Delayed Labour – risk factors, use of oxytocin and outcomes

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Cover illustration: Crystal structure of the neurophysin-oxytocin complex

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“Each single action, recommendation or quick procedure, no matter how small these things are for us, they so naturally accumulate that we no longer even realise that we are experiencing an intervention and what the side effects are.” (Schwarz, Stahl 2011: 8)

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ABSTRACT

Background and aim: Delayed labour refers to progress that is slower than what is considered normal and the most common cause of delayed progress is inadequate uterine contractions. It primarily affects nulliparous women and is associated with childbirth complications and negative birth experiences, both of which can have an impact on future pregnancy and labour. Delayed labour is one of the main reasons for the overall increase in the rate of caesarean section (CS) in nulliparous women. Infusion with synthetic oxytocin is a treatment commonly used to enhance uterine contractions in delayed labour, with the aim of achieving a spontaneous vaginal birth. Despite widespread oxytocin use, no consensus exists regarding the dosage. Together with an increase in the use of oxytocin to accelerate labour progress, the incidence of CS due to delayed labour is steadily increasing. The overall aim of the studies in this thesis was to investigate risk factors, the use of oxytocin and outcomes related to a delayed labour progress.

Methods: Two data collections (Studies 1 and 2) were performed, resulting in Papers I-IV. The first two papers (I-II) were based on a retrospective observational study (Study 1) in which 2,000 birth records from 2000-2001 were scrutinised. In Paper I, both nulliparous and multiparous women with a spontaneous or induced onset of labour were included. Risk factors for delayed labour, frequency of interventions and outcomes were analysed in 1,480 women. In Paper II, oxytocin use in 1,263 nulliparous and multiparous women with spontaneous onset of labour was analysed further. Multiparous women without previous vaginal delivery (n=35) were excluded. Papers III and IV were based on a double-blind, randomised, controlled trial (RCT) (Study 2) in which infusion with a high dose of oxytocin was compared with a low dose for augmentation of delayed labour in nulliparous women with spontaneous onset of labour. The hypothesis was that a high-dose regimen, compared with a low-dose regimen, would reduce the number of CSs without negative maternal and neonatal outcomes. In Paper IV, experiences of childbirth and of labour pain in the two randomised groups were compared via the Childbirth Experience Questionnaire (CEQ) sent out one month after birth. The primary outcomes were CS rate (Paper III) and childbirth experience measured with the three domains of the CEQ: Own capacity; Perceived safety; and Participation (Paper IV).

Results: Delayed labour occurred in 21% of all births and the main observed risk factors were nulliparity and multiparity without previous vaginal birth, epidural analgesia (EDA), gestational age ≥ 42 weeks and birth weight > 4,000 grams (*Paper I*). Among nulliparous and multiparous women with spontaneous onset of labour, oxytocin was administered in 72.8% and 38.1 % respectively, but, for the majority, the criteria indicating delayed labour were

not met. Oxytocin augmentation was also undertaken in an unstructured manner. The frequency of operative births (instrumental vaginal birth and CS) in nulliparous women was higher for oxytocin recipients with delayed labour than for oxytocin recipients without delayed labour (40.9% versus 13.6%; p<0.001) (*Paper II).* Augmentation with a high dose of oxytocin did not lower the CS rate in nulliparous women with spontaneous onset of labour, compared with a low dose, despite a higher total dose and higher dose increment. More events with tachysystole together with signs of fetal distress occurred with a high-dose regimen, but there were no differences in neonatal outcomes. (*Paper III*). Childbirth experiences in the three domains did not differ between the randomised groups but were associated with mode of birth (*Paper IV*).

Conclusion: The retrospective observational study found that nulliparous women ran an increased risk of delayed labour and operative birth (instrumental vaginal birth and CS). Multiparity without previous vaginal birth was also a risk factor for delayed labour and CS. As a result, a CS in a first birth might increase the risk of delayed labour and operative birth in a following labour. Oxytocin augmentation was used in an incorrect manner, both in excessive doses and by administration "too early or too late". The RCT showed that a high dose of oxytocin was not superior to a low dose in terms of intrapartum CS outcome. As more tachysystole together with suspicious or pathological fetal heart rate occurred with a high-dose regimen and childbirth experience did not differ between the high- and low-dose groups, a low-dose oxytocin regimen is recommended for the treatment of augmentation of labour.

Keywords: delayed labour, oxytocin use, caesarean section, childbirth experiences

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SAMMANFATTNING PÅ SVENSKA

När en förlossning går långsammare än förväntat eller progressen helt avstannar benämns detta oftast som ”förlängd förlossningsprogress” eller ”långsam förlossning”. I svenskt språkbruk används mestadels ordet ”värksvaghet” för att beskriva när förlossningen inte går framåt som förväntat. Inom förlossningsvården är en förlängd förlossningsprogress ett vanlig förekommande problem, som främst drabbar förstföderskor och som är förenat med ökad risk för komplikationer som operativ förlossning med kejsarsnitt eller sugklocka och en negativ förlossningsupplevelse. Behandlingen av förlängd progress är huvudsakligen inriktad på att stimulera värkarbetet med infusion av syntetiskt oxytocin, för att normalisera förlossningsprogressen och uppnå en spontan vaginal förlossning. Trots att användningen av oxytocin för värkstimulering har ökat, är andelen operativ förlossning fortsatt hög bland kvinnor med förlängd progress.

Det övergripande syftet med avhandlingsarbetet var att undersöka riskfaktorer och förlossningsutfall vid förlängd förlossningsprogress, samt att undersöka handläggning av värkstimulering med oxytocin under förlossning.

Två datainsamlingar har genomförts (Studie 1 och 2). Studie 1 var en retrospektiv observationsstudie med granskning av förlossningsjournaler avseende riskfaktorer, handläggning av värkstimulering med oxytocin och förlossningsutfall i relation till en förlängd förlossningsprogress. Detta genererade två delarbeten (delarbete I och II). I delarbete I ingick både förstföderskor och omföderskor med spontan start eller induktion. I delarbete II ingick kvinnor (förstföderskor och omföderskor) med spontan förlossningsstart. Kvinnor med induktion och omföderskor utan tidigare vaginal förlossning exkluderades. Studie 2 var en dubbelblind, randomiserad, kontrollerad interventionsstudie där behandling med hög- alternativt lågdos oxytocin vid förlängd förlossningsprogress utvärderades. Studie 2 genererade delarbete III och IV. I delarbete III och IV ingick förstföderskor med spontan förlossningsstart. Hypotesen var att hög dos oxytocin ger färre akuta kejsarsnitt än låg dos utan att påverka förlossningsutfallet eller förlossningsupplevelsen inklusive upplevelse av smärta. I delarbete IV studerades förlossningsupplevelsen i de två randomiserade grupperna via ett validerat frågeformulär (Childbirth Experience Questionnaire, CEQ) en månad efter förlossningen samt även specifikt upplevelsen av smärta direkt efter förlossningen och en månad efter. Den primära utfallsvariabeln i delarbete III var akuta kejsarsnitt och i delarbete IV förlossningsenkätens (CEQ) tre dimensioner: Egen kapacitet, Trygghet och Delaktighet.

Resultatet visade att riskfaktorer för förlängd förlossningsprogress var att vara förstföderska, omföderska utan tidigare vaginal förlossning, användning av EDA både i tidigt skede (cervix öppningsgrad ≤ 5 cm) och i senare skede (cervix öppningsgrad > 5 cm) av förlossningen, graviditetslängd ≥ 42 veckor, samt en födelsevikt hos barnet på > 4000 gram. Akut kejsarsnitt och sugklocka förekom i högre grad hos kvinnor med en förlängd förlossningsprogress (38.6 %) jämfört med kvinnor med en normal progress (6.4 %) (delarbete I). Det förekom en kraftig överanvändning av oxytocin för värkstimulering, samt felbehandling med både ”för tidig” och ”för sen” insättning av läkemedlet i relation till diagnostiserad förlängd progress. Trots oxytocinbehandling vid en förlängd progress, var frekvensen av akut kejsarsnitt hög hos förstföderskor, 17.1% jämfört med 2.3 % för kvinnor i gruppen med normal progress (delarbete II). Behandling med hög dos oxytocin gav inte färre akuta kejsarsnitt. Förlossningslängden var 23 minuter kortare vid högdosbehandling och det förekom fler överstimuleringar med fosterljudspåverkan vid högdosbehandling, även om det inte var skillnad i neonatalt utfall. (delarbete III). Det fanns inte heller någon skillnad i förlossningsupplevelse (CEQ) mellan de två randomiserade grupperna. En subgruppsanalys av hela gruppen visade att kvinnor vars förlossning avslutats operativt (kejsarsnitt eller sugklocka) skattade förlossningsupplevelsen mer negativt jämfört med kvinnor med spontan vaginal förlossning (delarbete IV).

Sammanfattningsvis visar avhandlingsarbetet att en förlängd förlossnings-progress var ett vanligt förekommande problem hos förstföderskor och innebar en ökad risk för operativ förlossning (kejsarsnitt och sugklocka). Detta bör särskilt beaktas då en komplicerad första förlossning kan öka risken för både medicinska och psykologiska konsekvenser inför en eventuell nästkommande förlossning. Behandling med oxytocin genomfördes på ett ostrukturerat sätt och följde inte de rådande riktlinjerna, vilket resulterade i att kvinnor utsattes för både onödig behandling och felbehandling. En hög dos oxytocin i värkstimulerande syfte gav inte färre akuta kejsarsnitt hos förstföderskor än behandling med låg dos och påverkade inte förlossningsupplevelsen jämfört med lågdosbehandling. Högdosbehandling gav fler överstimuleringar med fosterljudspåverkan, och studien visade inga fördelar av att rutinmässigt behandla med hög dos oxytocin vid en förlängd progress. I det kliniska arbetet på förlossningsavdelningen bör rutiner för värkstimulering med oxytocin kontinuerligt följas upp och diskuteras för att minska onödiga interventioner.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Selin L, Wallin G, Berg M.
Dystocia in labour – risk factors, management and outcome: a retrospective observational study in a Swedish setting.
Acta Obstetricia et Gynecologica. 2008;87:216-221.

II. Selin L, Almström E, Wallin G, Berg M.
Use and abuse of oxytocin for augmentation of labor.
Acta Obstetricia et Gynecologica. 2009; 88:1352-1357.

III. Selin L, Wennerholm U-B, Jonsson M, Dencker A, Begley C, Wallin G, Wiberg-Itzel E, Almström E, Petzold M, Berg M.
High-dose versus low-dose of oxytocin for labour augmentation: a randomised controlled trial. *Submitted.*

IV. Selin L, Berg M, Wennerholm U-B, Dencker A.
Women's childbirth experiences in relation to dosage of oxytocin for augmentation of labour: a randomised controlled trial. *Manuscript.*

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CONTENT

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
CEQ	Childbirth experience questionnaire
CS	Caesarean section
BMI	Body mass index, kg/m2
CTG	Cardiotocography
EDA	Epidural analgesia
FHR	Fetal heart rate
mU	microUnit
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
RCT	Randomised controlled trial
SFOG	Swedish Society for Obstetrics and Gynaecology
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analogue scale
WHO	World Health Organisation

PREFACE

I have spent virtually my entire professional life as a midwife on the labour ward at the NU Hospital Group (apart from nine years in the Amazonas region in Peru working on preventive health care). Being involved in and accompanying a women and her partner through a life event like childbirth still feels like a privilege. What is more, being given the opportunity to conduct research on a subject of interest has been thrilling.

Two circumstances have influenced my choice of research. First in 1997, the delivery wards from two different hospitals with different working cultures were merged (one of them was the NU Hospital Group). Two work environments intersected, with different procedures and different approaches. We were all influenced by our previous working culture and some of us were more influenced by the active management-of-labour approach, while others were more influenced by a more expectant approach. Secondly, I had been involved for several years in counselling women expecting their first child who had a fear of childbirth and pregnant women with a negative childbirth experience from a previous labour and birth. For many of these women with previous childbirth, the duration of labour had affected their birth experience. Labour that was both too short and too long had been a traumatic event and, instead of having positive memories, these women brought fear and worries into their new pregnancy and labour. Both these situations aroused my interest in increasing our knowledge of the occurrence of delayed labour and in investigating management during labour, especially with regard to oxytocin augmentation. I hope that my conclusions in this thesis could be useful in promoting the health of women in labour and also could add to a positive childbirth experience.

1 INTRODUCTION

Defining what constitutes "normal birth" is not easy, because the limits of what is considered to be "normal" are changing, as history develops and between cultures. Today, the definition of "normal birth" is close to what is defined as "natural", even though both interventions with pharmacological analgesia and augmentation of labour are used.

The most important criterion for a normal birth has been summarised by the World Health Organisation (WHO) and by SFOG in Sweden in a state-of-the-art document and is defined as:

> Low-risk singleton pregnancy with spontaneous onset of labour, low risk at the start of labour and remaining so throughout labour and birth. The infant is born spontaneously in the vertex position between 37+0 and 41+6 (weeks+days) of pregnancy. After birth, mother and infant are in good condition (1, 2).

A consensus statement that defines normal labour from a physiological perspective has been developed in a Delphi study consisting of a group representing three US midwifery organisations and members representing childbirth advocacy and consumer groups (3). The concept of normal physiological birth describes the usual, functional processes of an organism: "A normal physiological labour and birth is one that is powered by the innate human capacity of the woman and fetus" (Kennedy 2015) (4). This definition is based on evidence that suggests that, when healthy women and fetuses are left undisturbed and supported in an adequate manner, they usually experience normal physiological labour and birth (4).

1.1 Progress of labour

Defining what constitutes a "normal duration of labour" is a challenge, as consensus on the definitions of the onset of the active phase and the duration of the different stages of labour is lacking (5). Fifty years ago, up to 24 hours was regarded to be a normal duration for nulliparous women, compared with 12 hours today (5, 6). When considering labour progress, it is important to be able to distinguish what is normal and what is not, to be able to recognise the time for intervention (7).

In 1955, Friedman was the first to describe labour progress in a small group (n=100) of nulliparous women with a curve recording the status of cervix dilation throughout labour (8). The findings were plotted onto a schedule and formed a sigmoid shape, well known as the Friedman curve with a slow initial phase, the latent phase with a more rapid change in cervical dilation rate including cervical full dilation and the descent of the fetus. The latter phase was named the active phase of labour and starts, according to Friedman, when the cervix is dilated 2-2.5 cm and has an expected cervical dilation of approximately 1.5 cm per hour. Clinical practice norms have been strongly influenced by Friedman's findings, even though a debate related to what the normal progress of labour is, has been going on at the same time (9). Subsequent studies have indicated that labour is slower than Friedman's results indicate (9, 10). In the 1970s, Philpott and Castle suggested, according to their results, cervical dilation averaging one cm per hour in active labour and regardless of parity (10). Two decades later, Albers et al. showed that active labour in a low-risk population lasts considerably longer than Friedman's norm and without increased morbidity. The mean 7.7 hours for length of the first stage of the active phase was for nulliparous women and 5.7 hours for multiparous women (5). A reassessment of the Friedman curve was made by Zhang et al. in 2002 with a study of 1,329 low-risk women in whom both cervical dilation was slower at the start of the active phase and the dilation rate did not include a deceleration phase (11). The results indicated that, the progress of labour is more consistent with the results of Albers et al. The findings from Zhang's reassessment were confirmed in a large cohort of 62,415 women in 2010 (12). According to the WHO in 2018, the duration of the active first stage (from 5 cm to full cervical dilation) is usually no longer than 12 hours for nulliparous women and no longer than 10 hours for multiparous women (5).

1.1.1 First and second stage of labour

Latent first phase

Labour is usually divided into the first and second stage, where the first stage is further divided into the latent phase (or latent first phase) and the active phase (or active first phase) (5). The latent phase is characterised by irregular and more or less painful contractions, together with slow cervical dilation (5). The duration of the latent phase varies between women. According to Friedman, a prolonged latent phase is defined as longer than or equal to 20 hours in nulliparous women and 14 hours in multiparous women (8). In Sweden a duration of the latent phase of more than 18 hours is regarded as prolonged (13). The WHO has stated that a latent phase of more than eight hours is prolonged (14).

Active first phase

In the active phase of first phase of labour, contractions become more intense and longer, together with a more rapid change in cervical dilation and a descent of the fetal head (5). Defining the time point of transmission between the latent phase and the onset of the active phase of labour has been described as one of the most important judgements in maternity care and is essential in monitoring labour progress; both to warrant interventions and to avoid unnecessary interventions (15). However, the findings reported by Zhang et al. have shown that there may not need to be a specific time point for transmission to the active phase, that women may enter the active phase at different stages, mostly between 3 and 5 cm of dilation, and that the duration of progression varies from person to person during the active phase(11, 12).

There are different guidelines to define the onset of the active phase of labour and some are presented below.

Sweden: National Board of Health and Welfare 2001 (1)

- Two of three criteria
- Cervical dilation of 3-4 cm
- Three or more regular contractions every 10 minutes
- Rupture of the amniotic membranes

Swedish Associations of Midwives and Swedish Society of Obstetrics and Gynaecology 2015 **(revised recommendation**) (16)

- Cervical dilation of 4 cm or complete cervical effacement and dilation of more than one cm
- Two or more regular, painful contractions every 10 minutes
- Rupture of the amniotic membranes

WHO

- Cervical dilation of 3 cm 1994 (14)
- Cervical dilation of 5 cm 2018 (5)

American College of Obstetricians and Gynecologists

- Cervical dilation of 3-4 cm 2003 (17)
- Cervical dilation of 6 cm 2014 (18)

United Kingdom, NICE guidelines 2014 **(7)**

- Progressive cervical dilation from 4 cm
- Regular painful contractions

Second stage of labour

The second stage of labour is easier to define and refers to the duration from full cervical dilation to the birth of the child. The second stage starts with the descent of the fetal head, also called the passive stage, due to the absence of involuntary expulsive contraction. An active stage follows when the woman feels the urge to bear down or when the presenting part is close to or by the perineum. Consensus on what should be considered as a normal duration of the second stage also varies. (19). Swedish national guidelines define a normal descending phase with a duration of at least one hour and a bearing-down period of at least 30 minutes (20).

1.1.2 The partogram

A diagnostic tool for assessing labour progression

Based on the Friedman curve, Philpott and Castle developed the partogram (or partograph), an instrument for midwives and obstetricians to monitor labour and to detect deviations in progress and in maternal or fetal well-being. The partogram contains an alert line, which represents a cervical dilation of one cm per hour. This was the modified mean rate of cervical dilation of the slowest 10% of nulliparous women in the active phase in the study group of Philpott and Castle. To follow labour progress, information on cervical dilation is plotted on the partogram. An action line is placed after the alert line, usually after two or four hours. This will then process information when progress deviates from what is considered to be normal (1).

The partogram is recommended by the WHO to be used in active labour in both low- and high-resource settings (14) and it is suggested to be the main labour record, reducing unnecessary duplication of documentation (21).

The partogram appears to be widely accepted but with substantial differences in use (21). Critical opinions, however, mean that using the partogram can result in unnecessary interventions, reduce midwives' autonomy and limit the opportunity to treat each woman as an individual, (22) while other evidence suggests that midwives find the partogram a useful practical tool, as it is easy to use, saves time, gives continuity of care and can be an educational means of assistance (23).

Two systematic reviews assessed the benefits and harm of partogram use related to outcomes. Evidence from the RCTs suggests there are no differences in clinical outcome, such as caesarean section, instrumental vaginal birth or Apgar score at 5 minutes < 7, when a partogram is or is not used (21, 22).

Zhang et al. have suggested a revised partogram for contemporary nulliparous women. This partogram differs from the partogram from the WHO because, based on its results, cervical dilation is not recorded as a continuous measurement and the 95th percentile lines, equivalent to the action line, are exponential stair-like lines rather than straight lines. The partogram of Zhang et al. allows a much slower labour progression of cervical dilation before 6 cm but a much shorter duration than four hours after 6 cm. As a result, the active phase of labour is not recommended to be defined before 6 cm of cervical dilation (12). The partogram proposed by Zang et al. is now being compared with the traditional four-hour action-line partogram in an ongoing multicentre-cluster, randomised trial: the Labour Progression Study – LAPS, including nulliparous women with spontaneous onset of labour and with the primary endpoint of intrapartum CS (24).

1.2 Delayed labour

Delayed labour refers to a progress that is slower than what is regarded as normal and the most common cause of delayed labour is inadequate uterine contraction (6). It affects mainly nulliparous women and is one of the main causes of an adverse labour outcome such as caesarean section and instrumental vaginal birth (25). In the literature, slow progress is mostly described as labour dystocia, prolonged labour, delayed progress, failure to progress or delayed labour (26). One practical classification to categorise labour abnormalities is to describe them as slower than normal (protraction disorders) or the complete cessation of progress (arrest disorders) (27).

1.2.1 Definition of delayed labour

Delayed labour occurs and can only be defined during the active phase of labour (17). There is no common definition of delayed labour and the results presented in the literature can therefore be difficult to evaluate(1, 28). Despite the different definitions, they are all based on the same purpose for a decision to initiate intervention in clinical practice.

The Swedish definitions of delayed labour and recommendations for the augmentation of labour from year 2001 were replaced in 2011. See the definitions below.

Swedish Society of Obstetrics and Gynaecology. Normal labour practice, 2001 (1)

- *The active phase of first stage:* Expected normal progress (mean cervical dilation one cm per hour) is protracted by two hours*
- *The second stage:* Expected normal progress has lasted two hours

**The definition is based on the two-hour action-line partogram*

National Swedish guidelines 2011 (20)

- *Active phase of first stage:* Expected normal progress (mean cervical dilation one cm per hour) is protracted by three hours*
- *The second stage:* Expected normal progress has ceased during the descending phase for at least one hour or the expulsive phase for 30 minutes

**The definition is based on the three-hour action-line partogram*

According to the WHO, it is recommended that the diagnosis of delay in the first stage of labour should be based on a partogram, with a four-hour action-line (28).

1.2.2 Delayed labour: risk factors and incidence

Due to the lack of universal consensus of the definition of delayed labour, the incidence is not accurately known. Some evidence suggests that up to one in every five women experiences delay in labour (29). The incidence for nulliparous women has been reported to be as high as 44% in an English study and 37% in a Danish study both studies including healthy women with a normal pregnancy and spontaneous onset of labour (30, 31)

It has been suggested that various factors influence labour progress negatively; they include nulliparous women, the premature rupture of membranes, induction, hypertensive disorder, hydramnios, gestational diabetes, (32) birth weight > 4,000 g, occiput posterior position, (33) gestational age ≥ 42 weeks, prolonged latent phase, high maternal age, (32, 34) high maternal BMI, use of epidural anaesthesia, (33) (34) women admitted in early labour (35).

A long latent phase and few hours of rest and sleep during the preceding 24 hours have been shown to extend active labour duration (36). The same study showed that food intake as usual during the preceding 24 hours was associated

with shorter labour duration. During the latent phase, women can feel distress and lose their confidence (37). Early labour assessment and support by professionals has shown, albeit with weak evidence, increased maternal satisfaction and reduction in interventions during labour, such as epidural analgesia and augmentation of labour with oxytocin, compared with immediate admission to hospital. There is, however, no consistency in the evidence to suggest whether healthy pregnant women should be encouraged to spend the latent phase at home (38).

In a large retrospective cohort study of 11,368 women with a singleton pregnancy and spontaneous onset of labour, early admission (less than 4 cm cervical dilation) reduced the likelihood of giving birth within 12 hours of admission. In both nulliparous and multiparous women, early admission was associated with an increased likelihood of receiving oxytocin for augmentation and epidural analgesia for pain relief (39). This result is in agreement with earlier studies (35, 40, 41).

Furthermore a multicentre cohort study of 2,810 nulliparous women in term spontaneous labour with a singleton infant in cephalic presentation revealed that the descent of the fetal head above the interspinal diameter, poor fetal head-to-cervix contact and dilation of the cervix of < 4 cm on admission were all obstetric risk indicators for delayed labour (34).

Maternal fear and stress have been associated with delayed labour (42-44) labour, together with an increased rate of instrumental vaginal birth (44) and emergency caesarean section (43). Junge et al. found that women with a severe fear of childbirth used more anaesthetics for pain relief. Maternal mental health factors such as symptoms of depression and anxiety explained the association between severe fear of childbirth and labour pain (44).

Epidural analgesia is a commonly used drug in labour and it is suggested that it is effective for pain relief (45), although the literature is inconsistent on the effects on labour progress and on maternal and fetal outcomes (34, 45). Delayed labour progress and an increased use of oxytocin in relation to epidural analgesia have been identified (46, 47). The analgesia is given into the epidural space and acts mainly locally, but it also passes into the circulation and crosses the placenta.(48) Although only small quantities of the drug reach the maternal and fetal circulations after an epidural administration, (49) there are some concerns about possible adverse effects of the opioids (48, 50) Epidural opioids affect the Ferguson reflex in the late first and second stage of labour and the release of endogenous oxytocin due to the distension of the cervix and upper vagina will be inhibited. This then affects the urge to bear

down, which will be reduced (51) and may lead to delay in the second stage of labour, with a tendency towards more instrumental vaginal deliveries (52).

Traditionally, higher doses of local anaesthetic were used, given as a motor blockade, which inhibited the woman's mobility during labour (53). Today, lower concentrations of local anaesthetic are often given together with an opiate. Mobility is not affected, allowing women to move around during labour (45, 53).

In a Cochrane report from 2011, updated in 2018, 40 randomised, controlled studies (11,000 women), all but apart from six studies, compared epidural analgesia with injected opioid drugs. Both the first and second stages of labour were longer for women with epidural analgesia compared with women in the opioid group and they were also more likely to have oxytocin augmentation (45).

1.2.3 Delayed labour and adverse outcomes

The steady global increase in caesarean section is a matter of great concern. During the last few decades from 1990-2014, an increase in the global average rate of CS from 6.7% to 19.1% has been reported. The highest CS rate (40.5%) was in Latin America and the lowest in Africa with 7.3%. In Europe, the average increase was from 11.2% to 25% (54). Compared with Swedish data, the caesarean section rate in singleton births was 5.3% in 1973 and 17.7% in 2014. There was a difference in the caesarean section rate between the Swedish counties, from the lowest rate of 11.6% to the highest rate of 21.6% (55). Delayed labour is the most common reason for intrapartum caesarean section in nulliparous women (18, 42, 56, 57).

Delayed labour has also been associated with an increased risk of instrumental vaginal births (31), postpartum haemorrhage (31, 58), infection (58), perineal trauma (58), heavily meconium-stained amniotic fluid (31) and a negative birth experience (59-61). The risk of serious, yet rare, maternal or neonatal morbidity has been shown to be steadily increasing with an increased second phase (62).

Delayed labour in the first stage has been associated with maternal fever chorionamnionitis and endometritis (63-65). In a large cohort study, the 90th, 95th and 97th percentiles for progress in the first stage of labour were compared in relation to outcomes. Longer labours were found to be associated with a prolonged second stage, maternal fever, shoulder dystocia, a 5-minutes Apgar score < 3, an arterial cord pH < 7.0 and a cord-base excess of >-12 and admission to the NICU (63).

There is no consistency in the evidence relating to the effect of delayed labour progress in the second stage on neonatal outcome (19). A prolonged second phase of three hours and more has been associated with an increased risk of a low 5-minutes Apgar score in non-instrumental labours of first-born infants and the rate of acidosis was increased in labours with a long pushing time (66) Another study found lower Apgar scores after one minute but not after five minutes (31). Findings from a recent study show an association between most of the adverse neonatal outcomes (such as low 5-minutes Apgar scores, birth-asphyxia-related complications and admission to the NICU) with an increasing duration of the second stage. Umbilical artery acidosis increased with the duration of pushing but not with the duration of the second stage (55).However Menticoglou et al showed that a second stage of labour up to 5 hours could be allowed without adverse maternal or neonatal outcomes (67).

Study results regarding adverse outcomes in labours related to a delayed second stage can be difficult to evaluate and factors other than the progress per se may have influenced the negative outcomes, i.e. the duration and rate of augmentation with oxytocin or the time for pushing (31, 68) In some cases, delayed labour as an indication for a caesarean section is not correct. In an article, Gifford states that delayed labour was commonly falsely diagnosed in the latent phase of labour and to early diagnosed in the second stage. At least 16% of the women delivered by an intrapartum caesarean because of delayed progress were in fact in the latent phase (69).

1.2.4 Prevention and treatment of delayed labour

Endogenous oxytocin plays an important role in the physiological progress of labour. It is a peptide hormone, produced in the hypothalamus and released into the blood circulation in a pulsative manner. During labour, the release of oxytocin increases. It plays an important role during labour by stimulating the frequency and intensity of uterine contraction and cervical dilation. In addition, endogenous oxytocin has been shown to function as pain relief and reduce feelings of anxiety(70). Optimal physiological function enhances the release of endogenous oxytocin and beneficial catecholamines in response to stress (3). During labour, various non-invasive practices are used to relieve pain and to support the women to feel comfortable, safe and relaxed. These practices might promote the physiological process of a normally progressing labour by strengthening the release of endogenous oxytocin (25).

Continuous support during labour

Several studies have investigated continuous support during labour and its effect on labour outcome, as progress of labour, and women's childbirth

experience. Continuous support refers to a person *"who is present solely to provide support, is experienced in providing labour support, and has at least a modest amount of training (such as a doula)". (Cochrane 2017*) (71) Research shows that women value and benefit from the presence of a support person during labour and childbirth (52, 71). A woman's own choice with regard to any person chosen by herself as a companion to assist her with continuous support throughout labour and childbirth is recommended by the WHO. and is seen as an important component of respectful maternity care, as well as being in accordance with a human rights-based approach (5). Continuous support given by a midwife has been shown to result in a shorter duration in both the first and second stage of labour (52). Continuous support by a doula (untrained lay person) throughout labour and childbirth has been assessed to give the most consistent and beneficial effects on childbirth outcomes (52).

In a US randomised, controlled trial, participating middle-class women were supported by a male partner during labour and were fully educated about the process of labour. When additional support was provided by a doula, the likelihood of both caesarean section and the need for epidural analgesia decreased significantly (72). In a meta-analysis in 2012, Hodnett et al. reported a reduced duration of labour and a decreased risk of having a CS when continuous support was given compared with routine use (73).

According to a recent systematic Cochrane review, (71) continuous support during labour may *"shorten duration of labour, increasing spontaneous vaginal birth, decreasing caesarean birth, instrumental vaginal birth, use of any analgesia, use of regional analgesia, low five-minute Apgar score and negative feelings about childbirth experiences" (Cochrane 2017)*

Posture in labour

In the active phase, in normal labour, women should be encouraged to adopt the position they find most comfortable (52). During the second stage, the use of any upright or lateral position compared with supine or lithotomy has been associated with a reduced duration of the second stage of labour (7, 52). In a study of labour augmentation and fetal outcomes in relation to birth positions, women allocated to a birth seat had a significantly shorter second stage, without affecting neonatal outcome negatively (74). In the same RCT, giving birth on a birth seat was not associated with adverse consequences for perineal outcomes (74). However a later population-based study indicates a higher risk of obstetric anal sphincter injury for parous women giving birth on a birth seat (probably for the reason that the expulsatory phase in parous women can be too rapid) (75).

Non-invasive practices for pain relief and relaxation

The use of water for labour and giving birth in water (water immersion) is a widespread practice used for pain relief and relaxation. A recent Cochrane review in 2018 revised 15 trials with water immersion during both the first and the second phase of labour (76). The results of these trials show no differences in the duration of labour, which is in agreement with another study (77). There was no difference in mode of birth, but a reduced use of epidural/spinal analgesia and episiotomy with immersion in water compared with no immersion. Women undergoing immersion described increased satisfaction with their labour experience (76). The evidence level was assessed to be between moderate and very low. It was not possible to conclude whether the differences that were found were due to the water alone or due to the whole water-pool environment with a supporting caregiver nearby (76).

A systematic review was conducted revising of seven double-blind RCT studies comparing sterile water injection with normal saline for women in the active phase of labour. Despite the fact that all the studies reported increased pain relief with sterile water injections, no meta-analysis was performed, due to the use of different scales and a failure to demonstrate a normal distribution of pain intensity or relief. As a result, no robust evidence that sterile water injection is effective as pain relief during labour could be presented. No differences were found in mode of birth. Information on labour duration or the use of epidural analgesia was not available (78). When comparing water injection with acupuncture, women receiving water injections were more satisfied with pain relief (79).

Another review of 13 trials examined evidence supporting the use of acupuncture or acupressure for pain management (80). Single or limited numbers of trials reported less intense pain, increased satisfaction with pain relief, the reduced use of pharmacological analgesia and fewer instrumental births with acupuncture compared with placebo or usual care. Reduced pain intensity was also reported in women using acupressure. The active phase of labour was shorter in the acupuncture group compared with the control group. Length of labour from the initiation of acupuncture was significantly reduced by 71 minutes. There was a reduction of instrumental birth with acupuncture compared with standard care. Despite these findings, no general conclusions or recommendations for clinical practice could be drawn, due to the lack of high-quality trials, together with the small number of studies. There is still insufficient evidence relating to the treatment effect of acupuncture .(80).

Moreover, other practices used during labour are massage, hypnosis and different relaxation techniques, such as relaxation, yoga and music (81). A recent review reports that massage has given a major reduction in pain intensity and a reduced length of labour than usual care during the first stage of labour (82). The results of one study report that massage might help to relieve muscle spasm, give a sense of relaxation and reduce anxiety. The positive effects of massage may be an effect of the hormonal activation of endogenous oxytocin or the regulation of cortisol (70). Results have indicated that women participating in yoga have shorter labours compared with usual care or the supine position (81). Most of the non-pharmacological methods are non-invasive and appear to be safe to use, for both mother and child, but their effectiveness is difficult to evaluate due to the limited high level of evidence (48).

Inhaled analgesia such as nitrous oxide has been one of the most frequently used kinds of pharmacological pain relief (48). The literature suggests that nitrous oxide may offer safe, reasonably effective pain relief for women in labour. It could be an alternative for women who do not want a more pharmacologically invasive method (83). In a systematic review, with data from three studies, women during the first stage of labour reported less pain intensity from intermittent (self-administered) nitrous oxide, 50%, when compared with no analgesia. However, the quality of evidence was affected due to this unexplained heterogeneity and the result must therefore be evaluated with caution (48).

Active management of labour

The concept of the active management of labour was advocated almost five decades ago by O'Driscoll and colleagues to be used as a labour ward protocol for low-risk women in labour. The concept includes both non-invasive practices and more invasive methods. The purpose was to reduce the frequency of labours lasting more than 12 hours, which were defined as delayed labour, and accomplish a reduction in the high rate of intrapartum CS (84). Active management is a complex package of interventions and, in its original form, it includes antenatal education; one-to-one support in labour (continual presence of a nurse/midwife during labour); strict criteria for the diagnosis of labour; routine amniotomy when the active phase of labour is defined (uterine contraction together with cervical effacement); strict monitoring of progress in labour (e.g. by plotting on a partogram); vaginal examination every two hours; strict criteria for identifying slow progress and signs of fetal asphyxia; augmentation with oxytocin when labour progression was less than one cm of cervical dilation per hour; liberal use of analgesia and regular audit of operative births (6, 85). The different components of the concept have been modified

over time and the concept has been adopted worldwide, despite differing opinions regarding the effectiveness in reducing the CS rate (85).

Amniotomy

Amniotomy (artificial rupture of the amniotic membrane) is a common routine intervention to prevent (i.e. amniotomy performed early in labour with the aim to prevent delayed labour) or treat delayed labour. Amniotomy has been considered effective for women with delayed progress and reduces labour duration by between 60 and 120 min (52).

Studies have compared routine amniotomy (i.e preventive treatment)) with conservative treatment (i.e. keep membrane intact as long as possible). In a meta-analysis of spontaneous labour, with routine amniotomy, no evidence was found of a shortening of the length of the first stage of labour or a decrease in CS rate when routine amniotomy was performed in comparison with keeping the membrane intact for as long as possible. In a further sub-group analysis of nulliparous women, however, labour duration decreased by 58 minutes with amniotomy. No information regarding increased labour pain and amniotomy was found in the 14 included trials. Only two trials reported maternal satisfaction (86).

In a recent RCT, nulliparous and multiparous women were randomised to either routine amniotomy by cervical dilation of 3, 4, and 5 cm or amniotomy performed as treatment in the event of delayed labour or signs of a need for surveillance of the fetus or at cervical dilation of 8 cm or more. The results showed a significantly shorter labour, reduced by just over two hours in the routine amniotomy group. Caesarean section did not differ between the two randomised groups and no negative fetal outcomes were found (87).

An association between early amniotomy and adverse outcomes such as fetal heart deceleration, increased SC, fetal distress, infections and an increased risk of cord prolapse has been found (52). However this is not consistent with the findings from Smyth et al. (86). In spite of the common use of amniotomy to prevent delayed labour in clinical practice, there is no clear evidence that the potential benefits outweigh the potential harm (5) and the use of amniotomy to prevent delays in labour is not recommended by the WHO (28).

1.2.5 Synthetic oxytocin for augmentation of labour

Synthetic oxytocin was the first hormone to be isolated, sequenced and synthesised and it has been used clinically as an invasive pharmacological method in labour since the 1950s (88). The drug is used during labour to improve uterine contractions in delayed labour. In addition, it is used to induce

labour and used after birth to prevent haemorrhage (89). When used in delayed labour, the aim is to shorten labour duration to prevent adverse labour outcomes, such as instrumental vaginal delivery or CS (28).

Infusion with synthetic oxytocin is now a common routine for augmentation of labour and one of the most frequently used medications in obstetric care (90). An accelerating trend towards using synthetic oxytocin in labour has been reported (68, 90). There is wide disparity in clinical use between countries and between hospitals in the same country (20, 90, 91). A study comparing 11 hospitals in Sweden revealed large differences in overall oxytocin use, varying from 18.6% to 40.5% (68). Recent data from the Swedish Pregnancy Register from its annual report in 2016 report a large variation in oxytocin use between Swedish hospitals. (92). Considerable variation has also been reported in the dose of oxytocin, both initial doses and in the interval and frequency of dose increase (93). In Sweden, the document entitled *Indication for augmentation with oxytocin during active labour* (20) was published in 2011 with the aim of implementing evidence-based knowledge of oxytocin management and to reach a consensus between the Swedish labour wards in relation to oxytocin use. See Figure 1.

Figure 1. National Swedish guidelines 2011: Indication for augmentation with oxytocin during active labour (20)

Oxytocin infusion

- 1 ml (8.3 microgram/ml=5 IU/ml) of oxytocin in 500 ml of normal saline (6 ml/h = 1 mU/min) Starting dose of 20 ml/h, increased by 20 ml at intervals of 20min
  The maximum dose is 180 ml/h

Regimen

- Amniotomy should be performed prior to the commencement of augmentation with oxytocin.
- The dose should be adapted to individual responses and the minimum possible dose of oxytocin should be used, with the aim of normalising labour progress or achieving a maximum of four to five contractions every 10 min and with 40 s duration.
- The duration of treatment should be at least four hours with optimal augmentation (4–5 contractions/10 min) before a new assessment of progress is made.
- Continuous registration with CTG during time with augmentation and, in the event of any sign of tachysystole (> 5 contractions/10 min) and/or signs of fetal distress such as abnormal cardiotocographic (CTG) pattern, the infusion should be decreased or discontinued.

Three different regimens with oxytocin used to improve labour outcome

It has previously been documented that oxytocin augmentation significantly reduces the overall length of labour (94-96). However, the effectiveness of oxytocin in treating abnormal progress and increasing the frequency of spontaneous vaginal birth is still unclear (25, 95, 97), and different regimens to improve labour outcome have been investigated.

1. Trials with early or delayed oxytocin augmentation

Trials including the whole concept of AML for the prevention of delay in the first stage of labour were studied in a Cochrane systematic review in 2013 (85) including more than 5,000 women. No evidence of a reduction in CS rate in the AML group compared with standard care was found (RR 0.88, 95% CI 0.77-1.01). When data from one trial were excluded due to a large proportion of women being excluded after randomisation, a reduction in CS rate was seen

for women in the AML group (RR 0.77, 95% CI 0.63-094). Labour duration was shorter in the AML group, even though there was a wide variation between the trials in the size of mean reduction from five minutes to up to two hours. No differences in negative fetal outcomes were seen and maternal satisfaction with childbirth experience was similar in the compared groups (85). Another systematic review comprised fourteen trials, of which four were within the AML concept. The effects of both early augmentation with amniotomy and oxytocin for the prevention of delay in labour and of therapy were studied. A reduction in labour duration was observed consistently across the trials and a modest reduction in the number of CS was seen in the prevention trials (98).

A later systematic review of 1,338 trials compared the efficacy of 1) the use of oxytocin versus no use or placebo and 2) the early administration of oxytocin augmentation compared with the delayed administration of oxytocin. Oxytocin was used as a single agent for treating delayed labour. No effects were found on the CS rate in either groups but there was a reduction in labour duration of approximately two hours with early augmentation (97). In one of the trials, oxytocin was given after eight hours in cases of delayed augmentation (94).

2. Partogram trials

When comparing partograms with different action lines, more oxytocin was given with a two-hour action line compared with a four-hour action line. The caesarean section rate was lower when a four-hour action line was used compared with a three-hour action line (22). Evidence related to augmentation of labour based on the partograpm findings is limited (99).

According to women's preferences regarding the placement of the action line in relation to medical intervention, there are contradictory results. Older studies indicate that women are more satisfied with an early placement of the action line and early treatment with oxytocin (23, 100). More recent studies have indicated that women's childbirth experiences did not differ in relation to the early or more expectant management of oxytocin use (101, 102).

To summarise, when comparing early and delayed administration of oxytocin, it is important to take account of whether the early administration of oxytocin is a component in the whole package of AML or whether oxytocin is used as a single agent in the treatment of delayed labour. According to the Guideline Development Group (GDG) of the WHO in 2014, the positive effects on the CS rate in trials with an AML concept probably depend on the "continuous one-to-one care" component which has been shown to be the only component in the package that is beneficial (28).

3. Trials comparing high versus low doses of oxytocin for augmentation
Two systematic reviews have studied delayed labour and treatment with a high-dose regimen compared with a low-dose regimen. In the review by Wei et al, (103) published in 2010, 426 studies of oxytocin treatment were identified. From these 426 studies, 10 RCTs, (with a total of 5,423 women) comparing a high- and low-dose regimen for augmentation of labour among women with a spontaneous onset of labour were included in the review. Only one of these studies was double blinded. A high dose was defined as a starting dose and an increment of ≥ 4 mU per minute. A low dose was defined as a starting dose and an increment of < 4 mU per minute. The increase in the interval was between 15 and 60 minutes. The high dose ranged between 4-10 mU/min and the low dose ranged between 1-4 mU/min. In five of the included studies, the concept of AML (where a high dose of oxytocin was an integral part) was compared with usual care and with a low-dose regimen (103).

In a Cochrane report by Mori et al. in 2011 (104) and in an updated version by Kenyon et al. in 2013 (105) of 16 studies, four studies (three RCTs and one quasi-RCT) with a total of 644 women with spontaneous onset of labour were revised. All the studies which were undertaken in the context of AML were excluded, justified by the difficulty involved in evaluating the dosage effect in the high-dose group. A high dose was defined as a starting dose and an increment of ≥ 4 mU per minute. A low dose was defined as a starting dose and an increment of < 4 mU per minute. The increase interval was between 15 and 40 minutes. The high dose ranged between 4-7 mU/min and the low dose ranged between 1-2 mU/min. In both reviews, the primary outcome was the CS rate. See Table 1 for further information (104, 105).

Table 1. An overview of primary and secondary outcomes in two systematic reviews (Wei et al. 2010 and Kenyon 2013) (103, 105) comparing high versus low doses of oxytocin for the augmentation of labour

	Wei et al. 2010 **10 studies, 5,423 women**	**Kenyon et al. 2013** **4 studies, 644 women**
Caesarean section	0.85 (0.75-0.97) 10 studies, 5,423 women	0.62 (0.44-0.86) 4 studies, 644 women
Instrumental vaginal birth	1.00 (0.86-1.15) 7 studies, 2,817 women	0.83 (0.61-1.13) 3 studies, 444 women
Spontaneous vaginal birth	1.07 (1.02-1.12) 7 studies, 2,817 women	1.35 (1.13-1.62) 3 studies, 444 women
Labour duration > 12h	0.46 (0.30-0.70) 3 studies, 1,504 women	
Length of labour		-0.10 (-0.51-0.31) 1 study, 92 women
Tachysystole	1.91 (1.49-2.45) 5 studies, 1,446 women	1.47 (0.73-2.94) 4 studies, 644 women
5-minute Apgar < 7	1.18 (0.61-2.28) 6 studies, 2,163 women	0.37(0.02-8.50) 3 studies, 444 women
Admission to NICU	1.05 (0.76-1.46) 5 studies, 2,329 women	0.50 (0.22-1.15) 2 studies, 404 women
The results are given as the risk ratio or mean difference (95% CI)		

Both reviews found that a high-dose regimen was associated with a statistically significant reduction in caesarean section, an increase in the frequency of spontaneous vaginal birth and shorter labours. Negative fetal outcomes were not associated with a high dose, even though more events with tachysystole were reported in the review by Wei et al. The results from Wei et al. suggest that the high-dose oxytocin might be more important in preventing caesarean section than the timing of the oxytocin intervention, (103) while the results from Kenyon et al. were considered to have a low evidence grade. Furthermore, a subgroup analysis of nulliparous women in the review by Kenyon et al. did not reveal any differences in CS rate between the two randomised groups (105).

Oxytocin and adverse neonatal outcomes

During labour with increasing cervical dilation, the uterus becomes increasingly sensitive to the given dose of oxytocin, especially when the cervical dilation is 9-10 cm (52). When augmentation of labour with oxytocin is properly supervised, however, few side-effects will occur (89). Despite this, oxytocin administration has been associated with various negative effects, in particular an increased risk of uterine tachysystole (68, 106-110) The violation of guidelines with regard to the use of oxytocin is probably one reason for adverse neonatal outcomes (68). Jonsson et al. have shown that a hyperactive uterine contraction pattern, usually caused by over-stimulation, is strongly associated with fetal distress and acidemia at birth (106, 108), something that has also been confirmed by others (107, 109, 110). In a Swedish study of severe asphyxia due to substandard care during labour, the incautious use of oxytocin was considered to be the cause of severe asphyxia in 71% of the cases (110).

In the USA, a high frequency of obstetric malpractice claims has been associated with oxytocin use (107). Oxytocin has therefore been designated as a high-alert medication (111). Checklists and different standardised protocols have been recommended, with the aim of reducing adverse neonatal outcomes. They include a simple checklist-based protocol mainly assessing uterine response and fetal response to uterine contraction.(93, 107) Moreover, oxytocin augmentation has been associated with excessive pain, escalating the need for analgesia (112, 113) .

1.2.6 Delayed labour and childbirth experiences

Women's experiences of childbirth are multifaceted and influenced by various factors (114) which can affect both following labours and life as a whole, in both a negative and a positive way (114-116). A systematic review by Shorey et al. found that a negative childbirth experience was associated with the decision both not to have another child and to delay the birth of a subsequent child. Maternal requests for caesarean section in a subsequent pregnancy were also seen more frequently together with a negative birth experience (117). In findings reported by Nystedt et al., one third of women with delayed labour had a negative childbirth experience and two-thirds stated that the experience had marked them for life. Labour pain experienced as worse than expected was the main factor that influenced the childbirth experience and women described feelings of being severely ill (59, 60). The association between delayed progress and labour pain leading to the greater use of epidural analgesia and an increased risk of operative intervention has been reported (31). An increased risk of negative and depressive memories has been seen in primiparous women with delayed progress one month after birth (102). Memories over time related

to pain experienced during labour appear to be strongly associated with women's overall birth experience. For women with a negative birth experience, the pain score has been found to be high and unchanging years later, whereas, women with a positive birth experience have been associated with a lower pain score and the potential to forget labour pain over time (114, 118).

Delayed labour and factors, such as a persistent, intensive fear of childbirth, post-traumatic stress disorder and depression, have all been associated with a negative childbirth experience, sometimes as an isolated factor contributing to childbirth experience or interconnected with each other (119-121). One common finding is delayed labour and its relationship with adverse labour outcome such as instrumental vaginal birth, CS and negative fetal outcomes, with admission to the NICU. These are all factors that, in addition to delayed progress per se, have an influence on a negative childbirth experience (61, 114, 122).

In an interview study, women with delayed progress described feelings of loss of control, together with a distrust of their own body capacity (123). Another study by Hardin et al. of women undergoing planned unmedicated labour revealed that the ability for women to remain in control of their own birth, both physically and emotionally, was a strong factor for a positive birth experience (124). Perceived control during labour has been associated with childbirth self-efficacy (125) and that findings reported by Stevens et al. suggest that a woman's à priori preferences for control influence the relationship between perceived control of the birth environment and overall satisfaction with the childbirth experience (125).

2 RATIONALE

Delayed labour is a common problem for women expecting their first child and represents an increased risk of negative outcomes for the mother and the newborn. Moreover, delayed labour is associated with a negative childbirth experience, which can influence the women's daily life in the long-term perspective.

In the 1960s, the Active Management of Labour (AML) model was launched in the belief that, among other things, the early use of oxytocin would lower the caesarean section rate related to delayed labour. But, a common problem in modern obstetric care, is the high frequency of delayed labour among nulliparous women, an excessive use of oxytocin augmentation and an increased frequency of caesarean section, mostly with the indication of delayed labour. It is important to reduce the numbers of CS, especially in nulliparous women with an uncomplicated pregnancy and spontaneous onset of labour. Studying management during labour may increase our knowledge of the intrapartum risk factors for delayed labour. For instance, the use of epidural analgesia and its influence on labour duration is the subject of debate. It is known that oxytocin shortens labour duration, but its effect on reducing the CS rate due to delayed labour is still unclear. Both knowledge and consensus regarding the dose of oxytocin for the augmentation of delayed labour are lacking. Women's childbirth experiences and experience of labour pain related to the dose of oxytocin have not been studied sufficiently and, in addition, oxytocin has been designated as a high-alert medication due to its negative effects when not used in the appropriate way.

Oxytocin use in clinical practice and in relation to delayed labour has not been sufficiently studied. The increased medicalisation of childbirth is a topic for discussion and observational studies can increase our knowledge of routines and compliance with guidelines.

The foundation of knowledge derived from this thesis can optimise the quality of labour and childbirth care. In addition, an increased knowledge of women's experiences of childbirth and labour pain related to the dose of oxytocin makes it possible to take account of not only obstetric outcomes when deciding on the appropriate treatment, but also women's preferences.

3 AIMS

3.1 Overall aim

The overall aim was to investigate risk factors, the use of oxytocin and outcomes related to a delayed labour progress.

3.2 Specific aims

- To investigate obstetric risk factors, frequency of interventions and delivery outcomes for delayed labour (I)

- To investigate the use of oxytocin for augmentation of labour and its relation to labour progress and delivery outcome (II)

- To determine the optimal dose of oxytocin infusion with respect to efficacy and safety when treating delayed labour in nulliparous women (III)

- To compare the childbirth experiences and experience of labour pain in primiparous women who had received high- versus low-dose oxytocin for augmentation of delayed labour (IV)

4 METHODS

To realise the aims, we performed two data collections (Studies 1 and 2) with two papers in each (*Papers 1-IV*) The first study *(Papers I-II*) was performed in 2001 and 2002. The findings in Study 1 (*Papers I-II*) have shown to continue to be of major obstetric concern, even in recent years. This has prompted us to continue the research and deepen our investigation into oxytocin use, in relation to delayed labour and adverse labour outcomes in nulliparous women with spontaneous onset of labour (Study 2, *Papers III-IV*). An overview of the two studies with their respective papers (*I-IV*) included in the thesis is shown in Table 2.

Table 2. Overview of the two studies (Papers I-IV) included in the thesis.

Study	Design	Aim	Analysis	Population
Study 1 Papers I- II	Retrospective observational study	To investigate obstetric risk factors, frequency of interventions and delivery outcomes for delayed labour	Descriptive and comparative statistics; multiple logistic regression	Nulliparous and multiparous women with spontaneous onset of labour or induction
		To investigate the use of oxytocin for augmentation of labour and its relation to labour progress and delivery outcome	Descriptive and comparative statistics	Nulliparous and multiparous women with spontaneous onset of labour
Study 2 Papers III- IV	Randomised, controlled trial	To determine the optimal dose of oxytocin infusion with respect to efficacy and safety when treating delayed labour in nulliparous women	Descriptive and comparative statistics; bootstrapping for calculation of difference between groups	Nulliparous women with spontaneous onset of labour
		To compare the childbirth experiences and experience of labour pain in primiparous women who had received high- versus low- dose of oxytocin for augmentation of delayed labour	Descriptive and comparative statistics	Primiparous women with spontaneous onset of labour

4.1 Population, study design and data collection

4.1.1 Study 1 (*Papers I-II)*

Study 1 (*Papers I-II*) was designed as a retrospective observational study and was conducted at the NÄL Hospital (NU Hospital Group) in Trollhättan, Sweden. Data from 2,000 women were randomly collected from electronic antenatal and birth records (Obstetrics®) for two years, between 2000 and 2001. The total number of births during this period was 5,702.

The inclusion criteria were:

- Nulliparous and multiparous women with a spontaneous or induced onset of labour
- Gestational age of 37 completed weeks and more
- Singleton gestation
- Fetal cephalic presentation
- A confirmed active phase of labour
- Partogram and a cervix dilation of less than 7 cm on admission

The active phase of labour and delayed labour in Study 1 (*Papers I-II*) were assessed and defined retrospectively during the data collection, by closely scrutinising every partogram. The definitions of the active phase of labour and delayed labour are shown in Figure 2.

Figure 2. Definitions of active phase of labour and delayed labour*

Active phase of labour

- Regular painful contractions
- An effaced cervix
- Cervix dilation ≥ 3-4 cm

Delayed labour

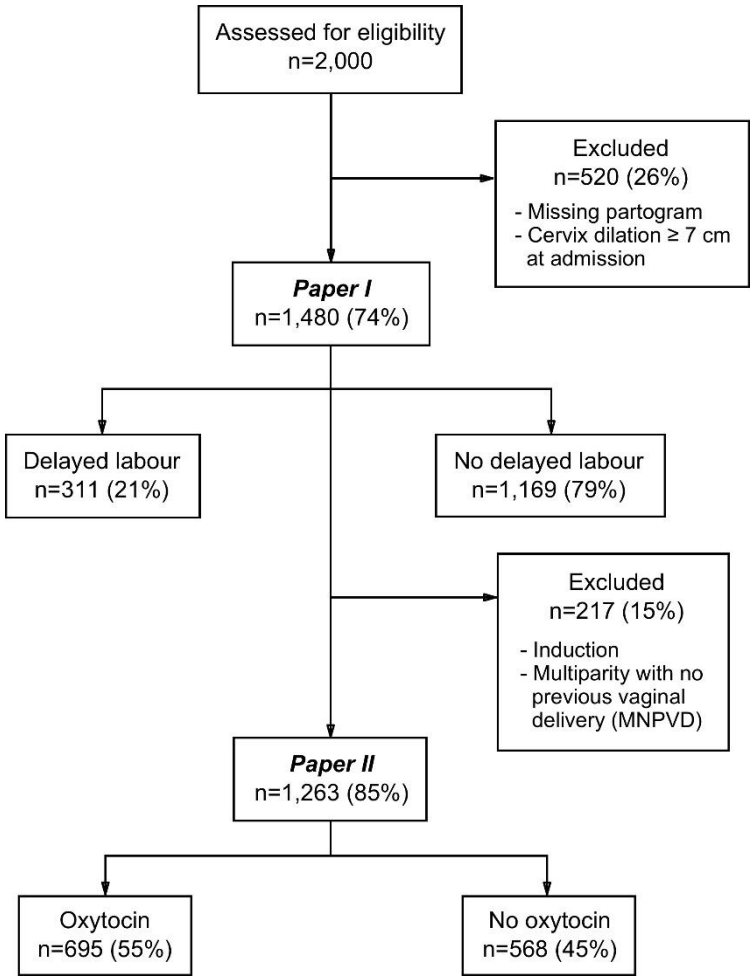
- First stage – based on the partogram alert and action line.
  A two-hour action line defined delayed labour.
- Second stage – a delay of more than two hours

**Based on the Swedish Society of Obstetrics and Gynecology*: Normal labour practice, 2001 (1)

Paper II comprised a subset of women from the data collection and consisted of nulliparous and multiparous women with spontaneous onset of labour. Multiparous women without a previous vaginal birth and women with induction were excluded.

A flow diagram in Figure 3 is showing in the selection procedure.

Figure 3. Flow diagram Papers I-II



Data collection

Data from the obstetric records were imported in an Excel form and transported to SPSS for the analysis. The extracted maternal and fetal information comprised parity; defined delayed labour; maternal age; gestational age; epidural analgesia; oxytocin augmentation; mode of delivery; postpartum haemorrhage; perineal trauma (third- and fourth-degree lacerations); birth weight; Apgar score and umbilical cord arterial pH. In addition, the data extracted for *Paper I* were multiparity without previous vaginal birth; high-

risk pregnancy; abnormal vertex presentation; induction of labour; time for amniotomy; retained placenta and, for *Paper II*, prolonged labour; duration from active phase of labour to defined delayed labour and oxytocin augmentation and administration of oxytocin (administered dose less than prescribed dose, prescribed dose administered, administered dose more than prescribed dose).

High-risk pregnancy comprised women with diabetes prior to pregnancy and gestational diabetes, essential hypertension, pregnancy-induced hypertension, pre-eclampsia and obstetric and medical complications requiring bed rest. Epidural analgesia was analysed for epidural analgesia administered at both cervix dilation of ≤ 5 cm and cervix dilation of > 5 cm.

4.1.2 Study 2 (*Papers III-IV)*

Study 2 *(Papers III-IV)* was designed as a multicentre, double-blind, randomised, controlled trial which was carried out at four hospitals comprising six labour wards in Sweden: Sahlgrenska University Hospital (SU) in Gothenburg (SU-East and SU-Mölndal); Stockholm South General Hospital (SÖS and South BB); NU Hospital Group in Trollhättan and Uppsala University Hospital between September 2013 and October 2016. The wards entered the study at different time points.

The inclusion criteria were:

- Healthy* nulliparous women with a spontaneous onset of labour
- Gestational age of 37+0 to 41+6
- Singleton gestation
- Fetal cephalic presentation
- Confirmed delayed labour
- Ruptured membrane

  * describe a pregnant woman who has no identified risk factors for herself or her baby and who otherwise appears healthy (5)

The definitions used for the active phase of labour and delayed labour are shown in Figure 4.

Figure 4. Definitions of active phase of labour and delayed labour progress.* Papers III-IV

Active phase of labour

- Regular painful contractions
- An effaced cervix and
- Cervix dilation of ≥ 3-4 cm

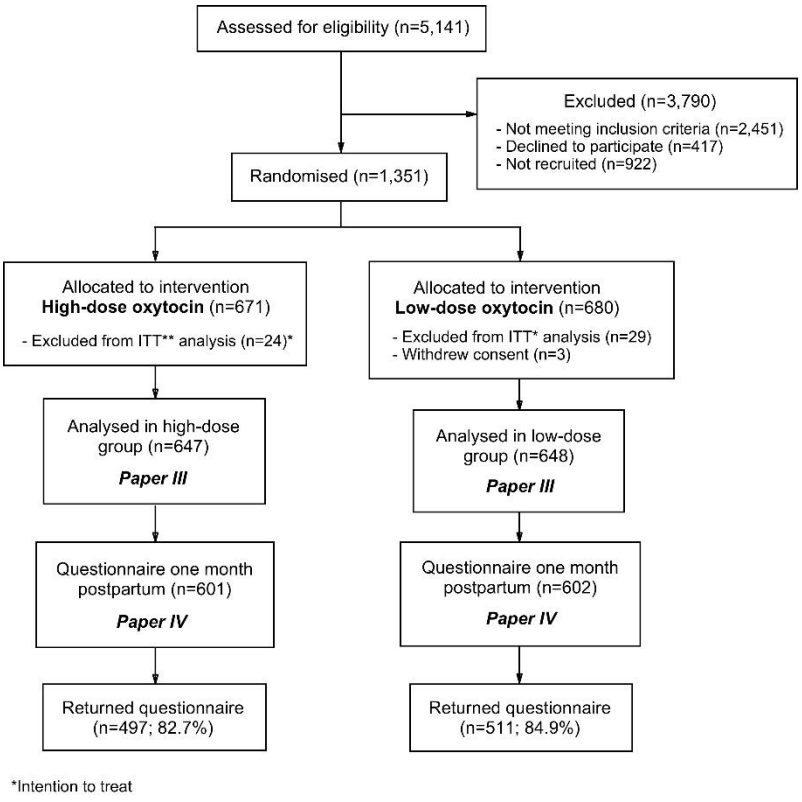
Delayed labour

- First stage – based on the partogram alert and action line. A three-hour action line defined delayed labour.
- Second stage – the arrest of the descent of the fetal head for one to two hours

* In accordance with the Swedish national recommendations 2011 (20)

A flow diagram in Figure 5 is showing the selection procedure. Women not meeting the inclusion criteria were those with a suspicious or pathological CTG, heavy meconium stained amniotic fluid, fever, medical or psychosocial history, pregnancy- or labour-related complications, suspected abnormal presentation, suspected fetal growth restriction (< -2 standard deviation) difficulty understanding written and oral information given in Swedish, age < 18 years and hypersensitivity to oxytocin therapy. Women with delayed labour and fetal head station below the ischial spine in second stage were also excluded. Some of the eligible women had already received oxytocin for augmentation before confirmed delayed labour and they were not included in the study.

Figure 5. Flow diagram Papers III-IV



Intervention and data collection

The intervention consisted of comparing two different doses of synthetic oxytocin administered to women with delayed labour progress. The hypothesis was that a regimen of high-dose oxytocin compared with a low dose will reduce the number of caesarean sections without negative maternal and neonatal outcomes.

- *High dose:* 33.2 micrograms of oxytocin in 1,000 ml of isotonic saline solution. The infusion began with 6.6 mU of oxytocin/min (20 ml/h) and could be increased every 20 minutes by 6.6 mU to a maximum dose of 59.4 mU /minute.

- *Low dose:* 16.6 micrograms of oxytocin in 1,000 ml of isotonic saline solution. The infusion began with 3.3 mU of oxytocin/minute (20 ml/h) and could be increased every 20 minutes by 3.3 mU to a maximum dose of 29.7 mU oxytocin/minute. This "low dose" is the recommended standard dose in Sweden (20).

General written information about the study was available on the included labour wards. Women in the active phase of labour were monitored according to current guidelines. If delayed labour was defined, together with an intact membrane, amniotomy was conducted. If there was still no progress one hour after amniotomy and the criteria for participation were fulfilled, oral and written information was given. After providing consent, the women were randomly allocated to receive a regimen of either a high or a low dose of oxytocin.

The oxytocin infusion was increased until adequate uterine contractions were obtained and the progress of labour was established (i.e. dilation of cervix and descent of the fetal head), or the occurrence of a maximum of five contractions during 10 minutes. The monitoring of the labour progress included assessing maternal and fetal health and followed established and known routines based on national and departmental guidelines.

The progress of labour was documented in each woman's medical record and in a specific check-list protocol. The following variables were assessed at every change of infusion rate and once an hour after a therapeutic dose was obtained:

- Actual infusion rate
- Frequency of contractions in 10 minutes
- Fetal surveillance (normal/suspicious/pathological cardio-tocography)
- Maternal blood pressure (mm Hg) by oxytocin infusion at 180 ml/h and every hour thereafter

Moreover, adverse advents (AE) and severe adverse events (SAE) were reported and assessed as mild, moderate and severe (according to guidelines from the Medical Products Agency)

During the study period, an external data and safety monitoring board (DSMB) consisting of three scientific experts, a statistician, a senior obstetric consultant

and a senior nurse midwife, made periodic reviews and interim analyses of study-specific data and gave recommendations on the continuation, modification or termination of the trial.

One month after birth, a revised version of the Childbirth Experience Questionnaire (CEQ) was sent out to the women who had received augmentation with oxytocin, 601 women in the high-dose group and 602 women in the low-dose group. The questionnaire consisted of 30 items; 25 related to the CEQ, two items related to support and three items related to breastfeeding. The revised CEQ used in this study includes 20 items evaluating childbirth experiences and experience of pain related to the dosage of oxytocin. The items are divided into three domains: *Own capacity* (eight items on sense of control, personal feelings during childbirth and labour pain), *Perceived safety* (six items on sense of security and memories from childbirth) and *Participation* (six items on information, midwifery care and own possibilities to influence the birthing situation) See Table 3.

In the analyses of the CEQ, most of the items were rated on a four-point Likert scale ranging from *Totally disagree*, *Mostly disagree* and *Mostly agree* to *Totally agree*. The visual analogue scale 0-100 (VAS) was used to rate the experience of labour pain, sense of security and control. These scores were classified as 0-40 = 1, 41-60 = 2, 61-80 = 3 and 81-100 = 4. For the negatively worded items and the pain item, the scores were reversed, which gave higher scores for a more positive experience. Self-reported experienced labour pain was assessed two hours postpartum and one month after birth. The anchors of both VAS scales were worded such as: 0 = no pain – 100 = worst possible pain.

The primary outcomes were the caesarean section rate (*Paper III*) and the childbirth experience measured with the three domains of the CEQ. *(Paper IV).* The secondary outcomes were various maternal and fetal variables regarded as important in evaluating the effect of the intervention. In addition, data on various aspects of the use of oxytocin were analysed *(Paper III)* and, for *Paper IV,* self-reported experienced labour pain and mode of delivery were additionally revised.

Table 3. The Childbirth Experience Questionnaire (CEQ)

Table 3. Dimensions and items included in childbirth experience
Own capacity
Labour and birth went as I had expected
I felt strong during labour and birth
I felt capable during labour and birth
I was tired during labour and birth
I felt happy during labour and birth
I felt that I handled the situation well
As a whole, how painful did you feel childbirth was? (VAS)
As a whole, how much control did you feel you had during childbirth? (VAS)
Perceived safety
I felt scared during labour and birth
My impression of the team´s medical skills made me feel secure
I have many positive memories from childbirth
I have many negative memories from childbirth
Some of my memories from childbirth make me feel depressed
As a whole, how secure did you feel during childbirth? (VAS)
Participation
I wish the staff had listened to me more during labour and birth
I took part in decisions regarding my care and treatment as much as I wanted
Both my partner and I were treated with warmth and respect
I received the information I needed during labour and birth
I would have preferred the midwife to be more present during labour and birth
The midwife conveyed an atmosphere of calm

4.2 Statistical analysis

For the analysis of the data, the Statistical Package for Social Sciences (SPSS) version 12 (*Paper I);* version 16 (*Paper II);* version 24 (*Papers III-IV*) were used (SPSS, Inc., Chicago, IL, USA). In addition, SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for *Paper III*. A p value of < 0.05 was considered to denote statistical significance.

4.2.1 *Paper I*

Group comparisons were made between women with and without delayed labour. Statistical associations between categorical variables were tested using the chi-square test or the two-tailed Fisher's exact test. The two-sample t-test was used to analyse normally distributed continuous variables. To predict risk factors for delayed labour, multiple logistic regression using a forward stepwise model was applied. Outcome variables were controlled for parity, birth weight and epidural analgesia, while unadjusted and adjusted odds ratios (OR) were reported together with 95% confidence intervals (CI). Dummy variables were created for parity (reference level "multipara") and EDA (reference level "no EDA").

4.2.2 *Paper II*

Group comparisons were made between women with and without oxytocin infusion and between women with and without delayed labour progress. Statistical associations between categorical variables were tested using the chi-square test or the two-tailed Fisher's exact test.

4.2.3 *Paper III*

The sample size estimation was based on an assumed decrease in primary endpoint CS from 17.5% to 13%, i.e. a reduction of 25%. A total size of 2,090 women was needed for 80% power at a significance level of $p < 0.05$.

An intention-to-treat analysis (ITT) was used with the exception of 56 women excluded from the ITT due to incorrect randomisation or withdrawal of consent. (Some of the women with incorrect randomisation were detected immediately after randomisation and without intervention.) In addition, per-protocol analyses were performed for main obstetric outcomes. Statistical associations between categorical variables were tested using the chi-square test or the two-tailed Fisher's exact test. The Mann-Whitney U-test was used for continuous variables. The calculation of differences between groups for the confidence interval (CI) in continuous variables was based on bootstrapping. For exploratory purposes, an interaction analysis was performed for major baseline variables and dose group in relation to the primary outcome variable of CS rate. Subgroup analysis were performed for the latent phase.

4.2.4 *Paper IV*

Statistical associations between categorical variables were tested using the chi-square test or the two-tailed Fisher's exact test. The Mann-Whitney U-test was used for continuous variables. Cronbach's alpha was used to assess the internal

consistency reliability of the CEQ domains. Childbirth experience between mode of birth (spontaneous vaginal birth, instrumental vaginal birth and caesarean sections) in high- and low-dose groups respectively was compared with the Kruskal-Wallis test. Experiences of labour pain changing over time were tested using the Wilcoxon signed rank test.

5 ETHICAL CONSIDERATIONS

Both studies (Study 1 and 2) in this thesis were approved by the Regional Ethics Board in Gothenburg (Study 1: *Papers I-II*: Dnr:520-02; Study 2: *Papers III- IV*: Dnr: 090-12) and followed the Helsinki Declaration. In addition, Study 2 (*Papers III-IV)* was approved by National Medical Products Agency (Eudra-CTnr: 2012-000356-33) and is registered at ClinicalTrials.gov (NCT01587625).

Papers I-II: No consent from the women was assessed to be necessary in these two studies, as data were retrieved from the patient records. The data were decoded in connection with the data collection and personal data could not be traced without the code key. With respect to the risk of breaches of privacy when using patient records in research, two people were responsible for the data collection and they worked together. A method was developed for the collection of data and data entry. The method was used to minimise the time taken for the review of every single patient record. This prevented the reviewer reading details irrelevant to the study.

Papers III-IV: Information about the study was available on the labour ward and women received written and oral information when a delayed labour progress occurred. Determining the optimal time to ask a woman in labour if she wants to participate in a study could be regarded as an ethical dilemma. We decided not to ask all the women on admission to the labour ward, but only women with confirmed delayed labour were asked to participate. The decision was made to avoid involving women with a normal labour progress in the study. Consent was obtained from the participating women and they were informed that they could withdrew consent at any time without any consequences in terms of care during labour and birth. The risks and benefits of performing a study comparing high and low doses of oxytocin infusion for the augmentation of labour has been assessed. The augmentation of labour with synthetic oxytocin can produce a hyperactive uterine contraction pattern with a risk of fetal asphyxia. However, when rigorous protocols for oxytocin dosage are followed, adverse fetal outcome has not been identified. When oxytocin is administered together with a safety protocol, it has the potential to be a safe and effective treatment for delayed labour that can minimise CS and increase the rate of spontaneous vaginal birth, together with a positive childbirth experience. During the study period, the Swedish national recommendations for augmentation with oxytocin infusion were strictly followed. In addition, a checklist was used to minimise the risks of tachysystole together with suspicious or pathological CTG.

6 SUMMARY OF THE FINDINGS

6.1 Paper I

Dystocia in labour – risk factors, management and outcome

Of the study population (n=1,480 women), delayed labour was identified in 21% of all labours. The frequency of delayed labour in nulliparous women and multiparous women with no previous vaginal birth (MNPVD) was 33.6% and 37.5% respectively, compared with 7.6% in other multiparous women. Independent risk factors for delayed labour, in addition to nulliparity and MNPVD, were gestational age ≥ 42 weeks, epidural analgesia (EDA) both at cervical dilation of ≤ 5 cm and at cervical dilation of > 5 cm, birth weight > 4,000 g and time for amniotomy *(Table 4).* The induction of labour was not associated with a delay in labour.

Table 4. Major independent risk factors associated with delayed labour

	OR (CI 95%)	p-value
Parity		
Nullipara	4.5 (2.8-7.1)	<0.001
Multipara	1(Reference)	
MNPVD*	6.0(2.2-16.2)	<0.001
EDA		
No EDA	1(Reference)	
EDA at cervical dilation ≤ 5cm	4.6 (2.8-7.7)	<0.001
EDA at cervical dilation >5 cm	2.0 (1.3-2.0)	0.003
Gestational age ≥42 weeks	3.1(1.5-6.3)	0.002
Birthweight >4000g	2.7 (1.8-4.2)	<0.001
Amniotomy (h)**	1.3 (1.2-1.4)	<0.001

Data presented as OR(odds), 95% CI and p-values. *Multiparaty with no previous vaginal birth. **Time given in intervals of 0.5 h, from active phase to amniotomy

Among labours with a birth weight over 4,000 g, 30.6% were affected by delayed labour compared with 17.4% of labours with a birth weight of less than or equal to 4,000 g.

Epidural analgesia (EDA) was given to 41% of the women (57.3% nulliparous and 24.4% multiparous) and delayed labour affected more women with EDA (33.4%) than women without (12.5%). Women with delayed labour more frequently received EDA at cervical dilation of ≤ 5 cm than EDA at cervical dilation of > 5 cm (37.3% and 27.7% respectively)

The frequency of operative deliveries, i.e. instrumental vaginal delivery or CS, was high among women with delayed labour Spontaneous vaginal birth occurred in 61.4% of women with delayed progress compared with 93.6% in women with normal progress and the CS rate was 16.7% compared with 1.7% (Table 5). Multiparous women with no previous vaginal birth (MNVPD) gave birth spontaneously in 75 %. In addition, outcomes such as postpartum haemorrhage of >1,000 ml and third- and fourth-degree lacerations did not show any association with delayed labour when controlling for parity, birth weight and epidural analgesia.

Table 5. Delayed labour and mode of delivery

	Delayed labour (n=311	No delayed labour (n=1.169	Unadjusted OR (CI 95%)	Adjusted OR (CI 95%)
Spontaneous vaginal birth	191 (61.4%)	1.094 (93.6%)		
Instrumental vaginal birth	68 (21.9%)	55 (4.7%)	5.7 (3.9;8.3)	3.5 (2.3;5.4)
Caesarean section	52 (16.7%)	20 (1.7%)	11.5 (6.8;19.7)	6.3 (3.5;11.2)

Neonatal acidemia referred to as an umblical cord arterial pH of < 7.10 and an Apgar score of < 7 at five minutes, was similar in women with and without a delayed labour.

6.2 *Paper II*

Use and abuse of oxytocin for augmentation of labour

This subset in Study I (*Paper II*) comprised nulliparous and multiparous women with spontaneous onset of labour. Multiparous women without a previous vaginal birth were excluded. Among the 1,263 women, the delayed

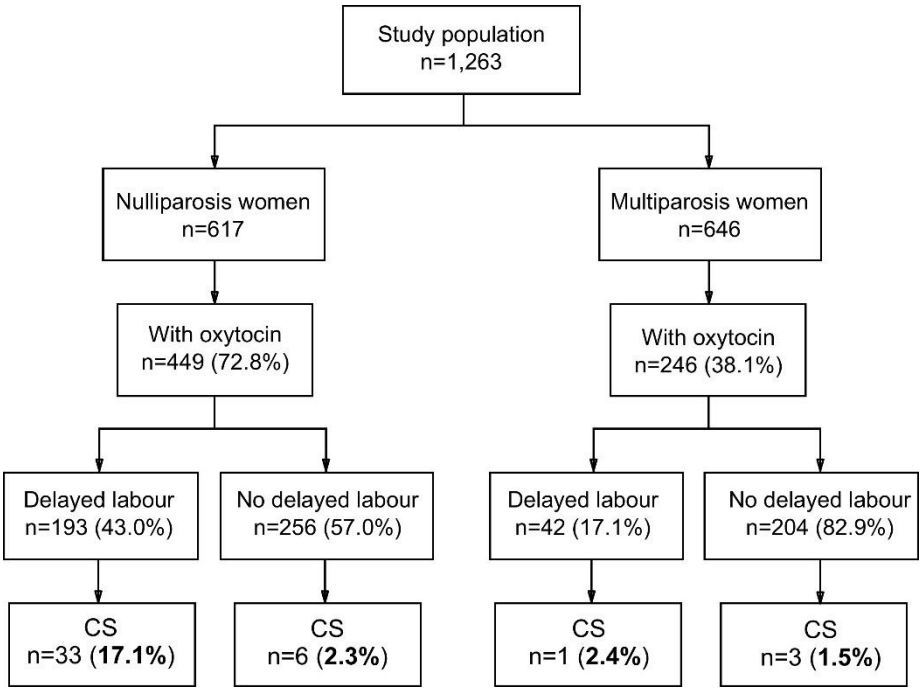
labour frequency was 19.8%, i.e. 32.7% in nulliparous and 7.4% in multiparous women.

Oxytocin was administered to 55% of the women (72.8% of nulliparous and 38.1% of multiparous). The majority of the women receiving oxytocin for augmentation, 57% of the nulliparous and 82.9% of the multiparous women, did not meet the criteria for delayed labour. For women with delayed progress, oxytocin augmentation was started both 'too early' and 'too late' in relation to the diagnosis.

The frequency of operative birth (instrumental vaginal birth and CS) in nulliparous women was higher for oxytocin recipients with delayed labour than for oxytocin recipients without delayed labour (40.9% versus 13.6%; $p<0.001$).

In nulliparous women, the frequency of CS in oxytocin recipients with and without delayed labour was 17.1% and 2.3% respectively and, in multiparous women, 2.4% and 1.5% respectively (*Figure 6).* The main indication for CS was delayed labour (74.5%). CS due to fetal asphyxia occurred in 23.4% and for other reasons in 2.1%.

Figure 6. An overview of delayed labour, oxytocin use and CS related to parity.



The neonatal outcome Apgar score of < 7 at five minutes did not differ between the oxytocin group and the non-oxytocin group.

6.3 Paper III

High dose versus low dose of oxytocin for augmentation of labour

The trial was terminated after results from the interim analyses showing futility. A total of 1,351 nulliparous women with spontaneous onset of labour were randomised and of these 1,295 were analysed on an intention-to-treat basis (high-dose oxytocin group n=647; low-dose oxytocin group n=648). The mean age of the participating women was 29 years and, in the majority (78%) of the women, labour had started with uterine contractions. By the time of admission to the labour ward, cervical dilation was on average 3.5 cm and 35% of the women had experienced a prolonged latent phase (> 18 hours) before entering the active phase of labour. Baseline characteristics related to pregnancy and labour were similar in the two oxytocin groups.

There was no difference between the high-dose and the low-dose group with respect to the frequency of CS, 80 of 647 women (12.4%) versus 80 of 648 women (12.3%). The frequency of instrumental and spontaneous vaginal birth was also found to be similar in the two oxytocin groups. The main indication for instrumental vaginal birth was fetal distress (43.8%) in the high-dose group and failure to progress (58.8%) in the low-dose group. Labour duration was 23 minutes shorter for women with a high-dose regimen.

No differences between the oxytocin groups were found in relation to secondary maternal outcomes, such as fever during labour of > 38.0 degrees, postpartum haemorrhage of > 500 and > 1,000 ml, manual removal of the placenta, anal sphincter injury (grade 3 or 4), or neonatal outcomes, such as intrapartum thick meconium, FHR abnormality, perinatal mortality, 5 minutes Apgar score < 4 or < 7, metabolic acidosis (pH<7.05 and base excess ≥ -12 or pH <7.0), admission to the NICU and stay in the NICU (days). The results of the per-protocol analysis comprising 1,130 women did not differ from the ITT analyses.

Women in the high-dose group received a larger amount of oxytocin compared with women in the low-dose group and the maximum dose per minute was higher. In addition, more women with a high-dose regimen suffered from events of uterine tachysystole. Mode of birth, labour duration and oxytocin given by treatment arm are shown in Table 6.

Table 6. Mode of birth, labour duration and oxytocin given by treatment arm.

	High dose of oxytocin (n=647)	Low dose of oxytocin (n=648)	p-value	Difference between groups Mean (95% CI)
Primary outcome				
Caesarean section	80 (12.4%)	80 (12.3%)	1.00	0.0 (-3.7;3.8)
Secondary outcomes				
Spontaneous vaginal birth	471 (72.8%)	471 (72.7%)	1.00	0.1 (-4.9;5.1)
Instrumental vaginal birth	96 (14.8%)	97 (15.0%)	1.00	-0.1 (-4.2;3.9)
Duration of labour (min)	744 (209) 732 (595; 873) n=645	768 (196) 759 (635; 891) n=648	0.021	-23.4 (-45.3; -1.5)
Total dose of oxytocin (µg)	7.98 (8.29).5.35 (2.70; 10.10) n=646	5.74 (5.54) 4.00 (2.00; 7.30) n=639	<.0001	2.25 (1.48;3.02)
Maximum dose of oxytocin per min (µg/min)	0.049 (0.034) 0.044 (0.022; 0.066) n=634	0.031 (0.019) 0.028 (0.017; 0.042) n=615	<.0001	0.018 (0.015; 0.021)
Total duration of oxytocin infusion (hours)	4.78 (3.07) 4.00 (2.50; 6.60) n=646	5.17 (3.16) 4.50 (2.80; 7.00) n=641	0.013	-0.39 (-0.73;- 0.05)
Uterine tachysystole (number of women with any episode)	279 (43.2%) n=641	215 (33.5%) n=641	0.0005	9.6 (4.2;15.1)
Oxytocin stopped or reduced *	136 (21.1%) n=646	102 (15.9%) n=641	0.021	5.1 (0.8;9.5)

For categorical variables, n (%) is presented. For continuous variables, the mean. (SD)/median. (Q1; Q3)/n = is presented

*Oxytocin stopped or reduced due to tachysystole with suspicious or pathological fetal heart rate pattern (number of women with any episode)

A significant interaction was seen between the latent phase and the two oxytocin groups (p=0.028). Further subgroup analyses of women with a prolonged latent phase (> 18 h) and women with a latent phase of ≤ 18 h did not reveal any differences in CS rate between the study groups. No interaction effects could be seen between the other baseline characteristics, such as maternal age (p=0.052) and stage of labour (first and second) (p=0.49).

The occurrence of adverse events (AE) was similar in the two dosage groups. Thirty-one (4.8%) were reported in the high-dose group and 39 (6.0%) in the low-dose group. The majority of these reported adverse events were nausea and vomiting. Three cases in the high-dose group and one in the low-dose group experienced a severe adverse event (SAE). None of the SAEs were regarded as drug related. one woman with an SAE in the high-dose group did not receive study treatment. In the low-dose group, one perinatal death occurred in a child with severe hypoxic encephalopathy. It was regarded as not being related to the study drug and one woman with a SAE in the high-dose group did not receive treatment.

6.4 Paper IV

Women's childbirth experiences in relation to dosage of oxytocin for augmentation of labour

The questionnaire was sent out to 1,203 women one month after birth and, of these, 1,008 (83.8% response rate) women answered and returned the questionnaire, 497 (82.7%) in the high-dose group and 511 (84.9%) in the low-dose group. Cronbach's alpha coefficients for the three domains were Own capacity: a=0.80, Perceived safety: a =0.81 and Participation: a=0.83.

The characteristics of the study group did not differ between the high-dose group and the low-dose group, except for oxytocin administration and labour duration. Women in the high-dose group were given a larger total amount of oxytocin (p<0.001) – the maximum dose of oxytocin per minute was higher (p=0.001), and labour duration was 29 minutes shorter (p= 0.018) compared with women in the low-dose group.

There were no significant differences in childbirth experience, measured in the three domains, between the high-dose group and low-dose group (*Own capacity* (*p*= 0.99), *Perceived safety* (*p* = 0.43), *Participation* (*p* = 0.55) (*Table 7).*

Table 7. The three domains of childbirth experience (CEQ) and comparisons between dose of groups.

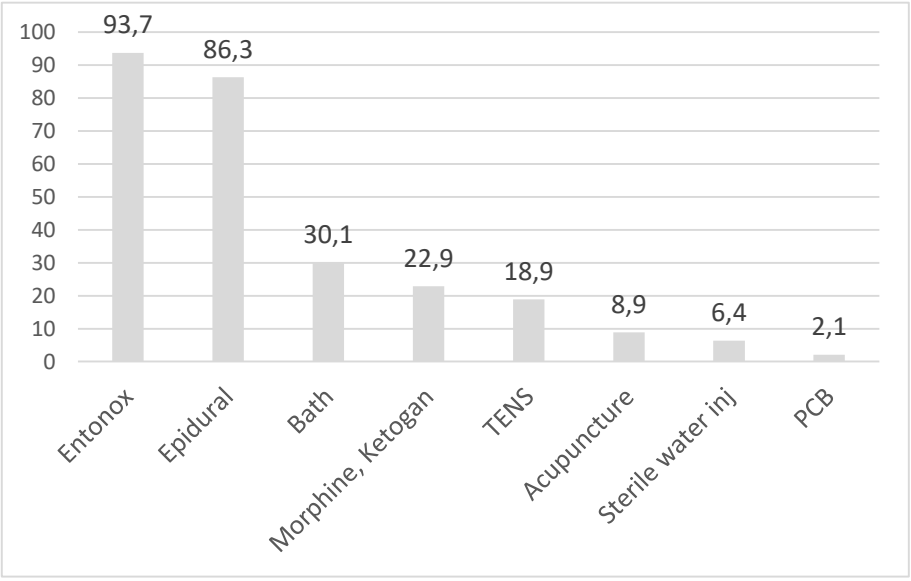
	High dose of oxytocin (n = 497)	Low dose of oxytocin (n = 511)	*p*-value*
Own capacity	2.43 (0.55)	2.46 (0.56)	0.99
Perceived safety	3.03 (0.72)	3.06 (0.71)	0.43
Participation	3.56 (0.54)	3.58 (0,50)	0.55

The data are given as the mean (SD). Min value = 1, max value = 4. * Mann-Whitney U-test

When comparing childbirth experiences with mode of birth (spontaneous vaginal birth, instrumental vaginal birth and caesarean section), a higher mean score in all three domains was seen for women with a spontaneous vaginal birth compared with women with an instrumental vaginal birth and caesarean section *($p<0.001$).*

Epidural analgesia was used by 870 (86.3%) of the women and was administered both before and after delayed labour was defined and augmentation with oxytocin had started. None of the intrapartum analgesics used during labour differed between the oxytocin groups. Nor did reported labour pain scored two hours postpartum (mean score 65.9 in high-dose(n=329) versus 67.5 in low-dose (n=346); p=0.67) and one month after birth (mean score 73.4 in high-dose (n=497) versus 71.7 in low dose(n=511); p=0.25) differ between the two dosage group. Labour pain scored postpartum was compared with labour pain scored one month after birth in 565 women who reported labour pain on both occasions. Experienced labour pain was scored significantly higher one month after birth compared with two hours postpartum (mean score 73.1 versus mean score 66.9; p=0.012). Different pain reliefs used during labour are shown in Table 8.

Table 8. Pain reliefs used during labour (%)*



*Morphine and Ketogan were given in the latent phase
TENS-Transcutaneous nerve stimulation,
PCB-Paracervical nerve block

7 METHODOLOGICAL CONSIDERATIONS

The study design used in this thesis consisted of both a retrospective observational study (Study 1) and a randomised, controlled trial (RCT) (Study 2). The first step (Study 1) was based on an exploratory, descriptive approach to collect more knowledge of delayed labour and the use of oxytocin in relation to delayed progress. Based on the findings from this first study and from the literature a gap of knowledge regarding oxytocin use was identified. We formulated a hypothesis of oxytocin use which could be tested in an intervention study with an RCT design (Study 2).

The research quality of observational studies and RCTs is evaluated in terms of both internal and external validity. Internal validity refers to the strength of the inferences from the study and to a lack of systematic error. The key question when assessing internal validity is whether an observed change can be assumed to be associated with the exposure and not with other possible factors. External validity refers to the ability to generalise study results to a wider population of interest, i.e. for other persons in other places and at other times (126).

The observational study design

In observational research, the direct observation of individuals in their natural setting is performed and inferences are drawn about the effect of an "exposure" or intervention on subjects through the observation without manipulation (e.g. through randomisation) by the investigator (126). To select the study sample in observational studies, a random sampling system is used, which means that each person in a defined population has the same chance of being selected. Random sampling is unable to protect from extraneous variables that may confound the result in a study (127). For this reason, the main limitation of an observational study is the existence of alternative explanations for study results due to confounding by both factors within the study material and factors not observed in the study.

Furthermore, the direccion of causality is not clear in observational studies. For example, an association between epidural analgesia and delayed labour can have different explanations, such as whether epidural analgesia causes delayed labour or whether delayed labour is painful and requires pain relief. In addition, associations found in exploratory and descriptive research are weaker than in hypothesis-testing research, but they can open the door to new research questions.

In our retrospective observational study (Study 1), the sample was obtained by random sampling and via a computer random number generator in Excel. All the data were collected from the women's electronic birth records®. The variable of interest was "delayed labour", but, at the time of the study, our labour ward did not have a clear definition of delayed labour and all women receiving oxytocin for augmentation also received a diagnosis of delayed labour. In the study, the definition of delayed labour was based on the partogram two-hour alert line and in accordance with the *Swedish Society of Obstetrics and Gynaecology, Normal labour practice (1).* The definition of delayed labour was assessed by two midwives retrospectively and together with the collection of data.

The RCT study design

RCTs are perceived as the best standard research design for evaluating the effectiveness of treatments and interventions, as they have good internal validity and minimise confounding. Through random allocation, the study participants are allocated to the groups in such a way that each one has an equal chance of being allocated to either group. With random allocation, the risk of extraneous variables confounding the result is minimal and the probability that any differences observed between the groups is dependent on the interventional variable increases (127). In addition, RCT studies can yield causal relationships through the controlled design. However, RCT studies are not always possible to conduct in medical research for various reasons, not least for ethical reasons.

The RCT (Study 2) in this thesis had a multicentre design, was pre-registered and a statistical analysis plan was formulated before closing the data file and starting the analysis process. In addition, the study was conducted in accordance with the CONSORT guidelines (128). An intention-to-treat approach was used for the analysis to strengthen the internal validity. The study protocol was approved by the Swedish National Medical Products Agency.

Threats to the internal and external validity

Different threats to the internal and external validity can be seen in observational studies and, as mentioned above, *confounding* is a threat to internal validity. Methods to control confounding include restriction, stratification and multivariate techniques (129). In Study 1 (*Paper I),* no restriction was made, as the study design had an exploratory and descriptive design comprising the population on the delivery ward (nulli- and multi-parous women with both spontaneous and induced labour). For *Paper II,* a restriction was made with the aim of analysing women with spontaneous onset of labour. Multiparous women with no previous vaginal birth and women with induced

labour were excluded. Finally, in the RCT, Study 2 (*Papers III and IV*), only nulliparous women with spontaneous onset of labour were included. A logistic regression method was used in Study 1 (*Paper I).* Adjustments were made using the variables known to or suspected of having a relationship with the dependent variable. However, we were only able to control for confounders in the variables obtained from the birth records and included in the analyses. Unfortunately we did not have information about parameters such as women's BMI, continuous support during labour, fear of childbirth etc. to include in the analyses.

When *selection bias* occurs, the obtained sample is not representative of the defined population of interest and is a threat to validity. When using a central randomisation system, selection bias is considered to be a low risk. The randomisation process in both studies was performed via a computer random number generator. There might have been a threat to internal validity due to selection bias in Study 2 (*Papers III and IV).* A large number (n=922) of eligible women were not included in the study because they had not been informed and asked for consent to participate by the responsible midwife. The midwives were asked to give reasons for not including eligible women in the study and, in most of the cases, the reasons were that they had simple forgotten to ask the woman to participate or because of a heavy workload. In a few cases, the women were "too afraid" or had "too much pain" to be disturbed with questions about participating in a study. In most of the cases, no reason was given.

In terms of women's childbirth experiences evaluated in the CEQ questionnaire (*Paper IV),* 16% of the women did not answer the questionnaire sent out one month after birth. No analyses were made of non-responders, which could have created some selection biasis. We do not know whether this group differs from the one answering the questionnaire and the degree to which this could have influenced the childbirth experiences. However, a response rate of 80% is regarded as strengthening the external validity.

When it came to *external validity*, only Swedish-speaking women were asked to participate in the RCT, which might be a threat to the external validity for geographical areas with a population with many non-Swedish-speaking women. On the other hand, the external validity of the study was strengthened by the multicentre approach and the fact that the trial was conducted in different regions of Sweden, which increased the opportunity to generalise. In study I external validity was threatened by that the research was limited to one hospital

Blinding is necessary to control bias in clinical trials. Through blinding, threats to internal validity and construct validity are minimised (126). The intervention in the RCT was double blinded, i.e. neither the women receiving the treatment nor the responsible midwife knew which dosage group the women had been allocated to. The randomisation process was performed via a computer random number generator. The randomisation was performed and the intervention was prepared by another person on another ward, but, in spite of this, we are unable to guarantee the security of full blindness. The most ideal solution would have been to have used special vials with the study drug produced exclusively for the trial, but we did not have the financial resources for this option.

Statistical conclusion validity refers to whether the research design together with the statistical measurements is able to detect a true relationship (130). In our retrospective observational study, associations between the explanatory and dependent variables must be interpreted with caution, as associations in observational studies are weaker than those in an experimental study and causality cannot be proved.

When designing the RCT, we used the data from Study 1 (*Paper II*) to calculate the sample size needed to detect a true difference between the dosage groups for our primary endpoint of CS. The results from Study 1 (*Paper II*) had shown a CS rate of 17.2% in nulliparous women with spontaneous onset of labour and with confirmed delayed labour. Other Danish study has reported similar result for the CS rate in the same defined group (31). The sample size calculation for the RCT was based on this finding and the estimated decrease in the primary endpoint, CS rate, from 17.5% to 13%, i.e. a reduction of 25%, which also was considered clinically relevant. To achieve this, it was thought that 1,045 women would be needed in each group, resulting in a total of 2,090 women. The result of the RCT, however, showed a CS rate, in both groups (12.4% vs 12.3%), (*Paper III)* that was less than that estimated in the power calculation, something that might depend on much stricter inclusion criteria than in our retrospective observational study as exclusion of labours with meconium stained amniotic fluid and suspicious or pathological CTG.

After the interim analysis and recommendations from the Data Monitoring Safety Board, the RCT was ended before we had reached full inclusion. The reason was the extremely small numerical difference in the CS rate between the two study groups and, with the assumption that even with a completed study, with the inclusion of 2,090 women, it would be unlikely to achieve a statistically significant difference in CS rate between the two dosage groups.

Information bias can occur when information is either measured, or collected inaccurately. In the retrospective observational study, data were collected by the same two midwives and, on some rare occasions, by a third midwife. All three were trained in scrutinising the women's labour records, definitions of delayed labour and the entry of data.

In the RCT, all manual data were double checked. Missing values from the Obstetrix® database were checked in the women's pregnancy or labour records and, when possible, entered in the CRF. For instance, the women's last weight was seldom filled in from the pregnancy record to the labour record. This was found at all participating centres and assessed by the research team as important to collect in order to avoid any information bias.

Regarding validity in the Childbirth Experience Questionnaire (CEQ), the first version has shown good measurement qualities and has been validated in Sweden (131),United Kingdom (132) and in Spain(133). The questionnaire has previously been used in women with delayed labour (102). The CEQ used in the RCT *),(Paper IV)* is a revised version where validation has been performed for the two subscales *Own capacity* and *Perceived safety*, but not yet been completed for the subscale *Participation*.

8 DISCUSSION

The overall aim of this thesis was to investigate risk factors, the use of oxytocin and outcomes in relation to a delayed labour progress. This was investigated in two studies, one retrospective observational study and one RCT, resulting in four papers: Paper I and II for the first study, and Paper III and IV for the second study.

The result showed that nulliparous women ran an increased risk of delayed labour and operative birth (instrumental vaginal birth and CS). Multiparity without previous vaginal birth was also a risk factor for delayed labour and CS (*Paper I*). Oxytocin augmentation was used in an incorrect manner, both in excessive doses and by administration "too early or too late"(*Paper II).* When comparing a high dose with a low dose for the augmentation of delayed labour, neither dose was shown to be superior in outcomes as intrapartum CS, childbirth experiences or other secondary outcomes, despite a moderately shorter labour duration for the women in the high-dose group. More events of tachysystole and signs of fetal distress occurred with a high-dose regimen (*Paper III-IV*). As a result, a low-dose oxytocin regimen is recommended for the treatment of delayed labour.

Risk factors for delayed labour and outcomes

In the retrospective observational study multiparity without a previous vaginal birth was found to be the main independent risk factor for delayed labour (*Paper I*). Our results correspond with the results of a recent Swedish population cohort study investigating the risk of recurrence and operative birth following labour, using data from the Swedish Medical Birth Register (134). The population cohort study result showed an increase in the risk of a recurrence of delayed labour in women with a previous CS.

In our study, nulliparity was a strong risk factor and the frequency of delayed labour in nulliparous women was 32.7%, i.e. almost one in every three women expecting their first child was considered to require intervention to augment labour progress. (*Paper II*). The fact that nulliparous women run an increased risk of delayed progress is well known from other studies reporting an incidence of between 35.6-44% (29-31). However, according to Zhang et al., there is a need for a re-evaluation of contemporary practice in assessing labour progress for nulliparous women, due to a possible overly stringent definition of delayed labour. In current obstetric care, labour progression in the active phase takes longer than was considered when the Friedman curve was shaped. This may be due to changes in both population and current obstetric care. For

instance, women are older and heavier and fetal birth weight has increased, together with an increase in the use of medical and technological interventions. Allowing labours to take longer before cervix dilation of 6 cm may reduce the rate of interventions like amniotomy and oxytocin use as well as the CS rate (11).

Factors affecting labour progress shown in *Paper 1*, such as *gestational age* and *birth weight*, are known from earlier studies (31-33). At the time point when the data for the retrospective observational study were collected (*Paper I*), *management* on the labour ward *regarding amniotomy* did not follow a strict protocol and was often performed electively as a routine, following a decision by the responsible midwife or obstetrician. Our study (*Paper I*) showed an association between the time for amniotomy and delayed labour and we found that amniotomy was performed almost one hour later in the group of women with delayed labour. Other studies have reported conflicting results. Whether or not routine amniotomy is beneficial for women when there is no specific indication has been questioned (135) and it is not recommended by the WHO (28).

Latent phase and *early admission to the labour ward* are known risk factors for delayed progress, but these factors were not evaluated in our observational study. Despite this, it may be worth mentioning that the descriptive data of the women participating in our RCT showed that 35% of these women, subsequently diagnosed with delayed labour, had experienced a prolonged latent phase (> 18 hours) and were on average admitted in early labour. By the time of admission to the labour ward, cervical dilation was 3.5 cm on average (*Paper III)*.

Whether there is a cause-and-effect relationship between an epidural analgesia and delayed labour is a controversial issue. An association between longer labours and epidural analgesia has been reported in various studies (45), but the impact on labour duration in the first stage of labour is still unclear (53). In our observational study, after controlling for confounders, both early and late epidural analgesia were risk factors for delayed progress, with an increased risk when the analgesia was initiated at an early stage (by cervical dilation ≤ 5 cm) (*Paper I*). Compared with earlier randomised studies, the early or late initiation of epidural analgesia for labour had the same effect on labour duration in the second stage of labour (53).

Delayed labour and an increased risk of operative birth, especially in nulliparous women, have been reported previously in the background. We found a strong relationship between delayed labour and operative births. Just

over half (61.4%) the women in the group with delayed labour succeeded in having a spontaneous vaginal birth, compared with 93.6% of women without delayed labour(Paper I). The incidence of operative deliveries in nulliparous women with delayed labour was 40.9% (23.8% instrumental vaginal birth and 17.1% CS), despite oxytocin treatment (Paper II).

For multiparous women without a previous vaginal birth, the CS rate was 25.0% (Paper I). This can be compared with the Swedish cohort study where delayed labour and CS in the first labour were associated with instrumental vaginal birth and CS in second labour (134).

Delayed labour and oxytocin use

Research on different regimens with oxytocin for improving labour outcome has been performed without recording a successful decrease in the CS rate in nulliparous women with spontaneous onset of labour. In trials of early or delayed oxytocin augmentation, when oxytocin has been used as a single agent, no differences have been found in obstetric and neonatal outcomes, apart from a reduction in labour duration.

When comparing a high-dose regimen with a low-dose regimen in the treatment of delayed progress in nulliparous women, no difference in the CS rate was found between the two oxytocin groups (*Paper III).* Our RCT study was unable to confirm the indication in two systematic reviews of a reduced CS rate with a high-dose regimen (103, 105). Furthermore, the mean labour duration was 23 minutes shorter with a high-dose regimen of oxytocin compared with a low dose. Labour duration has been shown to have an impact on women's childbirth experiences and labours lasting many hours can affect the childbirth experience negatively (29, 60). When the optimal dosage is discussed, this must be weighed up against the need for increased surveillance and control with a high-dose regimen due to the risk of overstimulation.

Oxytocin administration has been associated with adverse neonatal outcomes, usually due to a hyperactive uterine contraction pattern caused by overstimulation and described in the background (68, 107-110). In our observational study, we did not find a higher frequency of a 5-minutes Apgar score < 7. When comparing the use of a high versus a low dose to augment labour in the RCT (*Paper III*), no significant differences in 5-minutes Apgar score < 4 or 7 or symptoms of acidosis were found between the two oxytocin groups, despite an increased frequency of pathological CTG in the high-dose group. This demonstrates the awareness of the midwives and obstetricians to reduce or stop the oxytocin infusion when tachysystole occurred. One contributory factor in the vigilance relating to CTG changes might have been

the use of a modified checklist-based protocol during the study period; a protocol recommended by Clarc et al. with the aim of assessing uterine and fetal responses to oxytocin augmentation (107). According to Clarc et al., the use of checklist-based protocols may be one way of optimising the safety of oxytocin application (107, 136).

Oxytocin use in normal labour

One of the specific aims in this thesis was to investigate the use of oxytocin for augmentation and its relationship with labour progress and outcome (*Paper II).* The decision to augment labour with oxytocin was made by the attending midwife or obstetrician, either individually or together. We found that 72.8% of the nulliparous women and 38.1% of the multiparous women received oxytocin during labour and 57.0% of nulliparous and 82.9% of multiparous women received augmentation without an indication of delayed labour (*Paper II).* These data derive from 2000/2001, but other studies both later and more recently have reported similar results, with the large-scale overuse of oxytocin (90, 136-139)oxytocin, In its annual report for 2016, the Swedish Pregnancy Registry indicates that there is a large variation in oxytocin use between the different Swedish labour wards. The oxytocin use for augmentation in nulliparous women with a spontaneous onset of labour and regarded as low risk varied between 38.2% and 88.7% (92).

The issues that are necessary to reflect on are as follows: *Why are women, where the majority of them have uncomplicated pregnancies and normal labour, augmented with oxytocin and what can this mean for these women*?

In a recent Swedish interview study by Ekelin et al. (140), midwives' views and experiences of labour augmentation in the context of normal labour were examined. Despite awareness of intervening in a normal labour progress and of the possible consequences of medical interventions, midwives in the study felt forced to accelerate labour for different reasons.

A heavy workload, no free labour rooms and the midwife's own impatience were some of the reasons for speeding up labour. Midwives said they were influenced by the views of their colleagues and newly qualified midwives were especially influenced by older colleagues' opinions. If the women had received epidural analgesia or labour progress had simply paused, these were seen as permissible situations to start augmentation with the aim of preventing delayed labour. Preventing delayed progress was regarded as an act of kindness to the women (140). In an earlier interview study by Blixt et al., the midwives mentioned similar reasons for accelerating oxytocin augmentation; they

included decisions by the obstetricians, the opinions of colleagues or a need for a labour room (141).

In neither of the interviews did the midwives appear to reflect on their decision to intervene and the impact on women's feelings of control and confidence in their own strength and ability to give birth (140, 141). When medical or technological interventions during labour and birth are seen from a psychological perspective, intervening can pose a risk that midwives or other caregivers who are perceived to be more knowledgeable take over and undermine the woman's confidence in her own body (142).

In our observational study (*Papers I –II*), we did not have any information about the indication for oxytocin augmentation. The clinical practice on the labour ward at the time of data collection was to use a partogram without an action line and the alert line was very rarely filled in. Decisions to augment labour were based on observational skill and both the overuse of oxytocin in women without delayed labour and the fact that oxytocin was given both "too early" and too late" could be seen. The partogram with its alert and action lines has been the subject of of discussion about whether its use is beneficial or results in unnecessary interventions (22, 23). According to our results, the use of a partogram without the action line did not prevent the augmentation of labour in women with normal labour progress. A German study found that the timing of interventions during labour were similar, when a partogram without action lines was used.(139) To conclude, a partogram with an action line could be a useful tool for both midwives and obstetricians to remind them of normal progress; both for oneself and when pressure is coming from other caregivers to intervene in normal labour with the aim of accelerating progress.

In 2008, 62% of the Swedish labour wards did not have criteria for diagnosing delayed labour and, in 31% of the labour wards, there was no policy regarding the management of delayed labour (143). The implementation of guidelines is important (1, 91), but this may not be sufficient as a single tool when routines have to be changed (144). In 2011, new national guidelines were introduced on Swedish labour wards with recommendations for oxytocin use for the augmentation of labour (20). Five years later, data from the Swedish Pregnancy Registry indicated the continued high overuse of oxytocin in normal labour (92).

At the NU Hospital Group, where the observational study was conducted in 2001-2002, the frequency of oxytocin use in nulliparous women with spontaneous onset of labour was 72.8% (*Paper II*) and it decreased to 45.9% in 2016 (92). One explanation for the change in routines regarding oxytocin

management could be the intensive work that has been done to promote normal birth in clinical practice with the emphasis on delayed labour and oxytocin use. This action was started after the presentation of the study results. Moreover, in 2010, a systematic quality development project was set up with the aim of strengthening normal childbirth, where oxytocin use was one part (145) Similar results were obtained in two Scandinavian hospitals where the incidence of oxytocin use decreased significantly after introducing a protocol for the definition of delayed labour and for oxytocin use together with organised audits for all staff (144, 146).

According to the WHO, unnecessary clinical intervention in normal labour is a threat to women's autonomy and may negatively impact their childbirth experience (28). Nystedt et al. found that women without delayed labour but with oxytocin perceived their progress of labour as slow, despite normal progress (29).

Childbirth experience

There is little research regarding the association between different doses of oxytocin and childbirth experience. In our RCT, no difference was found in women's childbirth experience between a high-dose regimen of oxytocin compared with a low-dose regimen (*Paper IV*). Two previous studies have reported similar results (96, 147). In one of the studies, no differences were found in women's satisfaction with labour when a high dose of oxytocin together with early intervention was compared with a low dose of oxytocin and with a more expectant intervention.(96) In the pilot study by Kenyon et al., women's perception of support and control did not differ between a high and a low dose of oxytocin, when oxytocin augmentation was investigated as a single agent (147).

Labour and birth are regarded as a multidimensional experience, including intense physical, emotional, psychological, cultural and spiritual elements, all of which contribute to the childbirth experience (148). Most instruments used for assessing women's childbirth experiences relate to single aspects of birth experience (131). The Childbirth experiences questionnaire (CEQ) used in the RCT has the ability to measure different dimensions of childbirth experience (131). By using the CEQ, it was possible to assess three major dimensions of childbirth experience, namely *Own capacity*, *Perceived safety* and *Participation* in relation to oxytocin dosage. We did not find any difference in childbirth experience in any of the three domains measured by the CEQ between the two groups of women receiving either a high dose of oxytocin or a low dose. When comparing the three domains, the lowest mean score was found for *Own capacity*, containing items regarding sense of control, personal

feelings during labour and experienced labour pain (*Paper IV*). This may reflect a situation in which control over labour and in some cases also birth is no longer in the woman's hands. Previous studies have reported that it is important for women to be in control of their birthing process (124, 125). In addition, it is a well-known fact that women with delayed labour progress and an operative birth are more likely to have a negative childbirth experience than women with normal progress (61, 114) Women who participated in our RCT and underwent an emergency CS or instrumental vaginal birth gave their experience of childbirth lower scores than women with a spontaneous vaginal birth in all three domains and in both dosage groups *(Paper IV).* Women with delayed labour need extended support during labour and this is an important factor to consider when planning care on the labour ward (60, 123).

Pain relief during labour

Many women experience severe pain in labour. Delayed labour and worse than expected experienced labour pain have been reported to be two of the main factors influencing the childbirth experience negatively (60). Strategies for helping women to cope with labour pain can include the use of multiple non-pharmacological and pharmacological techniques, which can be used sequentially or in combination. Some non-pharmacological methods appear to be more beneficial in helping women to cope with labour pain than in relieving the pain and, on the other hand, pharmacological methods mitigate pain, but they may not relieve anxiety or suffering (135). According to ACOG 2006, "In the absence of a medical contraindication, maternal request is a sufficient medical indication for pain relief during labour and birth" (149). The choice of technique, agent and dose should be based on the woman's preference, her medical status and if there are any contraindications (149).

The majority of the women in our RCT used epidural analgesia and entonox as pain relief during labour. The frequency of epidural analgesia use was as high as 85% in both oxytocin groups (*Papers III and IV*). Non-pharmacological pain relief was used to a moderate to low degree.

When comparing our finding of epidural analgesia use with data from the Swedish Pregnancy Register from 2016, there was a large variation in the use of epidural analgesia between Swedish hospitals and the use in nulliparous women with a spontaneous vaginal birth varied between 23.2% and 67.5% (92). It seems reasonable to assume that the decision on which pain relief to use by women in labour is more a decision for the caregivers based on local routines and labour ward culture than the woman's preference. The choice of pain relief ought to be based on the woman's request and she ought to be informed and offered both pharmacological and non-pharmacological

management techniques and, in addition, receive information that epidural analgesia might have an effect on the duration of labour. Despite the high use of pharmacological management during labour, women report greater experienced pain one month after birth than two hours post-partum (*Paper IV).*

When it comes to the approaches to limit interventions during labour and birth, ACOG recommend the use of non-pharmacological management techniques in the latent phase (135). We do not have any information on the extent to which this was used in our study (*Papers III and IV)*, but more than one fifth of the women used parenteral or oral opioids in the latent phase. Evidence from a recent Cochrane review from 2018 suggests that parenteral opioids might provide some pain relief in labour, but, at the same time, they are associated with drowsiness, nausea and vomiting in women. In addition, the effects on the newborn are unclear (150).

Care during labour

This thesis has been conducted within the field of health-care sciences, where the meaning of care is to support and strengthen health processes (151). According to a Swedish state-of-the-art document (1), the aim of care in normal birth is "to achieve a healthy mother and child with the least possible level of intervention that is compatible with safety. The approach implies that in normal birth there should be a valid reason to interfere with the natural process". Most women want a physiological labour and birth and to have a sense of personal achievement and control through involvement in decision-making, even when medical interventions are needed or wanted (5). Supporting the normal physiological processes of labour and birth, even in the event of complications that require medical attention, can increase best outcomes for the mother and infant (3).

When care is discussed from the professional's perspective, there is a risk that the patient will "be lost". As a result, when this perspective is used in health-care sciences, it is important to highlight the fact that the purpose is to improve care for patients and contribute to a caring culture (151). In current obstetric care, midwives and obstetricians are the central caregivers for a woman giving birth (152). In Sweden, midwives are responsible for normal labour and birth. If there is a pregnancy with risk factors or with complicated labour and birth, the midwives and obstetricians work together in the surveillance of woman and child. According to the Swedish Description of Competence for Registered Midwives, the midwife has the competence independently to handle a normal pregnancy, childbirth and postnatal period, together with the competence to identify and assess when a situation deviates from normal (153). In the philosophy and model of midwifery care, pregnancy and childbearing are seen

as usually normal physiological processes. According to the International Confederation of Midwives (ICM) model of midwifery care, midwives are responsible for promoting and protecting women's and newborns' health and rights and for promoting and advocating non-intervention in normal childbirth (154).

This can be a challenge when most births today occur in hospitals where a more biomedical view of childbirth dominates and labour is seen as a critical and medical event, and is regarded as normal in retrospect (155, 156). This was reflected on in the study by Ekelin et al. where midwives expressed their awareness of protecting normal birth but argued that the high-tech hospital environment where birth takes place results in a lack of confidence in the process of normal birth (140). Professional skills, such as intuition, expertise and empathy, in a hectic, busy clinical practice can be difficult to hear (157). Sandvik states that the modern midwife stands with both feet in midwifery care that originates from traditional female practice and modern biomedical discipline. The main challenge is relating to these two concepts (155).

The findings in *Paper III* regarding the use and misuse of oxytocin are discussed on the basis of the midwifery model of care by Kennedy, where "watchful expectancy" is described as "the art of doing nothing well" (158). This means ensuring that normality continues through vigilant and attentive care, fostering the normal processes of labour and birth intervention and using technology only when the individual situation requires (158). Knowledge and judgement when taking control of and intervening in a physiological process of labour is necessary (158). In this model, the midwife is seen as "an instrument" of care. Between the woman and the midwife, there is continual interaction between "taking control" and "letting go"(156). This perspective challenges midwives' professional skills in midwifery care; recognising birth as a unique, normal process and trusting their own knowledge when it comes to whether or not to interfere.

In this thesis, risk factors and outcomes in delayed labour have been investigated. Furthermore, expectancy in management versus interventions in relation to treatment with oxytocin infusions has been further explored (I-II). In addition, maternity care routines relating to oxytocin use for supporting normal childbirth in women with delayed progress, together with experiences of childbirth and labour pain, have been studied (III-IV).

CONCLUSIONS

- Nulliparous women and multiparous women without previous vaginal birth ran an increased risk of delayed labour and an adverse labour outcome, such as CS or instrumental vaginal birth, compared with women with normal progress.

- Epidural analgesia was a risk factor for delayed labour, with an increased risk when administered at an early stage at cervical dilation of ≤ 5 cm.

- An incorrect use of oxytocin for augmentation was found. It consisted of both inadequate and excessive use and administration both too early and too late in relation to a delayed labour diagnosis.

- Oxytocin recipients with delayed labour ran an increased risk of CS and instrumental vaginal birth compared with oxytocin recipients without delayed labour, indicating that the main reason for CS was not the oxytocin augmentation but the underlying problem of delayed labour.

- No advantages were found for the routine use of a high-dose regimen of oxytocin for the augmentation of delayed labour when compared with a low-dose regimen.

    - The CS rate did not differ between the two dosage groups.
    - More events of tachysystole occurred with a high-dose regimen.
    - A larger amount of oxytocin was used with a high-dose regimen.
    - Childbirth experiences when evaluated one month after birth with the three dimensions of *Own capacity*, *Perceived safety* and *Participation* did not differ between the two dosage groups.
    - Experienced labour pain evaluated two hours post-partum and one month after birth did not differ between the two dosage groups.

9 FUTURE PERSPECTIVES

Different regimens for oxytocin administration need to be further evaluated

Research on different management of oxytocin has not been successful in improving labour outcomes such as CS rate. Further investigations of dose-response to oxytocin in specific groups of women, for example women with obesity or women with a prolonged latent phase, should be encouraged. In addition, evaluate whether discontinuation of oxytocin infusion could affect the duration of the active phase of labour, compared with continuation of oxytocin until birth, and without adverse maternal or neonatal outcomes.

Increase women's access to nonmedical interventions during labor

Alternative and non-pharmacological interventions, techniques and methods related to labour progression and to women's preferences have not been studied sufficiently. There is a need to extend research in these areas and include research on both preventing and treating delayed progress, such as research regarding techniques for coping with pain.

Revisit the definition of delayed labour

Labour progression ought to be re-evaluated according to the partogram and the definition of the active phase of labour to adapt it to the current population of women and obstetric practice. This would mean, among other thing, allowing nulliparous women to progress more slowly before six centimetres of dilation. This may prevent interventions and CS in early labour.

Stop the abuse of oxytocin augmentation in normal labour

The incorrect use of oxytocin augmentation must be further investigated and discussed and together with underlying reasons for unnecessary interventions. Women's knowledge and participation in decisions regarding interventions have not been studied sufficiently.

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