time, the delivery process should be a positive experience, with adequate pain-relief and support provided. According to ***studies III*** and ***IV***, clinical fetal surveillance is of outmost importance, especially with increasing durations of second stage and pushing. Metabolic acidosis at birth is commonly associated with substandard care, oxytocin misuse, hyperactive labour and failure to respond to pathological cardiotochographic patterns.[69, 70] A prolonged second stage of labour therefore warrants close clinical reassessment of the delivering woman, the contractions and the fetus.

# 7 CONCLUSIONS

- The overall recurrence risk of labour dystocia is only one in ten.
- The risk of dystocia in second labour is associated with previous dystocia and previous mode of delivery, especially caesarean section.
- Long interpregnancy interval, maternal age ≥35 years, high BMI, short maternal stature, not co-habiting with the infants father-to-be and postterm pregnancy are in addition associated with dystocia in second labour.
- Accounting for obstetric history, maternal anthropometríc and demographic factors is important in the risk assessment for dystocia and instrumental delivery in second labour.
- Use of low-molecular weight heparin (LMWH) during pregnancy is not associated with diagnosis of labour dystocia.
- Increasing duration of second stage of labour is associated with increased risk of 5-minute Apgar scores of less than 4 and less than 7 in offspring of nulliparous women.
- Increasing duration of second stage of labour is associated with increased risks of birth-asphyxia related complications and admission to neonatal intensive care unit (NICU) in offspring of nulliparous women.
- Risk of umbilical artery acidosis increased with duration of pushing, but not with the overall duration of second stage of labour.
- The absolute risk differences for neonatal low 5-minute Apgar score, birth-asphyxia related complications and acidosis are low.
- A prolonged second stage of labour and pushing warrants clinical assessment of fetal well-beeing.

# 8 FUTURE PERSPECTIVES

- Reassessment of the labour curves (partograms) among nulliparous and parous women in a prospective manner in a Swedish setting is warranted.

- Different regims (indications and duration of use) for oxytocin administration in first stage of labour needs to be further evaluated with regard to successful vaginal birth rates and adverse maternal and neonatal outcomes.

- Studies on the effects of low-molecular weight heparin (LMWH) on the labour process could be assessed in other settings or as a randomised controlled trial since all current studies are from Sweden, and all women included had an indication for use of LMWH.

- The relationships between durations of second stage and pushing and adverse maternal and neonatal outcomes needs to be studied in a well-powered longitudinal prospective manner with detailed information. Actions should be standardised (i.e. no interventions without an indication), and if possible randomised at different time-limits. The causal effect of the duration of second stage could then be studied.

- To clarify if fetal surveillence can become improved with increasing duration of second stage, and if such improvements reduce the risks of adverse outcomes.

- To demonstrate if the cervical dilatation rate and level of cervical dilation prior to epidural influence the dilatation rate in first stage after administration.

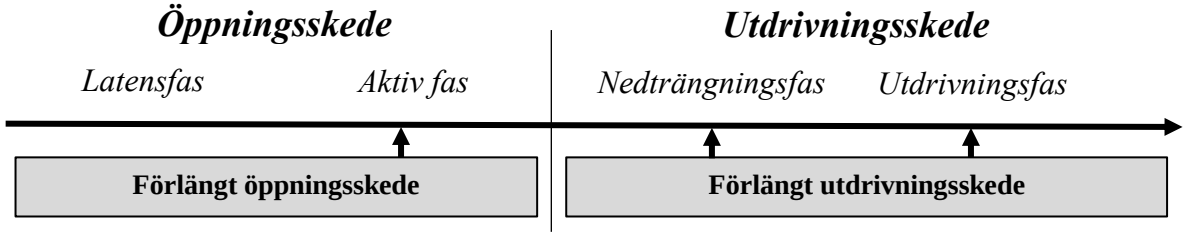
- To find out if the level of cervical dilation at administation of epidural, and the total duration of epidural, influence the passive and pushing phases of second stage of labour.

- Furthermore, to update official national Swedish guidelines of definitions of active phase of labour and normal labour are recommended as a complemet to the Swedish national recommendations for augmentation with oxytocin.

# 9 POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Förlossningsförloppet kan delas in i öppningsskedet (*eng. first stage of labour*), utdrivningsskedet (*eng. second stage of labour*) samt efterbördsskedet (*eng. third stage of labour*). Öppningsskedet kan i sin tur delas in i latensfas och aktiv fas. Latensfasen börjar med sammandragningar, den är ofta diffus och varierar mycket i längd mellan olika förlossningar. En vanlig definition av övergången mellan dessa faser är att två av följande tre kriterier är uppfyllda: att livmodertappen (cervix) är utplånad och öppen 3-4 cm, att kvinnan har regelbundna smärtsamma sammandragningar eller att fosterhinnorna har brustit. Den aktiva fasen håller på tills livmodertappen är helt öppen och varar vanligtvis omkring 6 timmar hos förstföderskor. Därefter börjar utdrivningsskedet som indelas i nedträngningsfas, som varar i 1-2 timmar och utdrivningsfas (krystning) som pågår i 0,5-1 timme.[26] Efterbördsskedet är efter barnets födsel tills moderkakan har krystats ut.

Värksvaghet, som även kallas dystoci eller utdragen förlossning, drabbar ungefär 21-37% av förstföderskor och 2-10% av omföderskor under aktiv förlossning. I utdrivningsskedet är motsvarande siffra för förstföderskor ungefär 7-15%. Värksvaghet kan diagnostiseras under den aktiva fasen av öppningsskedet samt under utdrivningsskedet (Figur 9.1).




**Figur 9.1:** Förlossningsförloppets olika skeden och faser.

Det råder oenighet kring definitionen av startpunkten för aktiv förlossning. Även definitionerna för värksvaghet i de olika faserna skiljer sig. Enligt svenska riktlinjer är värksvaghet under öppningsskedet när öppningshastigheten av cervix i genomsnitt är mindre än 1 cm per timma under tre timmar. En vanlig definition av dystoci under utdrivningsskedet för förstföderskor är mer än 2 timmar och med epiduralbedövning, mer än 3 timmar. För omföderskor är motsvarande gränser 1 och 2 timmar. Värksvaghet behandlas vanligtvis med att ta hål på fosterhinnorna om fostervattnet inte redan har gått. Därefter rekommenderas vanligtvis behandling med oxytocin som stimulerar livmoderns värkar.

Dystoci är associerat med en ökad risk för komplikationer hos modern, som t.ex. blödningar i samband med förlossningen, bristningar i underlivet, infektioner samt instrumentella vaginala förlossningar med sugklocka eller tång. Värksvaghet är en vanlig orsak till akut kejsarsnitt. En utdragen förlossning kan ofta uppfattas mer traumatisk och smärtsam än en normallång förlossning. Detta kan även påverka kvinnan i hennes beslut om framtida graviditeter och förlossningssätt. Angående effekten på barnet av en utdragen förlossning råder det ingen vetenskaplig konsensus.

Syftet med detta avhandlingsarbete har varit att öka kunskapen om riskfaktorer för värksvaghet och konsekvenser av värksvaghet för mödrar och nyfödda barn. Alla fyra studier är baserade på fullgångna och överburna graviditeter (≥ 37 graviditetsveckor), enkelbörder med barn i huvudbjudning. Alla studierna har godkända etiska tillstånd.

**Studie I: Återupprepningsrisk för värksvaghet och risk för instrumentell vaginal förlossning eller kejsarsnitt i efterföljande förlossning**

Vi använde det svenska Medicinska Födelseregistret (MFR) mellan 1992 och 2006 och undersökte nästan 240 000 kvinnor som födde sitt första och andra barn. De analyserades avseende risken att drabbas av värksvaghet, instrumentell vaginal förlossning och kejsarsnitt i andra förlossningen i relation till värksvaghet och förlossningssätt i första förlossningen.

Endast 12% av kvinnorna med tidigare värksvaghet drabbades av värksvaghet i sin andra förlossning. Risken att drabbas i efterföljande förlossning ökade om man tidigare haft värksvaghet och framförallt i kombination med tidigare kejsarsnitt. Ytterligare riskfaktorer för värksvaghet i andra förlossningen var ett graviditetsintervall på 4 år eller mer, moderns ålder ≥35 år, kortvuxenhet, övervikt och fetma hos modern, att ej vara sammanboende med barnafadern samt överburenhet (≥42 graviditetsveckor).

Bland kvinnor med tidigare kejsarsnitt på grund av värksvaghet och flera av dessa riskfaktorer hade 66% en instrumentell vaginal förlossning eller kejsarsnitt i nästkommande förlossning (17% instrumentell vaginal förlossning och 49% kejsarsnitt). Bland de kvinnor som tidigare var förlösta med kejsarsnitt utan värksvaghet och inte hade någon av ovanstående andra riskfaktorer, blev motsvarande 32% förlösta med instrumentell vaginal förlossning eller kejsarsnitt (14% respektive 18%). För en kvinna med tidigare värksvaghet och vaginal förlossning (spontan eller instrumentell), var återupprepningsrisken endast 1 av 10, med låga risker för både instrumentell vaginal förlossning och akuta kejsarsnitt.

**Slutsats:** Man bör ta hänsyn till tidigare värksvaghet, förlossningssätt och andra riskfaktorer i riskbedömningen för värksvaghet och instrumentell förlossning eller kejsarsnitt i nästkommande graviditet.

**Studie II: Associationen mellan användning av lågmolekylärt heparin (LMWH) under graviditet och risk för värksvaghet**

Det finns studier som visar att LMWH kan påverka livmoders förmåga att dra ihop sig och att behandling med LMWH skulle kunna minska förlossningens totala längd. Ungefär 1% av alla gravida i Sverige använder LMWH under graviditeten som förebyggande behandling mot eller som behandling av blodproppar under graviditeten. Vi sammanställde information från MFR, Läkemedelsregistret, Patientregistret och Utbildningsregistret hos mer än 500 000 förstföderskor och omföderskor. Användning av LMWH i tredje trimetern (sista tredjedelen av graviditeten) samt i första och/eller andra trimestern undersöktes med avseende på risken att få en värksvaghetsdiagnos.

Värksvaghet drabbade 21% av förstföderskor och 5% av omföderskor. Vi fann inte någon association mellan LMWH användning under graviditet och risken för att få en värksvaghetsdiagnos, varken hos förstföderskor eller omföderskor. Resultaten var oförändrade efter att vi tagit hänsyn till ett flertal maternella, fetala och förlossningsrelaterade faktorer.

**Slutsats:** LMWH under graviditet minskar inte risken för att drabbas av värksvaghet.

**Studie III och IV: Förlängt utdrivningsskede och risk för negativa neonatal utfall för barnen**

I studie III och studie IV användes en databas med detaljerad information från alla graviditeter och förlossningar i Stockholms och Gotlands län, motsvarande ca ¼ av alla förlossningar i Sverige. Förlossningar hos förstföderskor från 2008 till 2012 inkluderades i studie III (drygt 32 000) och till och med 2013 i studie IV (drygt 42 000). I studie IV användes även det Nationella Neonatala

Kvalitetsregistret (SNQ) för att få tillgång till mer detaljerad information om de barn som vårdats på neonatalavdelningar i anslutning till förlossningen.

Sambandet mellan längden på utdrivningsskedet och risken för låg Apgar score vid 5 minuter hos barnet vid förlossning analyserades i studie III. I studie IV undersöktes utdrivningsskedets längd, samt krystningsfasens längd i relation till acidos (lågt pH-värde i arteriellt blod i navelsträngen), asfyxi (syrebrist)-relaterade tillstånd hos barnet och inläggning för vård på neonatalavdelning. I analyserna tog man hänsyn till maternella, förlossningsrelaterade och fetala faktorer.

De absoluta riskerna för 5-minuters Apgar score mindre än 7 och mindre än 4 var låga (Apgar score <7: 7/1 000 förlossningar, och <4: 1.2/1 000 förlossningar). Jämfört med ett utdrivningsskede på mindre än en 1 timma, ökade dock risken för låg Apgar score för varje timma som längden på utdrivningsskedet ökade. Detta gällde även när vi bara studerade spontana vaginala förlossningar.

Risken för asfyxi-relaterade tillstånd och inläggning för vård på neonatalavdelning ökade också med längden på utdrivningsskedet. Acidos i navelsträngsblod ökade vid lång krystningsfas men inte vid långt totalt utdrivningsskede. De absoluta riskerna för asfyxi och acidos var också låga. I gruppen med utdrivningsskede på mindre än 1 timma blev dock 5% inlagda på neonatalavdelning, i jämförelse med 9.5% vid en längd på 4 timmar eller mer.

**Slutsats:** Det finns en liten, men ökad risk för negativa konsekvenser hos barnet vid förlängt utdrivningsskede. Vid förlängt utdrivningsskede bör därmed förlossningen övervakas noggrant.

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