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Oxytocin augmentation and its association with labor outcomes

Doctoral thesis

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Trondheim, June 2017

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Stimulering av rier med oxytocin og sammenheng med fødselsutfall

Oxytocin blir ofte brukt under fødselen for å øke styrken på riene. Mangel på klare indikasjoner for bruk av oxytocin har ført til ulik praksis og tilfeldig bruk. Hensikten med studien var å undersøke om det kan være en sammenheng mellom bruken av oxytocin og hvordan fødselen blir for kvinnen og for barnet.

Studie I

Vi undersøkte retrospektivt risikofaktorer for blødning over 1000 ml etter fødselen og om dette hadde endret seg fra 1998 til 2007. Blødning over 1000 ml økte i studieperioden og risikoen var dobbelt så stor etter keisersnitt sammenlignet med vaginal fødsel (2.8 % vs. 5.9 %). Igangsetting av fødsel, stimulering av rier og keisersnittfrekvens økte, og disse faktorene viste sammenheng med alvorlig blødning etter fødselen. Bruk av oxytocin for stimulering av rier økte fra 5.8 % til 29.3 %.

Studie II

Målet med denne studien var å presentere en metode for å evaluere og kvalitetssikre utfall og hendelser for mor og barn i forbindelse med fødsel. Michael Robson har laget en metode der fødende kvinner kan klassifiseres i ti ulike grupper. Metoden ble først utviklet for å klassifisere bruken av keisersnitt. I denne studien presenterer vi hvordan vi kan klassifisere 16 fødselsutfall i henhold til de ti gruppene. Vi presenterer resultater fra fødeavdelinger i Stavanger, Dublin og nasjonale data fra Slovenia.

Studie III

Fødeavdelingen ved Stavanger universitetssjukehus endret indikasjonene og rutinene for oxytocinbruk i 2010. I løpet av en 5 års periode ble bruken av oxytocin under fødselen signifikant redusert fra 35.5 % til 23.6 %. Antall akutte keisersnitt og antall barn med lav pH i navlesnora gikk ned i samme tidsperiode og vi diskuterer om dette kan ha en sammenheng med redusert bruk av oxytocin. Flere kvinner opplevde blødning over 1000ml og varighet av fødsel over 12 timer.

Studie IV

Fødselsregistrene i Norge og Danmark ble brukt for å undersøke bruken av oxytocin for ristimulering hos førstegangsfødende kvinner med spontan fødselstart til termin. Vi fant at bruk av oxytocin økte med kvinnenes alder, bruk av epiduralbedøvelse og med akutte keisersnitt. Formålet med studien var å vurdere samspillet mellom disse faktorene. Ristimulering viste sammenheng med lavere forekomst av keisersnitt hos kvinner med epiduralbedøvelse, spesielt hos kvinner over 35 år.

Konklusjon

Målrettet bruk av oxytocin for stimulering av rier førte til redusert bruk av oxytocin og viste sammenheng med færre akutte keisersnitt og færre barn med lav pH i navlesnora. Kvinner med epiduralbedøvelse kan imidlertid ha fordel av ristimulering. Flere ulike faktorer har innvirkning på fødselsforløp og fordeler og ulemper må vurderes i forhold til hverandre. Robsons 10-gruppe klassifikasjonssystem kan være et nyttig hjelpemiddel for å kvalitetssikre fødselsutfall og for å sammenligne ulike fødeavdelinger.

Kandidat: ***Janne Rossen***

Institutt: ***Laboratoriemedisin, kvinne- og barnesykdommer, Norges teknisk naturvitenskapelige universitet (NTNU)***

Veiledere: ***Torbjørn Moe Eggebø (hovedveileder) og Ingvild Vistad***

Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden Doctor Philosophiae i klinisk medisin
Disputas finner sted i Undervisningssenteret, Sørlandet sykehus Kristiansand, fredag 16.juni 2017 kl.12.15

Table of contents

1 Acknowledgements

The work presented in this thesis started in the corridors of the delivery ward at the Stavanger University Hospital. Inspired by the wonderful colleagues and their traditions of working with quality assurance there, my curiosity was raised. I will always be thankful for this time with you.

After I moved to Kristiansand, the research department at Sørlandet hospital Kristiansand provided financial support, giving me the opportunity to pursue a doctorate degree in medicine. For this I am very grateful. I would also like to express my thankfulness to my current and previous department leaders, Randi Andersen and Aud Askevold, for their continuous support through the following years.

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I also want to express my gratitude to my co-supervisor PhD Ingvild Vistad, for sharing your outstanding knowledge and guidance during my whole PhD study period. I am deeply grateful for your help and constructive feedback, in particular your critical revision of this thesis.

I want to credit all the coauthors for the good teamwork and their contribution to the papers. Special thanks to Michael Robson for sharing your substantial knowledge with me and to Finn Egil Skjeldestad for introducing me to epidemiology and thereby broaden my horizon.

My deepest gratitude goes to Torunn Eikeland, my first mentor. Through dedicated enthusiasm combined with knowledge she showed and taught me obstetrics. She eagerly conveyed her fascination and interest in statistics and work of clinical quality, inspiring me in this work. I can still hear your voice and see your smile. Thank you!

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I dedicate this thesis to my loving children, Birk and Liva. I smile, hoping you some day will benefit from the research conducted if you come to have children of your own. You fulfill my life.

Janne Rossen

Kristiansand, February 2017

2 Abstract

Background

Augmentation of labor with oxytocin is commonly used in labour wards. Oxytocin stimulates the uterine muscle to contract either due to the hormone produced by the mother or the synthesized hormone added as infusion during labour. One of the main indications for its use has been poor labour progress with the intention to increase the probability of a vaginal delivery. However, lack of clear definitions without a proper indication for the use of oxytocin augmentation has affected its widespread and non-systematic use. Prevalence's of oxytocin augmentation of 20-70% are reported across hospitals and countries. Knowledge of how oxytocin augmentation may be used to achieve the best outcome for the mother and fetus, are still to be revealed.

Objective

The overall aim of this thesis was to evaluate the varying use of oxytocin augmentation and its associations with labor outcomes based on a systematic method

Paper I

In the first paper we explored changes of and possible risk factors associated to severe postpartum hemorrhage >1000ml over time. Originally the research question was based on an impression of a rise in severe hemorrhage, causing concern in the labor ward. The study was a retrospective cohort study, including 41 000 delivering women at Stavanger University hospital from 1998 to 2007. During the study period we observed a continuous rise of severe postpartum hemorrhage >1000ml with a doubled risk after a cesarean section compared to a vaginal delivery (5.9%; 95% CI 5.3–6.6 vs 2.8%;95 CI 2.6–2.9, respectively). In addition, a rise in obstetrical interventions such as cesarean section, vaginal operative deliveries, induction of labor and in particular use of oxytocin augmentation (from 5.8% to 29.3%) was observed. By conducting this study we became aware of the unstructured approach of the use of oxytocin augmentation in labor wards. We concluded on that the observed rise in severe postpartum hemorrhage may be related to more frequent use of obstetric interventions.

Paper II

In this paper we present a method, a standardized approach to assess outcomes of labor by using the 10-Group Classification System defined by Michael Robson. Originally this system was used to evaluate cesarean section rates by stratifying all women in 10 groups depending on parity, gestational age, number and presentation of the fetuses and onset of labor. However, other labor outcomes can easily be added, such as oxytocin augmentation and postpartum hemorrhage, and these observations can be used to guide further improvements if necessary. The study population from three perinatal databases (Stavanger University Hospital: 9848 women; National Maternity Hospital: 9250 women; and Slovenian National Perinatal Database: 106 167 women) were stratified using this system and are presented as examples.

Paper III

In this paper we explored changes of labor outcomes for the mother and fetus after implementing judicious use of oxytocin augmentation for the management of prolonged labor. The implementation was based on a clear definition of start of the active phase of labor in addition to WHO's definition of prolonged labor according to their partograph. By this we introduced a clear indication for the use of oxytocin augmentation. In this prospective observational study we included 20 000 delivering woman using four of the 10-Groups (as described in paper II) at Stavanger university hospital from 2009 to 2013. During the study period the overall use of oxytocin augmentation decreased from 35.5 % to 23.6 % and the decrease was significant in all of the four subgroups evaluated. The rate of acute cesarean section and fetuses with low pH in the umbilical cord decreased. This association might be related to the reduced use of oxytocin augmentation, but simultaneously more women experienced labor length > 12 hours and severe hemorrhage > 1000ml which needs further attention.

Paper IV

Possible effects and interactions of oxytocin augmentation, epidural analgesia and maternal age on the risk of cesarean section among nulliparous women in spontaneous labor (group 1 as explained in paper II) was investigated in this paper. Data was extracted from the Medical birth register in Norway and Denmark and over 400 000 women from 2000 to 2011 were included. The design of the study was defined as an observational cross-sectional study, but analyzed as a case-control study (cesarean section (cases) and no cesarean section (controls)).

We observed increased use of oxytocin augmentation with increasing maternal age, epidural analgesia and cesarean section. The observed relation between these three variables on the associated risk of cesarean section deserves more attention. Oxytocin augmentation might benefit women with epidural analgesia, especially those of advanced maternal age if a vaginal delivery is the preferred outcome. Hence, we hypothesize that oxytocin is an effect modifier on the risk of cesarean section in women with epidural analgesia.

Conclusion

Oxytocin augmentation increased over time and the use was associated to cesarean section, use of epidural analgesia and maternal age in Norway and Denmark. Implementing judicious use of oxytocin augmentation reduced the use and was further associated with a decrease in the acute cesarean section rate and the rate of low pH<7.1 in the umbilical cord.

Labor is affected by interactions between several different variables such as oxytocin augmentation, epidural analgesia, prolonged labor, postpartum hemorrhage and maternal age. Pros and cons must be weighted in relation to each other to guide measures in the labor ward if indicated. We observed a lower rate of cesarean section among women with epidural analgesia if oxytocin augmentation was used compared to no use, especially among women with advanced maternal age.

An agreed set of labor outcomes to guide obstetric quality should be determined and incorporated in an agreed classification system. Thus, we propose the 10-Group Classification System as the standardized method of assessing events and outcomes and comparing inter-institutional rates.

3 List of papers

Paper I

Rossen J, Okland I, Nilsen OB, Eggebø TM

Is there an increase of postpartum hemorrhage, and is severe hemorrhage associated with more frequent use of obstetric interventions?

Acta Obstet Gynecol Scand. 2010; 89(10):1248-55

Paper II

Rossen J, Lucovnik M, Eggebø TM, Tul N, Murphy M, Vistad I, Robson M

A method to assess obstetric outcomes using the 10-Group Classification System: a quantitative descriptive study

Submitted

Paper III

Rossen J, Østborg TB, Lindtjørn E, Schulz J, Eggebø TM.

Judicious use of oxytocin augmentation for the management of prolonged labor

Acta Obstet Gynecol Scand 2016; 95(3):355–61

Paper IV

Rossen J, Klungsøyr K, Albrechtsen S, Løkkegård E, Rasmussen S, Bergholt T, Skjeldestad FE

May oxytocin augmentation modify the risk of epidural analgesia for cesarean delivery among nulliparous women in spontaneous labor at term? A case-control study

Submitted

4 Abbreviations

BMI	Body mass index
CI	Confidence interval
cm	Centimeters
DNPR	Danish National Patient Register
MBRN	Medical Birth Registry of Norway
min	Minutes
NMH	National Maternity Hospital
OR	Odds ratio
PPH	Postpartum hemorrhage
RCT	Randomized controlled trials
RR	Relative risk
SLO	Slovenian National Perinatal Database
SPSS	Statistical package for social sciences
SUH	Stavanger University Hospital
TGCS	10-Group Classification System
WHO	World Health Organization

5 Introduction

5.1 Oxytocin

Oxytocin is a polypeptid hormone produced in the hypothalamus and released by the posterior pituitary gland[1]. It is a uterine-contracting, milk-ejecting hormone that acts as a facilitator for childbirth and breastfeeding through the contraction of smooth muscle cells[2-4].

Oxytocin also plays a role in a wide variety of physiological and pathological functions, such as maternal behavior, social bonding, sexual activity and behavior, stress, and aggression[5].

The use of oxytocin for the augmentation of labor (also referred to in this thesis as oxytocin augmentation), not as an induction agent, will be further discussed in the present thesis.

5.1.1 History

Sir Henry Dale (1875-1968) observed uterine contractions in a pregnant cat using a substance extracted from the posterior pituitary gland. This work was published in 1906, and he named the pituitary extract "oxytocin", from the Greek "oxutokia" meaning "swift delivery"[6].

In 1909, Blair Bell was the first to publish cases on the clinical use of the extract, which was provided to him by Dale. He showed the efficient effect of the extract on PPH and it became a leading and important topic of discussion among obstetricians[4]. Indeed, posterior pituitary extract was considered potentially dangerous, as there was great variation in its effect, and the correct dosage and method of administration remained unknown[7,8]. Many women suffered from a dramatic contractive effect, causing the rupture of their uterus and intrauterine fetal asphyxia[7].

A standardized preparation of posterior pituitary extract was first introduced in 1930, and in 1948 it was further improved by implementing intravenous infusion, which is still used today[7,9].

A new era began in 1953, as Vincent du Vignaud synthetized oxytocin as the first polypeptide hormone[10]. In 1955 he was awarded with the Nobel Prize in chemistry for this work, and oxytocin became widely available for clinical use as a medication in labor wards[3]. During the 1960, obstetricians refined techniques for using oxytocin for augmentation and induction of labor in addition to prevention of PPH[11-13].

5.1.2 Physiology

Oxytocin acts through specific oxytocin receptors in the smooth muscle cells of the uterus: myometrical and decidual[14,15]. An increase in intracellular calcium interacts with actin and myosin proteins, leading to a shortening of the cell and, eventually, a contraction[15,16]. Oxytocin is produced as a response to the activation of strain-sensitive sensory cells in uterus.

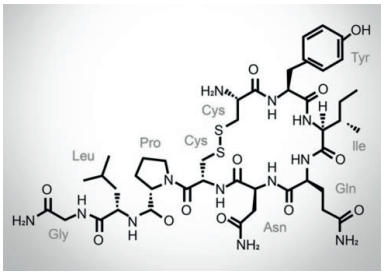


Figure 1
The structure of oxytocin, the first polypeptide hormone to be synthesized

Accumulating evidence has also indicated that oxytocin is produced in the decidua, where oxytocin may have an additional paracrine role[16]. This may explain the different effects of oxytocin, such as intermittent uterine contractions for start and progression of labor, as well as the tonic uterine contractions that are essential to prevent PPH[17,18]. Contractions during labor increase in frequency and strength due to a parallel rise in the density and sensitivity of oxytocin receptors[19]. In addition, the plasma concentration levels of oxytocin increases during the first and second stage of labor compared to the weeks before labor onset[16,19].

Oxytocin is metabolized in the liver and kidney, whereas oxytocinase, an enzyme produced in the placenta, plays an important role in the timing of different types of uterine contractions[17]. The regulation of oxytocin receptors and the oxytocin-mediated contraction of the myometrium is not yet fully understood. Oxytocin increases uterine activity, but there appears to be an individual sensitivity to the contractile response[17,20-22]. For instance, the effect is found to be more dependent on factors such as uterine activity than the actual dose of

oxytocin given or measured[20,23]. The therapeutic index is considered highly unpredictable with a substantial potential for overdose[17,20].

5.2 Labor

Labor is a physiological process by which uterine contractions occur that are sufficient to cause dilatation and effacement of the cervix[24]. The progression of labor depends on the three P's: the passage (pelvis), the passenger (fetus), and the power (the contractions). To pass through the female pelvis, the fetus needs to perform flexion, rotation, and extension, which are also referred to as the cardinal movements (Figure 2)[24,25].

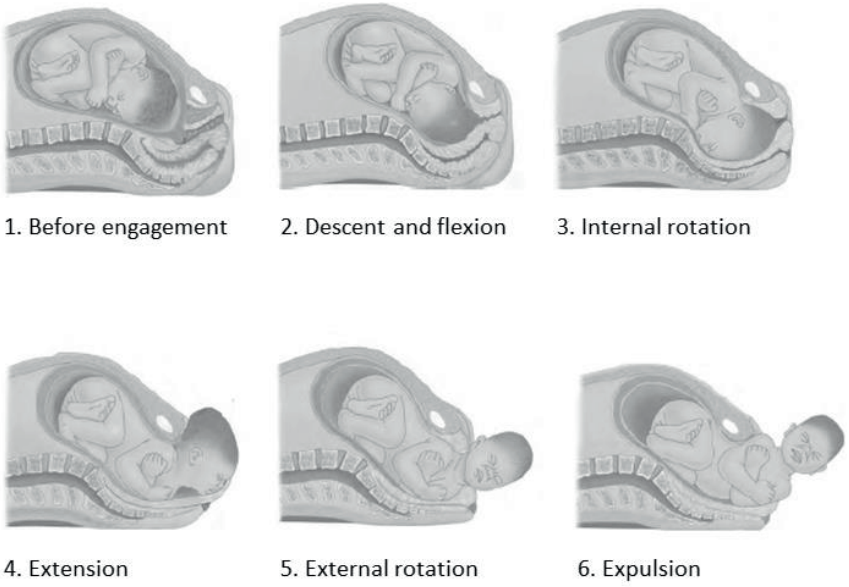


Figure 2
The Cardinal movements (from Williams Obstetrics 23rd edition. Copyright©2010 McGraw-Hill Company, Inc. All rights reserved. Reprinted by permission)

The order of the cardinal movements differs depending on the presentation of the fetus. The passenger (fetus) influences the progression of labor through factors like size, position, and vulnerability. The power (uterine contractions) influences this progression by causing the dilatation and effacement of the cervix, leading the fetus through the passage (pelvis).

5.2.1 Normal labor

For decades, obstetricians have discussed the concept of "normal labor", but at present there is no a clear, common consensus on the definition of this term[26-28]. One general perception of normal labor is a woman who had a low-risk pregnancy in addition to low-risk, at-term, spontaneous-onset labor and delivery, with mother and baby in good condition thereafter[27]. Of course, normal labor is easier to diagnose in retrospect than from a prospective point of view. In 1996, the rate of normal labor, as per the definition above, was estimated to be 70-80%[27]. Due to more use of epidural analgesia, induction of labor and cesarean section the rate of normal labor is decreasing, in particular in developed countries, where rates below 40% are reported[28-30].

5.2.1.1 Onset of labor

During pregnancy uterine activity is controlled by different inhibiting factors such as progesterone, nitric oxide and relaxin, but shortly before term the uterus changes its response to these factors and hormones[19,31,32]. Several studies have suggested that there is an increase in fetal oxytocin secretion shortly before labor, which means the fetus may play an important role in the timing of the onset of labor[16,17,21,32]. The diagnosis of labor onset is challenging as different symptoms and phases may overlap and is generally done by obstetricians and midwives through clinical observations[31,32].

Unfortunately, specific criteria to confirm the onset of labor are not available[33]. However, changes in the cervix, such as cervical dilatation, effacement, and consistency, can clinically be evaluated. One of the most well-known cervical scoring systems, the Bishop score, consists of a combination of these cervical changes, as well as fetal position and status in the pelvis. This schematic method was originally presented in 1964 to assess the safety of induction of labor [34].

5.2.1.2 Stages and phases of labor

Traditionally labor is defined as a continuous process separated into three stages. The first stage is divided into a latent phase and an active phase. The contractions in the active phase have the regular pattern necessary for the progression of labor and complete cervical dilatation (10 cm) before the second stage begins (Figure 3). The third stage begins when the fetus is born and ends with the delivery of the placenta and uterine contractions[25]. However, it is useful to note that there are various definitions of these stages and phases of labor in the literature, with different initiation and termination points.

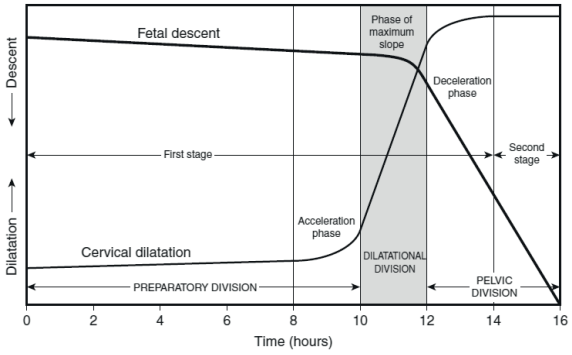


Figure 3
The first and second stage of labor presenting cervical dilatation and fetal descent. Composite of the average dilatation curve for labor in nulliparous women, redrawn from Friedman, 1978 (from Williams Obstetrics 23rd edition. Copyright©2010 McGraw-Hill Company, Inc. All rights reserved. Reprinted by permission)

First stage

According to the World Health Organization (WHO), the latent phase of the first stage of labor is categorized by irregular uterine contractions and progressive cervical effacement[35]. The latent phase can be exhausting and can last a very long time before advancing to the active phase of the first stage[36]. The latent phase is poorly understood and hard to measure, and it will not be discussed further in this thesis[37,38].

The progression of labor is generally considered to be difficult to predict before the cervix reaches a dilatation of 3.5cm[39,40]. When the start of the active phase is defined as a cervical dilatation of 3 cm, longer labors, more interventions and more complicated labors have been observed[41]. However when cervical dilatation reaches 4 cm, the progression of labor is expected to be more gradual and possible to predict, but a diagnosis of abnormal labor may be delayed and possible interventions initiated too late if the woman already is exhausted[39,40,42]. Since 2000, the WHO criteria to diagnose the start of the active phase of labor have been: cervix 4 cm dilated and effaced, regular uterine contractions, and fetal decent in the pelvis[43].

Second stage

The second stage of labor begins at a cervical dilatation of 10 cm. If the presenting part of the fetus has not reached the pelvic floor, maternal effort in the form of active pushing has traditionally been postponed by 1 hour. The following expulsive phase normally represents more stress and exhaustion for the mother and the fetus, and thus the duration of active pushing has traditionally been restricted to 1 hour [44]. These "clinical limits" have their origin in Friedman's studies from 1955[39]. However, several researchers would argue that these limits are based more on clinical opinions and experience instead of consistent scientific evidence and a longer duration is now commonly accepted[24,45-47].

5.2.1.3 Progression of labor

Progression of labor is assessed by cervical dilatation, descent and position of the fetus in the pelvis, as well as the strength of uterine contractions. The time aspect of the progression of labor varies widely, and depends on the definition one uses for the onset of labor[48].

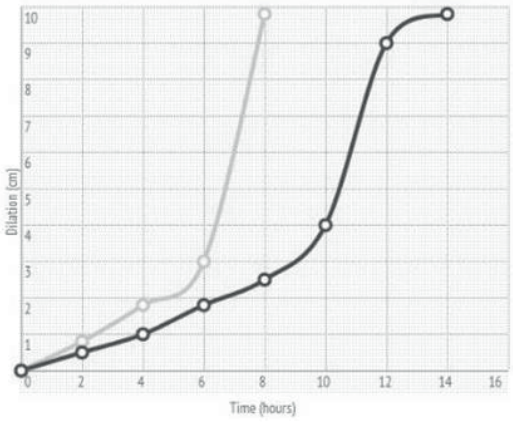


Figure 4
Labor curves of nulliparous (black) and multiparous (grey) women based on Friedman's graphicostatistical analysis in 1955 (nulliparous) and 1956 (multiparous) (published by Rebecca Dekker, PhD, RN, APRN, August 28, 2013.

In 1955 Friedman developed the first labor curve; a graphic recording of the progress of normal labor (Figure 4)[39]. Due to a sigmoid curve in this observation, a cervical dilatation of 1.2 - 3 cm per hour could be estimated in the phase between 4 and 10 cm of cervical dilatation. This curve was based on 100 nulliparous women with spontaneous onset of labor, in which cervical dilatation was observed retrospectively[39]. Despite repeated criticisms, the paper has had major influence on worldwide obstetric practice due to its originality[49,50].

In 1972, Philpott and Castle published a composite graph of the progression of labor based on Friedman's observations. A straight alert line (cervix dilatation of 1 cm/hour) and a straight action line (shifted 4 hours parallel to the right) were added to the cervicograph, representing cervical dilatation (Figure 5)[51,52].

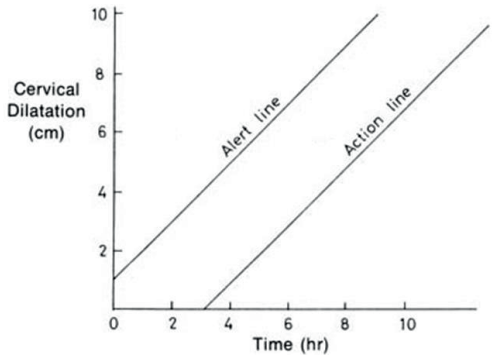
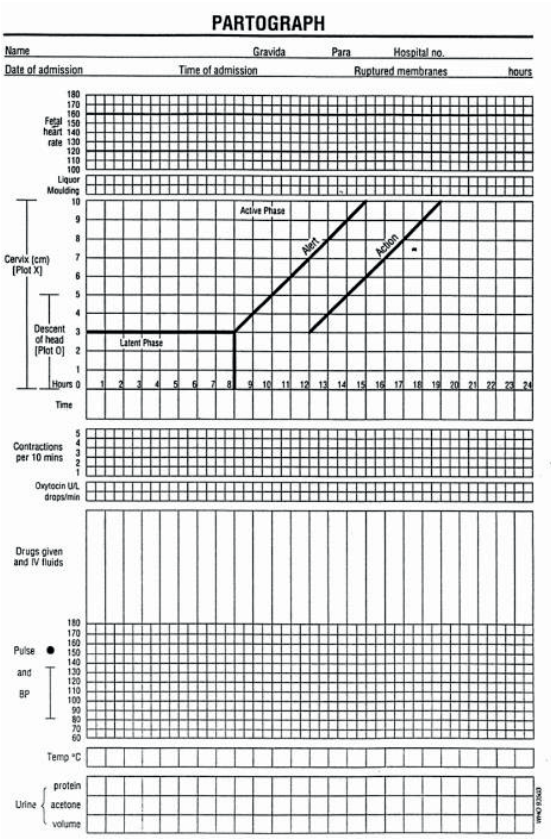


Figure 5
Cervicograph for evaluating the active phase of labor (R.H Philpott, Cervicographs in the management of labour in primigravidae. II. The action line and treatment of abnormal labour. J Obstet Gynaecol Br Commonw. 1972 Jul;79(7):599-602. Copyright©1972 John Wiley & Sons. All rights reserved. Reprinted by permission)

The primary aim of the alert line was to help midwives and house surgeons to detect abnormal labor and transport the women to a hospital if necessary. If the progression of labor reached the action line, steps were to be taken to correct the suspected insufficient uterine contractility such as amniotomy and oxytocin augmentation[52].



Not until 1994, 20 years later, the WHO initiated a multicenter study to evaluate the implementation of their modified partograph, which was based on the cervicograph from Philpott and Castle in addition to fetal descent[35]. It depicts a latent phase of 8 hours, and start of the active phase of labor was set at 3 cm of cervical dilatation. The study showed that the modified WHO partograph was simple to use and an implementation could improve labor outcomes (Figure 6)[35].

Figure 6
The modified WHO partograph (from World Health Organization, www.who.int)

The overall rate of labors augmented with oxytocin declined from 20.7% to 9.2% and despite this, the overall rate of prolonged labors >18 hours went from 6.4% to 3.4%[35]. Increased use of interventions in the latent phase and difficulties in defining the start of the active phase resulted in another modification in 2000, in which the latent phase was excluded from the partograph and the start of the active phase was set at 4 cm of cervical dilatation[43]. However, the efficiency of the 2000 partograph is considered to be unclear, and its routine use is not recommended[49]. Nevertheless, the use of this partograph is widespread and considered reasonable[49].

In 2002 and 2010 Zhang et al. reexamined the Friedman's partograph in retrospective studies of 1329 and 62 415 American women, respectively. Based on these reports, he constructed a new contemporary curve of the progression of labor (Figure 7) which shows that the start of the active phase was observed at 6 cm, not 4 cm as in earlier partographs[50,53]. Based on his results, Zhang suggested a reevaluation of existing recommendations, but the WHO has yet to comment on this. This use of this criterion to define the active phase is currently recommended by the American Congress of Obstetricians and Gynecologist.

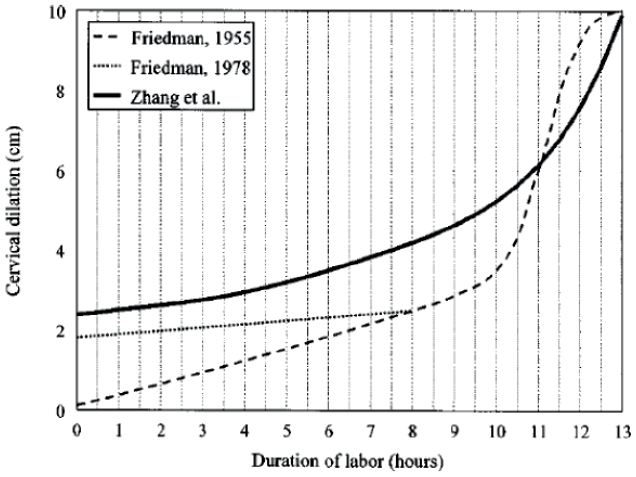


Figure 7
Comparison between the original and modified Friedman curve and the pattern of cervical dilatation based on contemporary data from 2002. (Zhang J. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol. 2002 Oct;187(4):824-8. Copyright©2002 Elsevier. All rights reserved. Reprinted by permission)

5.2.1.4 Length of labor

The length of labor varies according to the definition used, resulting in a wide range of normality[39,43,48,50,54]. Still, the length of labor remains clinically relevant and important to measure. The duration of the latent phase can be between 8 and 20 hours[35,55]. The normal

duration of the active phase of the first stage of labor is considered to be 8-10 hours (upper limit 18 hours) among nulliparous women and 4-6 hours (upper limit 12 hours) among multiparous women[50,56-58]. The mean length of the second stage of labor among nulliparous women is 54 min (with a maximum range 140 min) and 18 min among multiparous women (with a maximum range 60 min) [56,59,60]. Contemporary practice with supporting data suggests that the duration of labor is longer today than it was in the past[53,56,61]. If the goal is to agree on a normal length of labor, we should first reach a common definition of when the active phase starts.

5.2.2 Abnormal labor

In order to define abnormal labor, there must be a definition of normal labor[28]. In the literature, labor dystocia, dysfunctional labor, prolonged labor, and cephalopelvic disproportion are some of the traditional terms used to describe abnormal labor. Although these terms have different definitions, none of these conditions can be diagnosed until the woman has entered the active phase and thereby achieved an adequate trial of labor. Abnormal labor is the result of abnormalities in on or all of the three P's: the passage (pelvis), the passenger (fetus) and the power (the uterine contractions).

In clinical practice the differentiation between dysfunctional labor due to inadequate contractions or absolute cephalopelvic disproportion is difficult. As a rule, cephalopelvic disproportion can only be diagnosed in retrospect[24]. In the following chapters, the term "prolonged labor" is used to describe abnormal labor, as prolonged labor is the condition the clinicians can observe and treat.

5.2.2.1 Definition of prolonged labor

A set of agreed upon definitions is essential to diagnose prolonged labor[62]. A wide disparity has been observed in this arena, with both unclear and even non-existent definitions of prolonged labor[63-65]. According to the WHO partograph, when cervical dilatation crosses the action line 4 hours delayed from the alert line, it is defined as prolonged labor (Figure 8)[62].

Today, a frequent used definition of prolonged labor is labor with a duration of more than 12 hours[66].

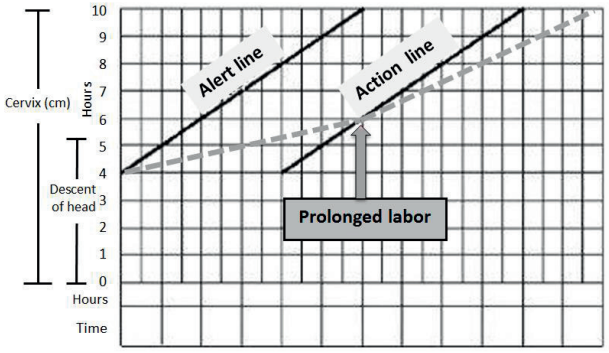


Figure 8
WHO definition of prolonged labor. Dotted line represents the cervical dilatation.

In a prospective study that used this definition by WHO, the incidence of prolonged labor was 12% among nulliparous women who delivered at term[67]. Others have observed that 20-37% of nulliparous women experience delay in the first stage of labor[64,68,69].

5.2.2.3 Risk factors for prolonged labor

Nulliparous women have the highest risk of experiencing long labor and eventually prolonged labor[69]. Other risk factors associated with prolonged labor include high body mass index (BMI), low bishop score at admission, occiput posterior presentation, high fetal birth weight, shape of the pelvis, and advanced maternal age[68]. These factors may interact and influence each other, sometime with an additive effect. Obstetric interventions such as induction of labor and use of epidural are associated with an increased risk of prolonged labor. However, due to confounding factors it is difficult to distinguish between associations and cause[68].

5.2.2.5 Complications of prolonged labor

Prolonged labor is the most frequent indication reported in the case of acute cesarean section (reported in 30-65% of cases)[70,71]. However, up to 40% of acute cesarean sections are performed not due to prolonged labor, but to unclear definitions in the latent phase[37,65,71].

Maternal and fetal morbidity and mortality rates are higher in abnormal labors compared to normal labors[44,72]. Prolonged labors have higher risk of chorioamnionitits, meconium staining in the amniotic fluid, postpartum hemorrhage (PPH), lower Apgar score, and admission to the neonatal intensive care unit[36,38]. Augmentation of labor with oxytocin, operative vaginal delivery, and cesarean section are more frequently used either as interventions or as treatment in prolonged labors.

Prolonged labor and the role of oxytocin

Oxytocin plasma concentrations measured during oxytocin infusion among women with dysfunctional labors were found to be similar to baseline levels of non-pregnant woman and pregnant women before labor[17,22,73,74]. In contrast, oxytocin plasma concentrations measured in women with induced labors by oxytocin infusion were similar those in women with spontaneous labor[19]. The primary low uterine activity among women with a slow progression of labor may represent poorer uterine sensitivity, which again reflects the unpredictable individual response to oxytocin[20,22,73].

Different studies have explored the uterine muscle response by measuring uterine activity while increasing the dose of oxytocin via infusion [20,21,75,76]. The relationship between uterine activity and dose seems to be logarithmic, i.e., the maximum level of effect is reached before the maximum dose of oxytocin is administered. Moreover, stimulation of the uterus above a certain level of activity may result in only a modest progression of labor, with an increased risk of fetal hypoxia[77].

The use of oxytocin augmentation among women with spontaneous onset of labor and normal progression of labor as defined by WHO, has not been evaluated in any trials. However, the effect of early versus late initiation of oxytocin has been explored among women with spontaneous onset of labor and slow progression. Early initiation of oxytocin augmentation reduced the length of labor by an average of 2 hours[78]. Among women with mild delay, early amniotomy and early oxytocin augmentation also shortens the length of labor by an average of 70 min[79]. The different definitions of prolonged labor are a recurrent problem when trying to assess the effect of oxytocin augmentation in prolonged labor[80]. The majority of women who receive oxytocin for augmentation of labor are not diagnosed with prolonged labor, and in the case of cephalopelvic disproportion, oxytocin is contraindicated[81].

A partogram can be used to determine when labor is prolonged, and thereby when to intervene. Different partograms have been suggested, defining the action line not only at 4 hours, but also at 2 or 3 hours to the right of the alert line. In a review comparing the outcomes of these different action lines, the rates of augmentation of labor with oxytocin were lower in studies that used the partogram with the 4 hour action line compared to the 2 hour action line[49].

5.3 Population characteristics

Clinical practice is based on the baseline risk that exists among the women in any given hospital's catchment region. The differences across these populations may explain some of the variation in the definitions and acceptance of normal labor[82,83].

5.3.1 Parity

Labors of nulliparous and multiparous women are fundamentally different[84,85]. The risks and complications of labor and delivery are generally higher among nulliparous compared to multiparous women. Indeed, some guidelines even present different definitions of the onset and progression of labor depending on parity[46,86]. All phases of labor are usually longer in nulliparous compared to multiparous women, and this should be taken into account in all clinical judgments[50,56].

Parity and the role of oxytocin

Far more nulliparous women have their labors augmented with oxytocin[87]. This is mainly due to the higher risk of dysfunctional contractions and prolonged labor in these women[20,88]. Many would argue that such augmentation has no place in the labors of multiparous women, but reports have shown that oxytocin is still used in up to 20% of them[87,89,90]. It has been reported that 50-75% of nulliparous women receive oxytocin for the augmentation of labor, with considerable variation between countries and units[81,87,91].

5.3.2 Ethnicity

Cervical dilatation and uterine contractility have been studied in different ethnic groups. Among women with spontaneous-onset labor, the differences were not of any clinical significance[59,90,92]. However, the risk of cesarean section does seem to vary across ethnic groups[93,94]. For example, a higher incidence of fetopelvic disproportion has been observed in women from the horn of Africa, which to some extent may explain the higher proportion of prolonged labor among these women[95,96].

5.3.3 Body mass index

In 2014, reported rates of obese pregnant women (pre-pregnancy BMI >30) were 25% in the United States of America (USA) and 9% in Scandinavia, with an increasing trend in both populations[97-99]. Obesity in pregnancy increases the risk of pregnancy-related health problems, such as diabetes and preeclampsia[100]. The risk of pregnancy-related complications such as placental insufficiency, prolonged labor, operative vaginal delivery, cesarean section, and PPH, is also higher[99,101-103]. The risk of poor neonatal outcome has also been reported to be higher among obese women[97,104].

BMI and the role of oxytocin

The contractility of the myometrium has been tested in vitro trials comparing obese and non-obese women. One study found that uterine myometrical strips in pregnant obese women contracted less forcefully and less frequently than in non-obese pregnant women[105]. Another study tested the effect of oxytocin, but did not find any difference in myometrical contractility[102,106]. The sensitivity of oxytocin receptors may be more important than their quantity, which may be influenced by higher BMI[102].

5.3.4 Maternal age

In Norway the rate of laboring women aged >35 years was 10.2%, 15.4%, and 19.5% in 1992, 2002, and 2012, respectively[107]. More interventions, risks, and complications are being observed in the labors of these women such as oxytocin augmentation, induction of labor,

prolonged labor, placenta previa and cesarean section[108-113]. Advanced maternal age is also associated with chronic diseases, increased risk of diabetes, and hypertensive diseases, which may have further associations with placental dysfunction and perinatal fetal death[110,113,114].

Maternal age and the role of oxytocin

In vitro investigations of myometrical strips among pregnant and non-pregnant women with increasing age have shown a decreased contractility with increasing age, although it was not statistically significant among pregnant women[115]. Hence, in theory, the effect of oxytocin augmentation with increasing age could reduce the risk of prolonged labor and cesarean section among these women, but further investigation is needed[116,117].

5.4 Obstetric interventions

The perception that giving birth is a normal, physiological process is fundamental. Any disturbance of or intervention into the birth process should only be performed if it is justified by a sound clinical indication[28,118]. Increasing medical knowledge and obstetric technology have extensively increased the safety of laboring women. However, the current routine use of obstetric interventions has long been questioned by increasing numbers of laboring women and health care providers[118-120]. The common goal is still to create agreed guidelines for these interventions to optimize the labor outcomes for mother and child; however, agreeing on the ideal guidelines is difficult. In the following, the three most common interventions will be discussed: augmentation of labor, induction of labor and use of epidural analgesia.

5.4.1 Augmentation of labor

To augment means to strengthen, reinforce, or increase. Amniotomy, artificial rupture of the membranes, and use of oxytocin are the two most frequent and effective methods used in labor[25]. The definition of the term “augmentation of labor” is to increase uterine contractions during the active phase of labor, thereby augmenting, or accelerating the progress of labor when necessary. Clinically this should be distinguished from the indication to force or reinforce the onset of labor, for which the term induction of labor is more correct.

The effect of increased uterine activity or induction of labor due to amniotomy was first described in 1756[121]. The mechanism is believed to be an increased release of prostaglandins from the amniotic fluid[121]. Prostaglandin is an uterotonic agent which increases the uterine contractions in frequency and intensity[79]. Among nulliparous women at term, 87% will go into labor within 71 hours if the membranes rupture spontaneously[122]. The role of amniotomy in labor is important, but indication for and traditions of its use vary between units and countries, depending on the type of labor management[85,87,121]. Amniotomy shortens the length of labor, but routine use is not recommended, and the procedure should be reserved for women with abnormal labor[121].

5.4.1.1 Administration of oxytocin

Oxytocin is administrated as a continuous intravenous infusion. A pulsatile administration has been explored to imitate the endogenous effect in spontaneous labor. Lower doses of oxytocin were administrated, but differences in labor outcomes were not observed[123]. The biologic half-life of oxytocin is 3-10 min, but a steady-state plasma oxytocin concentration is reached after 40 min of continuous intravenous administration[17,22,75].

Two dose regimens of oxytocin administration are most frequently used: a low dose of 1-2 mU/min or a high dose of 4-7 mU/min. The tradition in the Nordic countries has been the low dose. The high dose shortens labor by 3.5 hours and is associated with a reduction in cesarean deliveries (RR=0.62, 95% CI: 0.44-0.86)[54,79]. The conclusions regarding optimal dosage are considered week due to few studies and heterogeneity among the studies included. Hence, there is not enough evidence to comment on which regimen is preferable[48,54,79,124].

5.4.1.2 Side effects of oxytocin

Common maternal side effects of oxytocin are headache, nausea, vomiting, hypotension, and reflex tachycardia[125]. The identified antidiuretic effect of oxytocin may result in decreased urinary output in combination to hyponatremia and water intoxication[126]. More painful contractions, more precipitous progress, and less self-control are assumed to increase a women's risk of a negative birth experience[16]. High doses of oxytocin have been associated with changes in maternal electrocardiograms[125].

The most common side effect affecting the fetus is the hyperstimulation of the uterus due to an impaired gas exchange in the placenta[16,127,128]. In particular, an increased frequency of uterine contractions may lead to poorer oxygenation of the fetal blood cells and eventually cause fetal asphyxia[127,129,130]. This is associated with abnormal fetal heart changes on cardiotocography read-outs, such as variable and late decelerations[131,132].

5.4.1.3 Use of oxytocin in the active phase of labor

The reported use of oxytocin augmentation ranges from 20-70% across hospitals and countries[91,124,133]. The use of oxytocin is often reported as an overall rate, including both spontaneous and induced labors in addition to mixed parity and use of epidural analgesia.

O'Driscoll and colleagues at the National Maternity Hospital in Dublin, Ireland, have had a major impact on the management of laboring women during the last centuries. In his study of 1000 nulliparous women in 1969 he stated that by use of oxytocin augmentation, abnormal labor could be converted into normal labor. The overall use of oxytocin augmentation at that time was 20%, with a cesarean section rate of 4%. The hospital used Friedman's curve for labor progress and onset of labor was strictly diagnosed[89]. In 1973 labor was considered as an intensive care situation by O'Driscoll due to the need of oxytocin to regulate labor duration[134]. The use of oxytocin augmentation had increased to 55%, with a cesarean section rate of 5.4%. The labor ward did not have automatic intravenous infusion pumps to maintain a continuous administration of oxytocin, which kept the midwife in the delivery room.

The term "active management of labor" was first published in 1984 and received more attention. By preventing prolonged labor, O'Driscoll presented an alternative approach to stop the increasing trend of cesarean section. At the time, the cesarean section rate in the USA was 20%, compared to 5.5% at the National Maternity Hospital in Dublin. The use of oxytocin augmentation was 41% in Dublin and varied from 2-27% in the USA[85]. Fundamentally, the active management of labor meant adhering to a strict definition of onset of labor, early amniotomy and oxytocin if the progress of labor did not follow Friedman's curve, a limit on the duration of labor of 12 hours, continuous support by the midwife, and recognition of the differences between nulliparous and multiparous women[85]. In the following decade, active management of labor was widely implemented; however opinions diverged as newer studies were published showing results that were different from those in Driscoll's original paper[135-

[141]. Several provocative letters and correspondence on this subject were published in various journals, such as a letter by Olah and Steer, which referred to active management as "active mismanagement of labor"[142-145]. Philip Steer in particular has made it clear that oxytocin augmentation is used injudiciously, and recently in "The case against oxytocin", he stated that its use should be forbidden[146].

In 1994, the recommended modified partograph by WHO suggested a common definition of prolonged labor by use of the 4-hour action line[35]. The WHO considered oxytocin augmentation to be a major intervention that should have a valid indication, as already suggested by Philpott in 1972[35,52]. This WHO partograph was not recommended by the National Institute for Health and Clinical Excellence before 2007 where the importance of confirming delay and prolonged labor prior to use of oxytocin augmentation was highlighted[147].

In 2009, another method of reducing the cesarean section rates and improving the experience of childbirth was presented: the "proactive support of labor"[148]. This theory is derived from "the active management of labor", but routine amniotomy is not performed. The authors assumed that 10% of the nulliparous women experience onset of labor solemnly as painful contractions and a fully effaced cervix. In these cases and if labor is not progressed linearly, amniotomy and oxytocin augmentation are initiated. By this, proactive support of labor recommends against using the WHO partograph. At present there is little research on this method and randomized controlled trials (RCTs) are needed[149] .

Both active management and proactive support of labor attempt to avoid prolonged labor. This may also be described as prophylactic use, i.e., active management of labor and therapeutic use, i.e., waiting for and recognizing an abnormality first (described as routine use).

The active phase of labor and the role of oxytocin

Little attention has been paid to the overall concept of the active management of labor by O'Driscoll, which has resulted in its unstructured and misunderstood implementation in several units, and the adoption of only two of its components: early amniotomy and oxytocin augmentation[88,140]. The differences in the implementation of active management of labor have been proposed as one of the reasons this protocol did not lead to a reduction in the cesarean section rate in the hospitals that adopted it. Trials assessing early amniotomy and oxytocin

augmentation alone did not show any benefits, but rather side effects, such as more hyperstimulation of the uterus and more pain for the laboring women[79,140,141].

In 2008, a Cochrane review assessed the active management of labor protocol, including newer RCT's updated in 2013[150]. Studies exploring the association between active management of labor and a low cesarean section rate have shown diverging results with a conclusion of a not significant reduction of the cesarean section rate using active management of labor (RR 0.88, 95% CI 0.77-1.01)[88,150]. Fewer women experienced labor >12 hours (RR 0.47, 95% CI 0.32 to 0.69), but maternal satisfaction, use of epidural analgesia, operative vaginal delivery, neonatal outcome, infections, and PPH were no different when comparing active management of labor and routine care. The results should be interpreted with caution, because the rates of cesarean sections and augmentation of labor with oxytocin showed large variations in the studies included[150]. The WHO and National Institute for Health and Clinical Excellence guidelines do not recommend active management of labor as routine management[46,151].

In 2004, Daniel-Spiegel reported an attempt to discontinue intravenous infusion of oxytocin once the active phase of labor was verified, showing reduced use of oxytocin augmentation, shorter labor duration and no change in the cesarean section rate among the women where oxytocin was discontunied[152]. However, findings from other small studies have come to diverging conclusions[153-155].

5.4.2 Induction of labor

A massive increase (2% to 25%) in the overall incidence of the induction of labor has been observed over the last 50 years[156,157]. Joint guidelines and conditions that are judged by clinicians to be medical indications for induction are the highest contributor to this increase[157,158].

The increased use of induction has led to major concerns regarding the increased associated maternal and fetal risks, mainly based on observational studies[159,160]. Conclusions from RCTs diverge, as induction of labor at term is found to have a protective effect on the risk of cesarean section compared to expectant management[161]. However more evidence is needed to evaluate the maternal and neonatal risk, and the importance of keeping the number of

inductions without medical indications has been stressed. Clinicians should reserve induction of labor for cases where maternal and perinatal benefits outweigh the risks[156,162].

There are several different methods for cervical ripening and induction of labor. Some common methods include a catheter placed through the cervix for cervical dilatation, and a variety of prostaglandins in addition to intravenous oxytocin infusion. Different combinations are being used, as meta-analyses and reviews still have not been able to conclude which method, or order of methods, is preferable[163-165].

5.4.3 Epidural analgesia

Epidural analgesia is a regional block where a catheter is placed into the lower region of the lumbar spine. Epidural analgesia is commonly offered to women during labor for pain relief, and there are large variations in overall rates: from 18% in Scandinavia to 58% in the USA, with even greater variations reported between units and parity[107,166]. Epidural analgesia has been proven to provide the best pain relief to laboring women, compared to other types of pain medication, with little or no side effects on the fetus[166]. Additional positive side effects are the lowering of blood pressure, especially in women with hypertension. Further, if an emergency cesarean becomes necessary, general anesthesia and its risks can be avoided.

From the laboring women's perspective, being awake and able to participate in labor without excessive pain or somnolence because of opioids is valued as positive. Side effects of epidural analgesia include hypotension, weakness in the legs that can restrict mobility during labor, higher risk of operative vaginal delivery, and longer labors that require augmentation with oxytocin[166-168]. Post spinal headache is reported in around 1% of women and can be severe[169]. Less important common side effects are itchiness and fever, but severe adverse effects are rarely reported[166].

The effect of epidural analgesia on the cesarean section rate is a controversial topic[170-172]. An issue which deserves more attention is the heterogeneity in the incidence of epidural analgesia in studies examining the different risks and associations to mode of delivery[79]. In observational studies, the use of epidural analgesia has been associated with an increased risk of cesarean sections, but RCTs included in systematic reviews have refuted this association[166,170,173]. However, administering epidural analgesia as part of routine, compared

to administration on request, has been found to increase the probability of a cesarean section[174]. The timing of the epidural, i.e., early or late in the first stage of labor, has not been found to influence the risk of cesarean section[175].

Epidural analgesia and the role of oxytocin

Lower plasma oxytocin concentration levels among women who received epidural analgesia in the second stage of labor have been reported, leading to the hypothesis of epidural-induced oxytocin deficiency[16,176,177]. Indeed, epidural analgesia blocks pre-sacral nerves in the lower birth canal, which by distension triggers the secretion of oxytocin[16,178,179]. In addition, epidural analgesia influences a woman's urge to bear down in the expulsive part of the second stage of labor. This theory has also been disputed, at least among women with normal labor[177,179,180].

When comparing women who did and did not receive epidural analgesia, those who received epidural analgesia more often have their labors augmented with oxytocin[166]. The actual prevalence of augmentation varies and is difficult to explore, as the use of oxytocin augmentation among women with epidural is sparsely reported. Wang et al. examined epidural analgesia administrated in the latent phase compared to delayed analgesia and did not find an increased risk of cesarean section[181]. Of note, the use of oxytocin augmentation among these women was low, with an incidence of only 23%.

Costley et al reviewed the routine use of oxytocin augmentation among nulliparous women with epidural analgesia and its effect on labor outcomes[182]. Only two small RCTs could be included, and results on the incidence of operative vaginal deliveries or cesarean section rates were not statistically significant when oxytocin was compared to placebo[183,184]. However, observational studies have found that a shorter second stage of labor is associated with a reduced risk of cesarean section if a high dose of oxytocin is given instead of low dose among women with epidural analgesia[170,184,185]. These results highlight the complexity of this study population.

5.5 Cesarean section

A constant trend of increasing cesarean section rates with increasing ranges between countries and continents has been observed over the last decades (Figure 9), which has led to much debate[83,186-190].

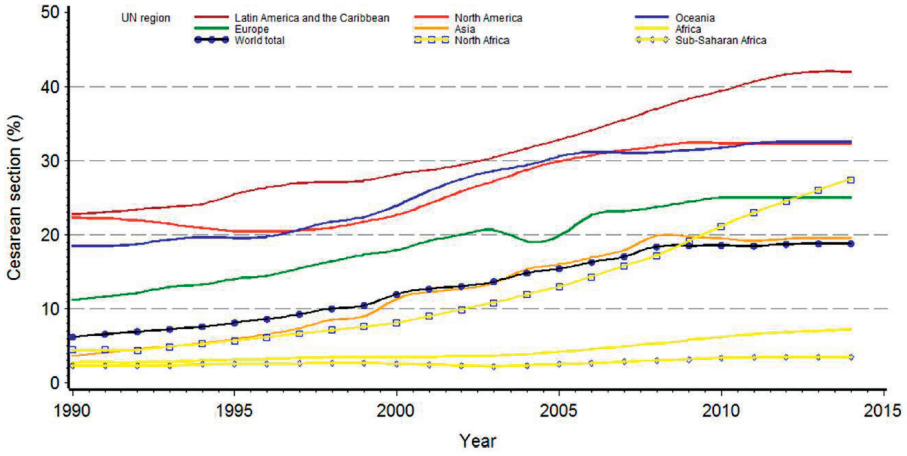


Figure 9
Trends in cesarean section rates (Betran AP. (2015) Increasing Trend in Caesarean Section Rates: Global, Regional and National Estimates: 1990-2014. Plos One. 2(5);11(2):e0148343.

In 1985, this was stated by the WHO: "There is no justification for any region to have cesarean section rates higher than 10-15%"[191]. Indeed, the increase in the cesarean section rate has not been accompanied by clear evidence of decreases in maternal or neonatal morbidity or mortality[190-192]. However, the WHO statement was later disputed, as the optimal cesarean section rate differs depending on population factors, level of care, and labor management, in addition to tradition and previous care[82,83,192].

In the Nordic countries, the increasing cesarean section rate plateaued in the last years, at around 16-20% (Figure 10)[192,193]. The focus on labor management in a relatively healthy population with good access to health care in these countries may have contributed to this stabilization.

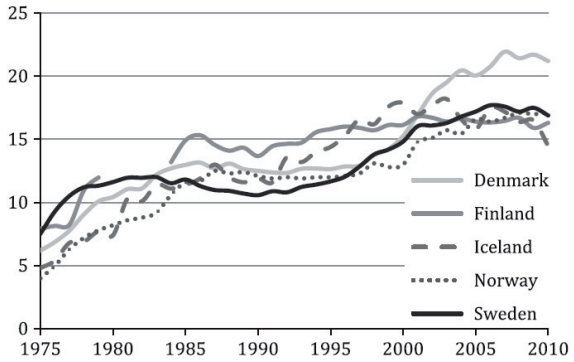


Figure 10
Trends in cesarean section rates per 100 births in the Nordic countries. (Langhoff-Roos J. The Nordic medical birth registers--a potential goldmine for clinical research. Acta Obstet Gynecol Scand. 2014 Feb;93(2):132-7. Copyright©2014 John Wiley & Sons. All rights reserved. Reprinted by permission)

When compared to vaginal delivery, cesarean section increases the maternal risk of thromboembolism, infection, PPH, and adverse pregnancy outcomes in later pregnancies such as abnormal placentation[190,194-198]. Moreover, acute cesarean section has a significantly higher risk of complications compared to elective cesarean section and vaginal delivery[199-202]. Many would argue that the overall risk of complications in an elective cesarean section has become so low that, if the mother prefers to have one, her opinion should be taken into consideration[203,204]. Some cesarean sections are inevitable, but some say that keeping the focus on performing cesareans with the correct indication, in particular among nulliparous women, is now more appropriate than focusing on a specific rate[188,203-206].

Prolonged labor is the main indication for acute cesarean section[70,79,85]. Lack of clear definitions to distinguish between the latent and active phase and the progression of labor are some of the reasons for the varying incidences of cesarean section (20-68%) reported among nulliparous women[70,71,151]. The second most common indication for acute cesarean section is fetal distress. This may be due to placental insufficiency, which can lead to poor fetal growth, and acute obstetric events like placental abruption and rupture of the uterus. The decision to perform an acute cesarean section is commonly based on fetal monitoring, when the fetal heart rate pattern shows sign of poor oxygenation[132,200]. These patterns are affected by uterine contractions, placental blood flow, and necessary gas exchanges for the fetus[127,129,130,132].

Cesarean section and the role of oxytocin

Only three RCTs have been performed in women with slow progression of labor to explore the effect of oxytocin versus placebo on the risk of a cesarean section[78]. These three RCTs included a total of only 138 women, resulting in a weak conclusion showing no significant differences in the cesarean section rate[78,151]. The preventive effect of early versus late

initiation of oxytocin among women with spontaneous onset of labor and slow progression has received more attention. There was heterogeneity between the five studies included in the Cochrane review, which included a total of 1200 women, but again there was no difference between these approaches on the risk of cesarean section[78].

Prevention of prolonged labor combined with an intention to reduce cesarean section rates has been explored in several studies. In nulliparous women diagnosed with primary dysfunctional labor, oxytocin augmentation alone did not reduce the cesarean section rate[77,78,207]. However, early amniotomy and initiation of oxytocin augmentation to prevent slow progression in labors with spontaneous onset were associated with a reduced risk of cesarean section. To prevent one cesarean section, it was estimated that 65 women needed to be treated[79]. The effect of different partograms has also been reviewed, and rendered one study that showed the use of partogram with a 4 hour action line compared to that with the 3 hour action line resulted in lower cesarean section rates (RR 1.70, 95% CI 1.07 to 2,70). No differences in cesarean section rates were observed when partograms with a 2 hours action line and 4 hours action line were compared or when using a partogram was compared to not using one[49].

5.6 Postpartum hemorrhage

PPH is the leading cause of maternal mortality worldwide[208]. In developed countries, PPH is the fifth leading cause of maternal death among pregnant women (2006)[208]. Severe PPH also increases maternal morbidity, which underlines how important it is for obstetricians to recognize possible near-miss cases, defined as: "A woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy"[209,210]. Many cases of maternal morbidity and mortality from severe PPH have been associated with substandard care, which is why severe PPH is considered to be preventable[211,212]. Up to eighty percent of PPH is due to atony of the uterus, followed by lacerations and retained placenta, and less commonly around 1% due to coagulopathy[213-215]. Figure 11 presents differences in morbidity and mortality rates by selected causes of PPH.

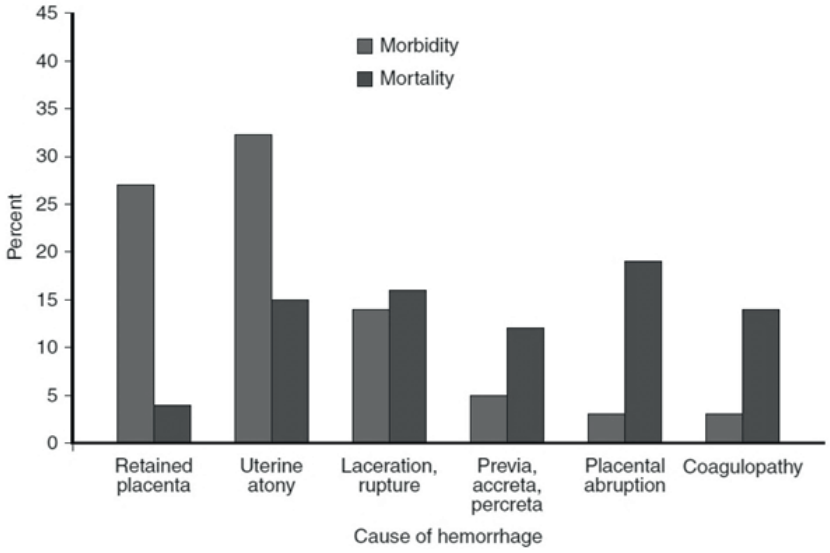


Figure 11
Incidences of selected causes of postpartum hemorrhage (PPH) and their contribution to maternal PPH-related morbidity and mortality. (from Williams Obstetrics 23rd edition. Copyright©2010 McGraw-Hill Company, Inc. All rights reserved. Reprinted by permission)

Traditionally, PPH is defined as blood loss of >500 ml, and severe PPH is defined as blood loss >1000 ml during birth and in the first 24 hours thereafter, also defined as primary PPH. Secondary or delayed PPH occurs 24 hours to 12 weeks after delivery and will not be further discussed. The reported incidence of PPH varies due to imprecise and diverging definitions of PPH, but also due to difficulties in correctly diagnosing PPH[107,216]. Despite an increased use of uterotonics, implemented guidelines of active management of the third stage of labor, and better health care service, the reported incidence of severe PPH has increased from 1.5% in 1999 to 4.2% in 2009[215,217-219]. Active management of the third stage of labor involves the routine use of oxytocin, early umbilical cord clamping, and active delivery of the placenta by controlled cord traction[220]. The placenta leaves a scar on the inner wall of the uterus, which has good circulation; thus the amount of blood loss is dependent on the uterine contractions that take place after the delivery of the placenta. Active management of the third stage of labor prevents atony of the uterus and reduces blood loss[220]. This recommendation was first implemented in Norwegian national guidelines in 2006[221].

Changes in the maternal population, but also in obstetric training i.e. reduced practical skills in management of the third stage of labor, have been put forward as possible explanations for the observed increase in the incidence of severe PPH[212,215,222]. In particular previous PPH,

higher maternal age, multiple pregnancies, and cesarean sections have been increasingly observed as risk factors. Other additional risk factors associated with severe PPH are prolonged labor, macrosomy, induction of labor, operative vaginal delivery, perineal lacerations, and oxytocin augmentation[212,213,222]. The increasing rates of uterine atony are highlighted as a concern requiring active measures[213]. The impact of blood loss on labor varies depending on the amount and speed of the bleeding, the woman's hemoglobin level, and her health status[215,220]. Standardized training may identify near miss cases due to excessive bleeding and improve the preventive management[223-225]. More important is that medical personnel are able to recognize the early signs of PPH, as the severity of the blood loss may not be immediately obvious and particularly because substandard care was detected in the majority of cases of severe PPH[212,222,225,226].

Of major concern is the high rate of abnormal placentation, which is mostly due to advanced maternal age and previous cesarean section. The amount of blood loss in women with abnormal placentation can lead to high maternal morbidity, even in high-resource countries and clinics[220,227,228].

Due to the increased maternal morbidity among women with excessive blood loss, severe PPH has been suggested to be an indicator of quality of obstetric care[212]. Observational studies have suggested a possible relationship between obstetric interventions and risk factors for PPH[215,222]. Therefore it is important to raise awareness that some obstetric interventions are avoidable.

PPH and the role of oxytocin

Labors with severe PPH due to uterine atony are more often augmented with oxytocin[229]. An opposite effect of exogenous oxytocin on the density and sensitivity of oxytocin receptors has been suggested as a possible cause of poor uterine contractility in these women[152,229,230]. Myometrical strips from elective cesarean section exposed to oxytocin for more than 4-6 hours showed a decreased response to subsequent oxytocin exposure, i.e., a decreased myometrical contraction[230]. A case-control study found a clear association between increased risk of uterine atony and PPH when oxytocin was used in maximum doses for more than 4 hours[229]. Another observational study found an independent dose-related association between oxytocin augmentation and severe PPH[231]. However, these observations need to be more thoroughly explored.

RCTs exploring the effect of active management of labor and severe PPH did not find an association to high dose, low dose or delayed use of oxytocin augmentation. However, the power of these studies to detect differences can be questioned due to their small sample sizes and the inclusion of severe PPH as a secondary outcome[79,150] A multicenter cluster RCT exploring the use of oxytocin in the early stages of labor and the effect of active management of the third stage of labor found no differences in PPH rates among women who did and did not receive oxytocin before delivery[232].

As previously mentioned, active management of the third stage of labor is recommended as a prophylaxis to reduce PPH[220]. Oxytocin is essential in this management, but this particular role of oxytocin is not discussed further in this thesis.

5.7 Other selected labor outcomes

5.7.1. Operative vaginal delivery

The incidence of operative vaginal delivery varies between 0.5% and 20% depending on the country and the obstetric unit[107,233-235]. Performing an operative vaginal delivery is considered safe and appropriate, but controversy exists as increased risk of maternal and neonatal complications has been highlighted[233,235].

The risk of an operative vaginal delivery must be compared with the alternatives available, i.e., the risk of compromising the well-being of the fetus by expectant management awaiting a vaginal delivery or performing an acute cesarean section when cervix is fully dilated[235]. The complications associated with operative vaginal deliveries are based on different indications, the experience of the operator, and clinical judgment[233,236]. Use of epidural analgesia is associated with increased risk of operative vaginal delivery[166]. The main indications are prolonged second stage of labor and fetal distress.

Operative vaginal delivery and role of oxytocin

Operative vaginal delivery rates are mainly observed as secondary outcome in RCTs assessing use of oxytocin augmentation and mode of delivery. In these, no differences in the rates of operative vaginal deliveries among nulliparous women in spontaneous labor at term are observed if oxytocin augmentation; is administered or not, is initiated early versus late or high dose versus low dose is administrated[78,79,183,184].

5.7.2 Sphincter rupture

Sphincter rupture is defined as partial or total rupture of musculus sphincter ani externus and/or internus. A rupture may cause permanent injury, resulting in impaired or complete lack of muscle control, ultimately leading to anal incontinence. Nulliparity, high fetal birth weight, and operative vaginal delivery are associated with an increased risk of sphincter rupture[237-239]. The protective effect of episiotomy on the risk of sphincter rupture is controversial[240-243]. The incidence of sphincter rupture is reported between 0.1-6.0% after vaginal delivery in high-resource settings and is the main reason for anal incontinence among younger women[237,238,244]. The incidence of sphincter rupture in the Nordic countries in 2009 varied from 0.6% in Finland, to 3.6% in Denmark, and 4.1% in Norway[245]. The importance of preventing sphincter rupture has been highlighted in the last decade, as long-term effects can have a major impact on quality of life[246,247]. A decrease in sphincter ruptures has been observed after preventive measures were implemented[242,246,248].

Sphincter rupture and the role of oxytocin

Higher rates of the use of oxytocin among women with sphincter rupture have been reported[243]. An association between its use and risk of sphincter rupture has been suggested, in which oxytocin may act as an effect modifier[249]. This may be due to stronger contractions leading to impaired control of the perineum during the expulsive phase of labor[248]. Different oxytocin regimens (high and low) have failed to show any differences in the risk of sphincter rupture[124].

5.7.3 Apgar score

The Apgar score is a standardized observation of the newborn mainly performed by the midwife 1, 5, and 10 min after birth. The score was originally developed by Virginia Apgar in 1953 to observe the newborn 1 min after birth and determine if further measures were necessary[250]. Heart rate, respiration, muscle tonus, reflex irritability, and color are evaluated, with a maximum score of 10. Based on an observation of 15 000 newborns, a score of 8-10 is considered normal, 5-7 mildly depressed, and at <5 the fetuses often needed resuscitation[250]. In 1964, the same score was performed again 5 min after birth, as a study on cerebral palsy found a correlation to the 5 min and not to the 1 min score[251]. The incidence of low Apgar score by definition (<7 after 5 min) is around 0.7-1.5 %[107,252]. Importantly, the Apgar score cannot predict long-term outcomes and should only be used as a screening tool in the systematic observation of the newborn[252,253]. However, the score is simple to use and is still compulsory worldwide[254].

Apgar score and the role of oxytocin

Substandard care has been observed in up to 75% of infants with an Apgar score <7 after 5 min, and the incautious use of oxytocin were cited as one of the main factors in this care[255]. Low Apgar score is mainly reported as a secondary outcome, and its association with the use of oxytocin in observational studies has been reported, but these findings have not been verified in RCTs[54,256,257]. The incidence of low Apgar score is relatively low, and if future studies are to detect changes, their sample sizes must be large.

5.7.4 Umbilical cord blood gas analyses

Blood samples from the umbilical cord are used to provide information on the condition of the fetus at birth. The umbilical cord blood gas analyses are recommended in all high-risk pregnancies and deliveries, and in some units they are routine[258].

Severe intrapartum asphyxia and the risk of neurologic, respiratory, cardiovascular, and gastrointestinal complications and neonatal intensive care unit admissions is increased if the pH in the umbilical cord blood is <7 at birth[259]. A base excess >12 increases the risk of newborn encephalopathy and severe complications. Neither a pH <7, base excess >12, or an

Apgar score <7 at 5 min alone are sufficient markers for poor neonatal outcome[260]. However, they may be used to screen for improvements or near miss cases where improvement is necessary, or in cases which need more focus. A combination of these three variables at birth increases the risk of a poor outcome for the fetus[260,261].

Umbilical cord blood gas analyses and the role of oxytocin

As with the Apgar score, the association between oxytocin augmentation and acidemia (pH <7 and base excess >12) at birth differs in the literature. Use of oxytocin or even use of high doses of oxytocin did not result in differences in the pH compared to no use of oxytocin in observational studies[262,263]. However, case-control studies have found that oxytocin augmentation doubles the risk of acidemia at birth[256]. The relationship between oxytocin and hyper stimulation is probably the main contributing factor, in addition to the individual response to oxytocin. Injudicious use of oxytocin has been observed, and it has been estimated that acidemia at birth can be prevented in up to 50% of cases[256].

5.8 Systems and standardization

Achieving quality of care in labor and delivery is essential in every labor ward. The perception of quality of care may vary and will be influenced by experience, traditions, and guidelines. It is important to have a set of agreed-upon core outcomes in order to assess the quality of obstetric care, but the lack of distinct definitions in obstetrics makes this challenging and needs to be highlighted[264-269].

To evaluate our own performance as clinicians we must compare our results with others when possible. Systematic collection of data is mandatory if awareness is to be raised[270]. We have a responsibility to review and interpret our performance and initiate improvements when needed. A standardization of registered outcomes is essential if these comparisons are to be reliable[265,270].

The cesarean section rate has been used as a quality indicator in obstetric for many years. A constant increasing trend of cesarean sections has caused concern and has been repeatedly debated. To investigate and identify possible factors influencing this trend, different cesarean section classification systems have been developed, and the need for a

common, international classification system is now being recognized[271,272]. An evaluation of 27 classification systems concluded that the ideal system that fulfills all expectations is yet to come[271]. At present, the 10-Group Classification System (TGCS) proposed by Michael Robson (also called the Robson classification) is recognized as the most appropriate to fulfill current international and local needs (Figure 12)[271].

Group	Description
1	Nulliparous, single cephalic, ≥37 weeks, spontaneous labor
2	Nulliparous, single cephalic, ≥37 weeks, induced or cesarean before labor
3	Multiparous (excluding previous cesareans), single cephalic, ≥37 weeks, spontaneous labor
4	Multiparous (excluding previous cesareans), single cephalic, ≥37 weeks, induced or cesarean before labor
5	Previous cesarean, single cephalic ≥37 weeks
6	All nulliparous breeches
7	All multiparous breeches (including previous cesareans)
8	All multiple pregnancies (including previous cesareans)
9	All single abnormal lies (including previous cesareans)
10	All single cephalic, ≤36 weeks (including previous cesareans)

Figure 12 *The 10-Group Classification System by Michael Robson*

5.8.1 The 10-Group Classification System

In 2001, Michael Robson presented a system in which all delivering women were stratified into 10 groups (Figure 12)[273,274]. The characteristics used for classification were parity, gestational age in weeks, fetal presentation, onset of labor, number of fetuses, and previous cesarean section. With this system he created a method of analyzing changes in cesarean section rates and ratios within these groups of women. The system is a simple tool, easy to implement in clinical practice, and collects data in a standardized way. He called the TGCS a framework, which was flexible and open to modifications if needed[274].

The TGCS has been increasingly introduced and incorporated in labor wards, but also in national registers and databases[107,275-277]. The original 10 groups have been adapted in many settings by subdividing the groups 2, 4, and sometimes 5 into induction of labor and pre-labor cesarean section, respectively (Figure 13)[272]. This subdivision is easily performed, as it relies on routine information that is generally already registered. In addition, classifying all women into the 10 groups requires accurate data registration, which itself is an indicator of quality[270].

Group	Description
1	Nulliparous, single cephalic, ≥37 weeks, spontaneous labor
2a	Nulliparous, single cephalic, ≥37 weeks, induced labor
2b	Nulliparous, single cephalic, ≥37 weeks, cesarean before labor
3	Multiparous (excluding previous cesareans), single cephalic, ≥37 weeks, spontaneous labor
4a	Multiparous (excluding previous cesareans), single cephalic, ≥37 weeks, induced labor
4b	Multiparous (excluding previous cesareans), single cephalic, ≥37 weeks, cesarean before labor
5	Previous cesarean, single cephalic ≥37 weeks
6	All nulliparous breeches
7	All multiparous breeches (including previous cesareans)
8	All multiple pregnancies (including previous cesareans)
9	All single abnormal lies (including previous cesareans)
10	All single cephalic, ≤36 weeks (including previous cesareans)

Figure 13 *The modified 10-Group Classification System*

Systematic stratification can be used to compare clinical practice over time within a delivery unit, between delivery units, or even internationally[271]. An overall cesarean section rate includes no information on differences in the population, such as variations in parity, induction of labors, or the amount of women with a previous cesarean section, and the risk of cesarean section in these groups in particular shows large differences.

Keeping the cesarean section rate low has received continuous attention. However, increasingly there has been a shift toward keeping the focus on performing the correct cesareans. The cesarean section rate should be evaluated together with other labor outcomes, which could be achieved by incorporating an agreed set of quality indicators into the TGCS. Some examples of these indicators would be use of epidural analgesia, operative vaginal deliveries, sphincter rupture, PPH, and oxytocin augmentation. Although this was suggested by Robson in 2001, it has received little attention[96,274,278].

5.8.2 Standardization of the use of oxytocin augmentation

Women have received oxytocin augmentation during labor for many years based on amazingly limited hard data[17]. Evidence on oxytocin augmentation has been inconsistent, and no expert guidelines have been available for many years[151,279]. Standardization and an evidence-based protocol on oxytocin augmentation have been debated[280]. Research has focused on improving safety by utilizing the lowest and most effective administration regimens. A common consensus on administration, dose, and timing is yet to come, but the establishment of such protocols will help to decrease errors and thereby improve outcomes[279,280].

An association has been observed between the oxytocin augmentation and poor fetal and maternal outcome in obstetric liability claims[87,255,256,281]. Incautious use and too little knowledge or awareness of the effects of oxytocin augmentation have been put forward as an explanation[81,256,282]. Side effects related to oxytocin augmentation highlight the importance of clear definitions and structured guidelines[279].

Almost 30 years ago, a review regarding the clinical use of oxytocin concluded that oxytocin for augmentation was safe and effective if used correctly with careful monitoring[17]. Oxytocin occupies an important place in modern obstetrics, but we should not lose sight of the associated risks[17,88]. The conclusions of this review on the use of oxytocin in labor were based on results from earlier studies with results that ranged from showing oxytocin as safe to showing that it was dangerous[20,81,85,88,127]. Of course this led to continued diverging opinions and a lack of guidelines on oxytocin dose, administration, and indication.

In 2007, 20 years later, oxytocin was defined as a high-alert medication by the Institute for Safe Medication Practices[283]. They administrate a list of medications which may cause significant harm to patients if used incorrectly. Oxytocin remained the most commonly used medication in obstetrics with no standardized protocol for administration and was added as the eleventh medicine on the high-alert list of medications in acute care settings. A re-evaluation of the current practice of use and administration of oxytocin during labor was suggested[80,131,279,280].

5.9 Summary of the introduction

A common definition for the start of the active phase of labor and for prolonged labor does not exist, even though recommendations have been made[46,86,151,284]. This makes it challenging to perform a quality audit of labor outcomes and clinical practice. There is still no consensus on a systematic presentation of the maternity population, nor on which defined labor outcomes should be used to assess the quality of obstetric care.

The role of oxytocin in the augmentation of labor is essential, however it is difficult to explore the incidence of oxytocin augmentation, as the populations used in previous studies vary and overlap. The overall use of oxytocin might not be of essential importance, however many delivery units do not know how many women receive oxytocin for the augmentation of labor. The presence of clear indication for its use is recommended, but in many delivery units it is not mandatory[62,279]. The reported injudicious use of oxytocin augmentation is reported as cause for concern[81,255,256].

6 Hypothesis and aims of the study

Null hypothesis:

Introducing judicious use of oxytocin will not influence labor outcomes

Overall aim:

To evaluate labor outcomes associated with varying use of oxytocin augmentation based on a systematic method

Specified aims:

Paper I:

The aim of this study was to analyze changes in postpartum hemorrhage during a 10-year period, and to explore factors possible associated with severe postpartum hemorrhage

Paper II:

The aim of this study was to present the TGCS as a method to assess outcomes of labor and delivery using routine collection of perinatal information

Paper III:

The aim of this study was to investigate whether judicious use of oxytocin augmentation would change how it was used and how it might influence labor and fetal outcomes

Paper IV:

The aim was to investigate possible effects and interactions of epidural analgesia, oxytocin augmentation and maternal age on cesarean section among nulliparous women in spontaneous labor

7 Summary of results

7.1 Paper I

The incidence of severe PPH increased between 1998 and 2007 at SUH. The observed risk of estimated severe PPH after cesarean section was two times higher than that observed after vaginal delivery (5.9%; 95% CI 5.3–6.6 vs. 2.8%; 95% CI 2.6–2.9). Among women with a vaginal delivery, the most important risk factors were twin deliveries (OR 6.8), retained placenta (odds ratio, OR 3.9), and induction of labor (OR 2.2). Twin deliveries also showed the strongest association with severe PPH among women with a cesarean section (OR 3.7). Interventions during labor increased throughout the study period. The cesarean section rate increased from 2.4% to 4.9% for elective and 5.5% to 8.9% for acute procedures. Operative vaginal deliveries increased from 9.3% to 12.5% and induction of labor from 14.3% to 15.8%. The most significant increase during the study period was the use of oxytocin augmentation, which increased from 5.8% to 29.3%.

7.2 Paper II

The study population from three perinatal databases (Stavanger University Hospital (SUH): 9848 women, 2010-2011; National Maternity Hospital (NMH): 9250 women, 2011; and Slovenian National Perinatal Database (SLO): 106 167 women, 2007-2011) were stratified using the TGCS. Using this standardized approach, outcome of labor can be easily assessed and results can be used to guide further improvements if necessary. Additional outcome variables were incorporated in the presentation of TGCS groups 1-5. There were differences in the sizes of the TCGS groups and also the incidence of events and outcomes within these groups and between the three perinatal databases.

The NMH had highest proportion of women with a BMI >30 and a maternal age >35 years, in addition the highest overall cesarean section rate. The SLO had the highest cesarean section rate in groups 1 and 2a. The overall use of epidural analgesia was 35.0%, 49.0%, and 2.7% in

the SUH, NMH, and SLO, respectively. The operative vaginal delivery rate at the SLO was low when compared to the SUH and NMH, but the rate of prolonged labor was about the same as that observed in the NMH. The overall frequency of the use of oxytocin augmentation was 23.6%, 28.3%, and 57.3% in the SUH, NMH, and SLO, respectively. The SUH had more women with prolonged labor, especially in groups 1 and 4. Estimated severe PPH was highest at the SUH, but it did not correlate with transfusion rates. Overall perinatal deaths were lowest, but the rates of hypoxic ischemic encephalopathy in groups 1 and 2a were highest at the NMH.

7.3 Paper III

The implementation of judicious use of oxytocin augmentation resulted in a significant reduction in its overall use, from 34.9% to 23.1% during a 5-year period. The study population comprised women in TGCS groups 1, 2a, 3, and 4a, and the reduced use of oxytocin augmentation was significant in all of them. Importantly, the protocol also contained a clear definition of start of the active phase of labor and prolonged labor. A distinct indication of the use of oxytocin for augmentation was thereby implemented in the delivery unit. The overall acute cesarean section rate decreased from 6.9% to 5.3% ($p<0.05$); cesareans performed due to fetal distress decreased ($p=0.01$) and those performed due to prolonged labor increased ($p=0.75$). More women experienced prolonged labor (from 4.4% to 8.5%) and the rate of severe PPH increased from 2.6% to 3.7%. The rate of children born with pH <7.1 in the umbilical cord was significantly reduced from 4.7% to 3.2% ($p<0.01$), but the reduction in pH <7.0 (from 0.7% to 0.4%) did not reach statistical significance.

7.4 Paper IV

The overall cesarean section rate in TGCS group 1 increased consistently with maternal age in Norway and Denmark, but also within strata of use of epidural analgesia and oxytocin augmentation. Strong interactions between these variables and associations with cesarean section were observed. When stratified by maternal age groups, oxytocin augmentation was

associated with a reduced risk of a cesarean section among women with epidural analgesia. This association applied to all maternal age groups in Norway, but it only applied in Denmark to women aged ≥30 years. Among women without epidural analgesia and aged <40 years, use of oxytocin augmentation was associated with an increased risk of a cesarean section in Denmark when compared to no use of oxytocin augmentation. This association among women without epidural analgesia was not observed in Norway. The analyses were adjusted for time period and fetal birth weight >4000g.

8 Discussion

8.1 Selected methodological considerations

8.1.1 Overview of the four studies included in this thesis

Table 1 Overview of the studies

	Paper I	Paper II	Paper III	Paper IV
Objective	Analyze changes in PPH during a 10-year period, and to explore factors associated with severe PPH	To present the TGCS as a method to assess outcomes of labor and delivery	To investigate an implementation of judicious use of oxytocin augmentation	To investigated the interactions of epidural analgesia, oxytocin augmentation and maternal age on cesarean section
Study population	Unselected, comprising 41 365 delivering women	Unselected, comprising 9848 (SUH), 9259 (NMH) and 106 167 (SLO) delivering women	Selected, comprising 20 227 delivering women in TGCS 1, 2a, 3 and 4a*	Selected, comprising 416 386 delivering women from Norway and Denmark in TGCS1**
Data source	Electronic birth journal	Electronic birth journal (SUH and NMH), National register SLO	Electronic birth journal	National register in Norway and Denmark
Main outcome	Severe PPH and obstetric interventions	Incidences of labor and delivery outcomes stratified by TGCS	Cesarean section	Cesarean section
Study design	Retrospective cohort study	Quantitative descriptive study	Prospective observational study	Cross sectional design, analyzed as case-control study
Study period	1998-2007	SUH 2010-2011 NMH 2011 SLO 2007-2011	2009-2013	2000-2011

PPH; postpartum hemorrhage, TGCS; the 10-Group Classification System,
SUH, Stavanger University Hospital; NMH, National Maternity Hospital; SLO, Slovenian National Perinatal Database,
*singleton pregnancies ≥37 weeks of gestation, cephalic presentation, spontaneous or induced onset of labor, without previous cesarean section,
**nulliparous, singleton pregnancies ≥37 weeks of gestation, cephalic presentation, spontaneous onset of labor

8.1.2 Study population

8.1.2.1 Papers I-IV

Papers I and III

The study population in Papers I and III comprised women giving birth at the department of Obstetrics and Gynecology, Stavanger University Hospital, which is localized in the western part of Norway. The delivery department is a secondary referral center in Rogaland county and serves an unselected population of 340 000 citizens. Few women are referred to nationally centralized services at other hospitals, resulting in an annual delivery rate between approximately 4350 (1998) and 4800 (2013)[107].

The use of a source population from a single hospital may have biased our results due to local strategies and guidelines reducing the external validity. Changes in the internal focus of the unit, such as use of oxytocin augmentation, active management of the third stage of labor, and perineal support, may have more transparent direct and indirect influences on labor outcomes. This was observed in Paper I, when an increased focus on perineal support to prevent sphincter rupture was implemented in the department protocols in the last part of the study period. Subsequently, the overall rate of sphincter rupture decreased. Hence, we cannot exclude the possibility that this influenced the overall rates of severe PPH in our study. However, as sphincter rupture was associated with increased blood loss, the observed severe PPH may have been even higher[210].

Differences in the population in the hospital's catchment area may also have influenced our results[82]. For instance, compared to larger cities like Dublin and Oslo, the population of Rogaland County tends to be younger at first child birth and comprises a low proportion of immigrants. Hence, important factors like age at delivery and ethnic background are not necessarily generalizable to the populations of other regions.

Paper II

In this paper we present populations from Stavanger University Hospital (SUH) in Norway, the National Maternity Hospital (NMH) in Ireland, and the Slovenian National Perinatal

Database (SLO) in Slovenia. Differences in these three populations are presented in Paper II (Table 2) using the TGCS. One can assume that the populations in the catchment areas of the two hospitals (SUH and NMH) are different in terms of ethnicity, education, BMI, maternal age, and parity. These factors may influence the baseline risk of obstetric complications and thereby influence the risk of interventions and adverse labor outcomes. This baseline risk will diminish to some extent when looking at the data from the SLO, which is a national register. Other factors such as health care systems and education are more prone to confound outcomes on a national level.

Paper IV

The study population in Paper IV was taken from the Medical Birth Registry of Norway (MBRN) and the Danish National Patient Register (DNPR). The MBRN collects its information through the compulsory birth notification form that is completed for every birth in Norway. The DNPR contains information on all patients discharged from Danish hospitals with diagnoses according to the International Classification of Diseases, 10th Revision.

Norway and Denmark have similar economies, standards of living, and education systems. The populations are comparable and nearly all births take place in public hospitals. The interpretation of the results could be generalized to Nordic countries, but not necessarily to low-resource countries or countries with different frequencies of obstetric interventions.

8.1.3 Data source

8.1.3.1 Papers I-IV

Paper I

The obstetric department in the SUH used an implemented local electronic birth journal (by Leif Gjessing, MD) for data registration. The local electronic birth journal contains normal ranges of the different variables registered to ensure correct registration. In addition, the recorded information was continuously cross-checked during registration by the midwives. For these reasons the data quality registration was regarded as high among the midwives

performing the registration, and in turn the validity of the variables recorded was considered high. Information on pregnancies, labor, and delivery was extracted from the local electronic birth journal.

Paper II

All variables used were collected separately at the SUH, the NMH and from the SLO.

Stavanger University Hospital

The local electronic birth journal (by Leif Gjessing, MD) at the SUH was replaced by a national electronic birth journal (NATUS) in 2010. Apart from that, the data collection and registration were as presented under Paper I.

The National Maternity Hospital

The NMH in Dublin routinely completes an Annual Clinical Report detailing each year's results[285]. In addition, the hospital has a reputation of conducting audits and focuses on internal awareness of audit results. These factors may increase the quality of the recorded variables, as they are continuously being cross-checked during quality assessments.

The Slovenian National Perinatal Database

The SLO is a national register in Slovenia. The rates of operative vaginal deliveries, sphincter rupture, and transfusion presented in Paper II differ from those in the SUH and the NMH. A validation of these variables would have increased the credibility of the data. However, the operative vaginal delivery rates in Slovenia were reported to be representative in a European study that explored the merging of datasets and the quality of data available for analyses in national registries[234]. Unfortunately, only PPH >500ml was reported in the SLO, and because we chose PPH>1000ml as our outcome variable these rates were not included in the paper. However, the estimated rates of PPH >500ml (not shown) were in line with the low transfusion rates reported in the SLO.

Paper III

In Paper III data from the SUH was captured from the electronic birth journal (NATUS) as described for Paper II. Registration of all variables was performed by the midwives. The tradition of correct registration continued to be a focus in the department. To ensure quality, one midwife cross-checked the variables used in the analyses during the study period. A

major weakness was the lack of information regarding the maximum doses and the duration of oxytocin administration.

Paper IV

This study was a part of the Nordic Robson Research Group, a collaboration between all Nordic countries and medical birth registries. The MBRN and the DNPR have long traditions of providing variables for analyses and publications[193,286,287]. Data used for analyses were extracted from these two registries only due to the low quality of the oxytocin augmentation variable in the other Nordic registries. The MBRN validated the oxytocin augmentation variable against medical records, with a positive predictive value of 98%. As our focus was on the use of oxytocin augmentation, a validation of the negative predictive value might have added further strength to our analyses[158,288]. Moreover, access to other variables, such as indication for cesarean section, indication and timing of the use of epidural analgesia, length of labor and BMI would have contributed to our analyses.

8.1.3.2 Register-based studies

The quality of the data available from national registries depends on the design of the data register and its data collection methods. Population-based registries with routine collection lead to minimal selection bias, which is considered a strength of registries-based studies. The main limitations are that some important variables may be unavailable, and the quality of the recorded data may vary[288,289]. Data quality is influenced by underreporting due to errors, inconsistencies in definitions and measurements of the variables, busy departments, and staff changes. To ensure data quality, validation studies of important variables may be performed prior to the analyses[288]. However, due to the size of the datasets in register-based studies, they are considered to be of great value as long as these limitations are acknowledged[193,289].

8.1.4 Study design

8.1.4.1 Paper I

This was a retrospective cohort study. Observations included in the study were already collected in the electronic journal. The retrospective design meant that exposure to possible risk factors was recorded before the occurrence of the outcome measured. A disadvantage and consequence of the retrospective design is that important and relevant risk factors identified later might not be recorded, and are thus unavailable to be included in analyses. The large, and most importantly, unselected, population minimizes the risk of selection bias and strengthens the observed associations. Estimations of blood loss are inherently inaccurate, but as the study design was retrospective the reported estimation was not biased by the study design. In a prospective study, the blood transfusion rates should be included in the analyses.

8.1.4.2 Paper II

Paper II contains a systematic observation of defined variables and is thereby defined as a quantitative descriptive study[290]. In this study we aimed to observe possible differences in labor outcomes in specific groups of women by comparing the incidences of these outcomes. A descriptive study design can uncover possible patterns that require further attention, and resultant hypotheses can be suggested and tested in further studies with another study design if warranted. Statistical analyses could not be performed due to different databases, time periods and populations in our study. The incidences of the outcomes reported in this study are perceived as representative due to the quality and quantity of the registration. A different study design is required to establish causality.

8.1.4.2.1 The 10-Group Classification System

The method of stratifying women giving birth by the TGCS increases the ability to observe possible differences and associations. This information can be used to compare outcomes and evaluate changes between hospitals or within hospitals, as presented in Papers II and III,

respectively. The TCGS provides a common language and starting point for any discussion, thereby allowing for more insight on labor outcomes and delivery[271].

The incidences presented in Paper II should only be considered as examples as the optimal frequency of labor outcomes will depend on differences in the population, practical skills, traditions, and routines. Observed differences between obstetric units when using the TGCS are also dependent on the quality of data registration and the definition of the variables used[291]. The classification alone enforces a validation of the registered data.

The TGCS has been criticized for not including induction of labor as a subdivision (Figure 14). Another reported weakness of the TGCS is the lack of information of the indications behind observed differences. Moreover, risk factors and important epidemiological variables, such as maternal age, BMI, and ethnicity are not adjusted for[291]. All this can lead to large variations between hospitals and countries, influencing the outcomes and thereby the generalizability of the TGCS. In addition, a validation of the optimal range of frequencies within the groups has not yet been performed, and rules of interpretation for the TGCS have not yet been created. Therefore the value of comparing frequencies of labor outcomes between countries and units can be argued. Additionally, presenting data from smaller groups limits a study's strength to demonstrate actual trends. Agreed definitions of when start of the active phase of labor begins, when a cesarean section should be classified as pre-labor or acute, and when an intervention such as amniotomy and use of oxytocin is defined as an induction agent or as augmentation are frequent causes of disagreement when discussing the TGCS. Differences in these definitions can lead to misclassification, which represents a shortcoming of its use.

Finally, the TGCS can only be used for observation, not causality. However, it is simple to use, reproducible, and allows units to evaluate their own performance in specific groups of delivering women[271,292]. We would argue that the TGCS can contribute to finding the best approach, or to detecting which approaches can improve the quality of obstetric care[293].

8.1.4.3 Paper III

This paper used a clear definition of the start of the active phase of labor, the WHO partogram to define prolonged labor, and when oxytocin augmentation was indicated in the labor ward of

the SUH. We then investigated changes in frequencies and labor outcomes. The study design of Paper III was a prospective observational study. All women giving birth in TGCS groups 1, 2a, 3, and 4a were included and followed up during the study period. The focus of oxytocin augmentation increased in the delivery unit during the study period. This may have influenced the motivation and decision making and thereby biased the results (Hawthorne effect). We would however argue that this effect had minimal impact on our results due to the strict definitions incorporated in the implementation. To claim causality the study design should have been performed as a RCT, but strong associations in large observational studies may be assessed as causality[294].

8.1.4.4 Paper IV

The aim in Paper IV was to investigate the effect and interactions of maternal age, use of epidural analgesia, and use of oxytocin augmentation on the risk of cesarean section. A cohort of women was studied at a time when interventions were performed consecutively in relation to each other (epidural analgesia, oxytocin augmentation, and cesarean section). The long study period (12 years) could have an influence on clinical practice and requires adjustment, but it does not affect the time point at which women gave birth. In Paper IV we obtained simultaneous information on the exposure (epidural analgesia, oxytocin augmentation and maternal age) and the outcome (cesarean). The design of the study was thereby defined as an observational cross-sectional study, but analyzed as case-control study (cesarean section (cases) and no cesarean section (controls)). Due to study design the distinction between effect and cause is difficult and observed associations must be interpreted with caution.

We aimed to estimate the risk of cesarean section associated with the use of epidural analgesia and oxytocin augmentation and to observe practice patterns in labor. The prevalence's we observed are of clinical value, and the observed relationship between maternal age, oxytocin augmentation, and epidural analgesia on the associated risk of cesarean section deserves more attention. Hence, we hypothesize that oxytocin is an effect modifier on the risk of cesarean section in women with epidural analgesia, in particular those with advanced maternal age. Women who receive epidural analgesia during labor represent a heterogeneous population due to wide variations in the indications for epidural analgesia and a wide range of baseline risks.

Because of this, a RCT may be challenging to conduct and results from other study designs should also be weighted[170,294,295].

8.1.5 Main study outcomes

8.1.5.1 Paper I

Postpartum hemorrhage

PPH was defined as blood loss visually estimated by the attending midwife or obstetrician. Blood cloths were also measured when possible. The estimation of blood loss is subjective, and the precision of the estimation is poor; it is commonly underestimated by half of the actual hemorrhage[210,296-298]. As severe PPH was the main outcome in Paper I, the reliability of the PPH variable, and therefore the results may be questioned. However, transfusion rates are considered to be a more objective variable, and we observed an increasing trend in transfusion rates during the study period, which was an important supplement to our findings. Changes in peripartum hemoglobin levels would have added even more reliability to our PPH variable[215,220].

The definition of severe PPH varies[216]. American guidelines accept blood loss up to 1000 ml after cesarean section and up to 500 ml after vaginal delivery[299]. The WHO defines severe PPH as blood loss of >1000 ml regardless of the mode of delivery, which is in line with Norwegian guidelines[284,300].

The differentiation in the association between severe PPH and elective and acute cesarean section may be further discussed. Acute cesarean section was not associated to severe PPH in the adjusted analyses, in contrary to the results of other studies[215]. This could be due to the overall low rate of planned cesarean section in the department and a higher proportion of cesarean section due to abnormal placentation. The association between severe PPH and acute cesarean section was stronger in the unadjusted analyses, probably due to the indication that led to the cesarean section rather than the operation itself. The addition of the indication for the cesarean section to the multivariable analyses would have been interesting.

Augmentation of labor

Augmentation of labor was defined as when the midwives or obstetricians suspected labor contractions to be insufficient and an intravenous oxytocin infusion was added. The department had neither a clear definition of when use of oxytocin for the augmentation of labor was indicated nor a standard definition of prolonged labor. This meant that the variable use of oxytocin augmentation was a subjective one, and because of this the absolute frequencies of oxytocin augmentation might not be comparable with those of other units.

It is difficult to distinguish between the use of oxytocin as an induction agent or for the augmentation of labor. Because of this, the increasing frequency of induced labors during the study period might have contributed to the observed rise in the use of oxytocin augmentation. However, this increase is believed to be valid because of the quality of the local electronic birth journal and the retrospective study design. The duration and dose of oxytocin augmentation would have added interesting information to the study, but was not available for analyses. To explore the possible association between severe PPH and prolonged labor over time could also have been interesting, since the increase in oxytocin augmentation during the study period was so distinct.

8.1.5.2 Paper II

Prolonged labor

The definition of start of the active phase of labor differed between the SUH, the NMH and the SLO. This definition is crucial in determining when the length of labor exceeds 12 hours. As we were aware of this, we choose to report the prolonged labor rates as they were recorded at each study location, leaving the interpretation of this knowledge to the reader. Units using active management of labor may look to the NMH, and units using the WHO definition may look to the SUH.

Postpartum hemorrhage

The inaccuracy of blood loss estimation was accounted for as previously described. The reported incidence of severe PPH at the SUH and the NMH diverged, with higher rates at the SUH than the NMH (Table 4, Paper II). Due to the assumed quality of the data, these

differences may be explained by different managements of labor at these study locations. Clearly the SUH should be aware of the higher rates of severe PPH when evaluating the association of possible near miss cases. However, the importance of incorporating objective variables such as transfusion rates should be highlighted. The incidence of severe PPH in groups 1 and 2a was 3-4 times higher at the SUH than the NMH (nulliparous women with spontaneous labor or induced labor), but the transfusion rates were higher at the NMH in group 2a (nulliparous women with induced labor) (Table 4 in Paper II).

Neonatal outcome

Neonatal outcome is of great importance when evaluating the quality of obstetric care. Sometimes data on umbilical blood gas analyses is available in national registers, but this was not the case in our study. Moreover, data was not available on hypoxic ischemic encephalopathy in the database of the SUH; instead it was subsequently recorded by a pediatrician and classified according to the TGCS. Hypoxic ischemic encephalopathy and perinatal death are rare events, and they may be too small to stratify according to the TGCS. However, if a trend if observed, additional analyses can be carried out using data collected prior to the occurrence of unrevealed suboptimal care.

8.1.5.3 Paper III

Augmentation of labor

Before 2014, the Norwegian national guidelines did not include a clear definition of when prolonged labor or when the use of oxytocin was indicated to augment labor[284]. This was also the case at the SUH during the study period of Paper I. Because of the observed increase in the use of oxytocin augmentation in SUH, a protocol was introduced in 2010 that included a clear definition of the start of the active phase of labor in addition to a partograph. This helped the medical staff to define prolonged labor and to determine when to administrate oxytocin for the augmentation of labor. The protocol was based on WHO recommendations.

The obstetric unit at SUH has a quality committee that holds monthly meetings assessing guidelines and clinical care. Additionally, regular audits discussing new guidelines or changes due to near miss cases are routine in the department. The staff is familiar with new and updated procedures and guidelines, which are well followed. After the introduction of the

protocol in 2010, one midwife was assigned to continuously cross-check the frequency of the use of oxytocin augmentation and to perform regular audits. There is no information on adherence to the 2010 protocol, which is considered as a weakness of the study. One could argue that regardless of how many people followed the 2010 protocol, the change that we observed in the use of oxytocin augmentation coincided with and was most likely associated with this protocol, but the result might be biased by a rise in the awareness of and focus on the use of oxytocin within the unit[301]. The impression in the department was clearly that the duration and maximum dosage of oxytocin for the augmentation of labor decreased after the protocol was introduced.

Especially in this study, information of the duration and dosage of oxytocin would have contributed to additional knowledge. In addition, and as mentioned above, we could not distinguish between the use of oxytocin as an induction agent or for the augmentation of labor.

8.1.5.4 Paper IV

Cesarean section

Cesarean section was the main outcome in Paper IV. Maternal factors such as BMI, maternal diseases (diabetes, preeclampsia, chronic diseases), and education are possible confounding factors for cesarean section. Placental dysfunction including growth restrictions increases the risk of fetal distress and thereby the risk of cesarean section. These variables were not included in our analyses due to their low quality. The timing of cesarean section, i.e., during the first or second stage of labor, would have added important information to our study. The effect of epidural analgesia and oxytocin augmentation might differ in the first and second stage of labor, as might the possible mediating effect of oxytocin among women with epidural analgesia. Unfortunately, there was no agreed upon classification of the indications for a cesarean section. This would, without a doubt, have added valuable information to our study.

Epidural analgesia

The primary indication for epidural analgesia during labor is pain relief. High blood pressure is only rarely the main indication for epidural, but due to the size of our dataset this ratio was not considered to affect the results. Our study population included only nulliparous women with spontaneous labor. We therefore assumed that the main indications for epidural analgesia in our study population were pain or prolonged labor. Adjusting for prolonged labor would have increased the reliability of our associations, especially as we aimed to investigate the interactions and effects between epidural analgesia and oxytocin augmentation. Unfortunately the quality of this variable was not considered to be trustworthy in the national register, mainly due to a lack of clear definitions.

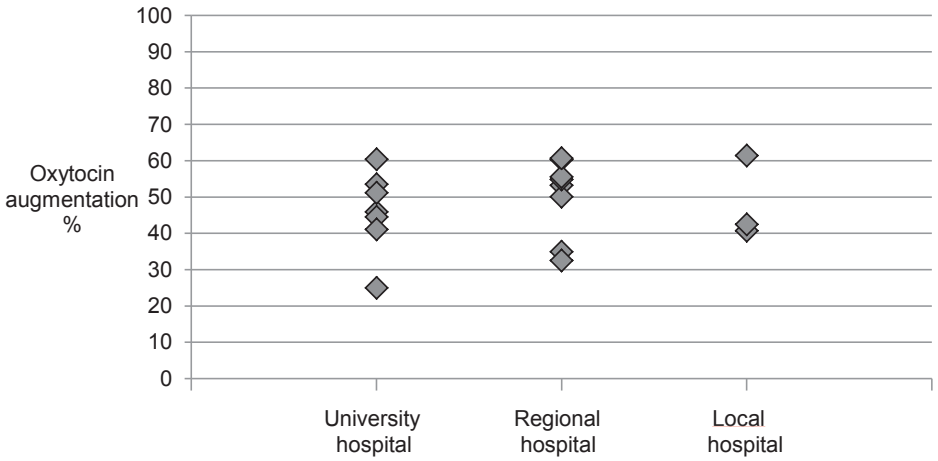
We have no information on the timing of the epidural. Even though no RCTs have shown an increased risk of cesarean section due to the timing of epidural analgesia, some observational studies have shown conflicting results[171,175,302]. Due to the higher risk of selection bias in observational studies, stratifying by early or late administration of epidural analgesia would probably have been very valuable in our analyses. Many midwives and hospitals have a practice of stopping the epidural infusion when the second stage of labor begins. The intention is to increase the women's contact with her pelvic floor and the possibility of a spontaneous vaginal delivery. This increases the heterogeneity of our study population, which may have influenced our associations. Most women who require an epidural are already in great pain due to a malpositioned fetus or prolonged labor. These factors may indeed be the indication for the epidural and could affect the outcome.

Augmentation of labor

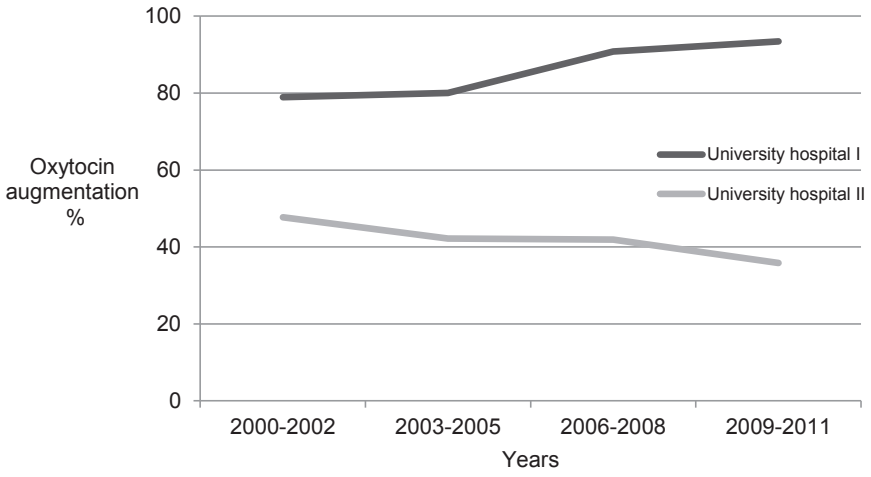
In Paper IV, it would have been very useful to know the timing of oxytocin augmentation in relation to the epidural. If the indication for the epidural was prolonged labor and oxytocin was indicated, the woman would most likely prefer to receive an epidural for analgesia in advance. One could also argue that women experiencing dysfunctional labor more often experience pain; therefore an epidural is initiated before oxytocin due to prolonged labor. Hence, we assumed that the epidural was administrated before oxytocin in most cases.

As previously discussed, the indication for oxytocin augmentation may vary between different hospitals. During the study period, the Norwegian national guidelines did not include a clear

definition of prolonged labor or indication for oxytocin augmentation. There was great variation in the overall use of oxytocin augmentation among hospitals, and of the use of oxytocin augmentation among nulliparous women with and without epidural in Norway (Figure 14 and 15, unpublished data presented by J Rossen at the annual meeting for the Norwegian Association of Obstetrics and Gynecology and at the pre-congress meeting of the Nordic Federation of Societies of Obstetrics and Gynecology in 2014). However, the size of our study population over several years with consistency of the data also between the two countries should outweigh some of these confounding effects.



Figur 14
Overall oxytocin augmentation (%) among nulliparous women, spontaneous labor, at term in institutions by level of care in Norway from 2000-2011 (during the study period of Paper IV)



Figur 15
Oxytocin augmentation (%) in two university hospitals in Norway among nulliparous women, spontaneous labor, at term with epidural analgesia (during the study period of Paper IV)

Maternal age

Maternal age remains one of the main factors that influence physiological processes, interactions, and confounders among delivering women[108,303]. Indeed, interactions between the different variables and confounders are most likely age-dependent[303]. The importance of advanced maternal age in obstetrics has increased over the last years, as the number of older women giving birth continues to rise. Many studies chose to adjust for maternal age, realizing that age is an important confounder. However it is difficult, and sometimes not possible to adjust for some confounding factors, such as changes in physiological processes. Because of this, we choose to stratify by maternal age. The observed associated risks of cesarean section reported in Paper IV are therefore age-specific.

8.1.6 Statistics

Paper I

Cross-tabulation with a chi-squared test was used to analyze categorical variables. Differences in mean PPH were assessed using the Student's *t*-test and one-way ANOVA with

Bonferroni's correction. The amount of PPH was not normally distributed and was therefore log-transformed before the analyses. Multivariable logistic regression analyses were used to examine possible factors associated with severe hemorrhage. PPH >1000 ml was used as the dependent variable. Factors were included in the multivariable logistic regression analyses if the unadjusted estimates had a p-value of <0.25. A p-value of <0.05 was considered significant. Data were entered into the Statistical package for social sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA).

Paper II

Data was presented as a quantitative descriptive study. We aimed to observe new patterns which possibly need further analyses and assessment in forthcoming studies. The variables used were agreed upon before the systematic collection of data was performed. Other possible variables may be added if indicated in future analyses.

Paper III

The linear-by-linear association trend test was used in categorical data analyses, and continuous variables were compared using one-way analysis of variance with Bonferroni correction. Data were analyzed with SPSS version 22.0 (IBM SPSS, Armonk, NY, USA) and p-values <0.05 were considered significant.

Paper IV

In Denmark and Norway, significant interactions between maternal age and use of epidural analgesia and oxytocin augmentation on the risk of cesarean section were observed. Accordingly, we created a new variable comprising age, use of epidural analgesia, and oxytocin augmentation. We defined women aged 20–24 years with no use of epidural or oxytocin as the reference group, as we considered this subset to be the women with lowest risk of cesarean section.

The chi-square test was used to evaluate linear trends, and logistic regression analyses was used to estimate odds of cesarean section in relation to maternal age, use of epidural analgesia, and oxytocin augmentation, while adjusting for birth weight (>4000 grams: yes/no)

and time period. Interactions were tested using multiplicative models, and since the dataset was large, we set the statistical significance level for interaction terms to $p<0.01$. Age-standardization was done by the direct method using the total and the age-specific subpopulations of the entire database as the reference population. Data were analyzed with SPSS version 21 (SPSS Inc., Chicago, IL, USA).

8.1.7 Ethics

A systematic collection of data must be accurate and appropriate, but ethical standards must also be ensured. One may consider that patients included in this type of data collection have an ethically responsibility to participate, as they will benefit from the analyses conducted. The responsibility to determine the need for written informed consent lies with the system used and the users of the system, but most importantly with the unit involved. Internal quality control should supervise the registration and variables used. External ethical committees should be consulted to evaluate whether the autonomy and anonymity of the patients is being compromised.

The original database in Papers I and III contained identity key numbers. This was necessary to merge the registered variables for mothers and their children. However, after the database was finalized the data were anonymized before further analyses. The study described in Paper I was approved as a quality assurance study in 2009, and the one described in Paper III was approved in 2014 (REK 2014/1912) by the Regional Committee for Medical Research Ethics in Western Norway.

Paper II presents descriptive data of which all available from the SUH, the NMH in Ireland and the SLO was anonymous. The Regional Committee for Medical and Health Research Ethics classified the study as a quality assurance study of routinely-recorded data (REK Vest 2012/1522) and the local committee for data protection (2012/41) approved the project.

All data available for analyses in Paper IV were anonymous. The Regional Committee for Medical and Health Research Ethics, South-East C (REK 2010/3256) assessed the Norwegian participation and the Danish Data Protection Agency governed the Danish participation (reference NOH-2016-006, med I-Suite no. 04548.

8.2 General discussion

Use of oxytocin for augmentation of labor should benefit the laboring women, thus the reported increase of incautions use needs attention[80]. The pros and cons of adding exogenous oxytocin to the physiological process of labor has been debated for many years, and conflicting study results have probably contributed to a lack of awareness and varying use. This, in addition to the individual response to oxytocin, may have contributed to why WHO guidelines for the augmentation of labor were introduced for the first time in 2014[151].

8.2.1 Strengths and limitations

Strengths

The study populations used in the studies included in this thesis are considered representative due to the sample sizes. A large sample size limits the ability to observe rare phenomena but strengthens observed associations. The risk of selection bias is considered to be low due to the unselected population in Papers I and II and the use of stratification by TGCS groups in Papers III and IV. In Paper IV we also stratified by maternal age, use of oxytocin augmentation, and epidural analgesia. All these variables showed strong associations with the defined outcome, namely cesarean section. By using this approach the effect of confounding is reduced. Especially among delivering women the presence of confounding is problematic, as adjusting for several of these factors is difficult.

The strong association between reduced cesarean section rate and oxytocin augmentation among women with epidural analgesia observed in Paper IV may support the role of oxytocin augmentation as an effect modifier in these women. The observed results from all papers provide a picture of the use of oxytocin augmentation in clinical practice and its association with severe PPH, use of epidural analgesia, and cesarean section. Paper IV differs from Papers I and III as the findings were on a national level with lower specificity to every-day practice. As such they may be regarded more as general guidance. The value of the external validity of large observational studies should be emphasized[170,295].

Limitations

All four papers are mainly based on variables already registered in electronic birth journals or national databases. The quality of register data can be affected by erroneous registration, lack of agreed upon definitions and diagnoses, and the amount of missing data. Correct registration is influenced by the quality of the systems used but also the time and precision devoted to the task by the midwife performing the registration. Unclear definitions of variables such as length of labor and prolonged labor increase the risk of misclassification bias, limiting our associations[288].

The main outcome in Paper I, severe PPH, was based on subjective estimation. The validity of PPH estimation has been questioned as is also the case for all the PPH frequencies reported in Papers I, II, and III. Although we are aware of this limitation, estimation of PPH during labor remains an easy and simple method for everyday use.

In Paper II we aimed to present a simple method of assessing labor and delivery outcomes for use in clinical practice. We used the TGCS as a framework, realizing the existence of different opinions regarding the clinical usefulness of this system. Due to the different databases, registrations, and definitions, we did not succeed in presenting labor outcomes in all of the 10 groups.

Observations from one hospital only, as in Papers I and III, may be influenced by local strategies and traditions, thus limiting the external validity of the associations. The aim in Paper IV, to investigate interactions of oxytocin augmentation, epidural analgesia, and maternal age on the risk of cesarean section, was challenging to explore. This was in particular due to the fact that variables such as prolonged labor, indication for cesarean section, and timing, dose, and length of oxytocin augmentation and epidural analgesia were not available. In addition, the validity of the negative predictive value of the oxytocin augmentation variable may be questioned, further compromising the associations. Due to the study design the papers included in this thesis, none of the conclusions drawn can claim causality.

8.2.2 Judicious use of oxytocin

As reported in Papers I and IV, increasing rates of oxytocin augmentation were observed both locally and nationally in 1998-2011. The varying use of oxytocin augmentation between hospitals in Norway was presented at an annual meeting in 2010 (Figure 14). In addition, the varying use between hospitals and countries is presented in Papers II and IV. These results are in line with other studies not only from Scandinavia, but also from the USA[80,87,256,279]. The unsystematic use of oxytocin augmentation without proper indications, or without any indication at all, has probably contributed to the observed abuse of oxytocin during labor[81]. Oxytocin augmentation is considered one of the strongest risk factors for uterine rupture, the incidence of which has been increasing[304,305]. Moreover, obstetric litigation claims have repeatedly reported use of oxytocin augmentation to be associated with adverse outcomes and near miss cases[255,256]. If used and monitored carefully, oxytocin augmentation can decrease the length of labor, and in some groups of women it may decrease the associated risk of cesarean section[79]. Our findings in Paper IV support further investigations regarding use of oxytocin augmentation among women of advanced maternal age and in particular in women with epidural analgesia.

Implementation of judicious use of oxytocin augmentation, as presented in Paper III, was recommended by the WHO in their 2014 guidelines for the augmentation of labor[151]. In particular, units with high rates of oxytocin augmentation without standardized definitions might observe changes in their labor outcomes by implementing these guidelines. Every unit should have a definition of prolonged labor and indications for oxytocin augmentation. Every unit should also know their incidence of oxytocin augmentation, as this may reveal an injudicious obstetric practices. The TGCS can be implemented as part of routine registration in obstetric departments by which labor interventions such as oxytocin augmentation can be visualized. As presented in Paper II, the TGCS may also be used as a tool to guide patterns of practice if necessary when comparing agreed upon labor interventions and outcomes. However, further studies exploring the possible benefits of the method suggested in Paper II are needed. We cannot draw conclusions about improvements in neonatal morbidity as this was not within the scope of Paper II. In addition, as these findings are less common, a larger study population or a different study design would be required to reveal these associations[306]. In case-control studies, oxytocin has been found to be an independent risk factor of acidemia at birth, and this seems to be related to an incorrect use of oxytocin augmentation without

indications[256]. The same author stated that there is a gap between evidence-based medicine and clinical practice regarding the use of oxytocin augmentation during labor[231,307]. We would argue that our findings of a reduced use of oxytocin augmentation, reduced overall cesarean section rate, and a trend toward fewer children born with low pH in the umbilical cord should be emphasized in the ongoing debate concerning guidelines on the use of oxytocin augmentation[306]. Recently, a high level of lactate in the amniotic fluid was found to be predictive of who could benefit from oxytocin augmentation and of labor outcomes[308]. These results seem promising and should be explored in further studies.

Since 1984, active management of labor has received at lot of attention, and Slovenia has a tradition of using this approach. As presented in Paper II, the rates of oxytocin augmentation in the SLO were clearly higher than the rates at the NMH, where this concept originated[85]. This may be an example of a change in the perception of active management of labor. The NMH had a higher overall cesarean section rate than the SLO (Paper II). However, among women with spontaneous labor, the cesarean section rate was lower in both nulliparous and multiparous women (groups 1 and 3, Table 1, Paper II). This observation supports the finding that several factors in the active management of labor package are associated with a decreased cesarean section rate. These factors are not limited to oxytocin augmentation, but include a strict definition of the start of labor and one-to-one support from midwifes during labor[78,309].

8.2.3 Systems and standardization

Unclear definitions may lead to unnecessary interventions, which may increase, instead of decrease, the risk of complications for the mother and fetus during labor. Different definitions of the start of labor, progression of labor, and prolonged labor makes it even more important to agree on local guidelines and definitions[279]. A Swedish study from 2008 observed that 73% of the labor wards did not have a definition of prolonged labor[310]. In 2011, a national guideline defining prolonged labor using the 3 hours action line was proposed for the first time in Sweden[311]. Denmark introduced the use of a partograph with the 4 hours action line and a clear definition of prolonged labor in 2011[312]. The same partograph defining prolonged labor was introduced in Norway in 2014 and oxytocin augmentation was recommended after defining prolonged labor[284].

Health care providers have met any heavy focus on standardizing guidelines and procedures with skepticism, and strict guidelines may be perceived as an invasion of personal autonomy[280,313]. Moreover, guidelines have to be recommended on a general basis and are not always appropriate for individuals[313]. Nevertheless, the quality of and adhesion to guidelines remains an important issue in obstetric care, as suboptimal care is reported in 60% of units that have a written policy on the use of oxytocin augmentation, suggesting negligence in following the guidelines[87,310,313,314]. This should be emphasized as oxytocin augmentation is commonly associated with preventive events[315]. In Paper III we do not know how many health care providers actually followed the new protocol, but because the observed changes in outcomes coincided with the new protocol, it is assumed to have played a role.

An overall impression of a more clinically uniform practice regarding oxytocin administration was observed in Paper III. Uniform clinical practice is believed to lead to bigger improvements in outcomes of care when compared to unsystematic practice, which may have biased our results further[280]. Following the implementation of a checklist for oxytocin augmentation, Clark et al. reported reduced use of oxytocin, no increase in cesarean section rate, and improved neonatal outcomes. The authors suggested that such a protocol was one appropriate way to manage the use of oxytocin augmentation, and their results are in line with ours. Interestingly, the use of oxytocin augmentation in this protocol was guided by uterine and fetal response, not the oxytocin dose administered. The protocol consisted of a checklist registration competed every 30 min after the start of intravenous oxytocin infusion. This has benefits, but was more time-consuming than the protocol implemented in our study. The checklist-based protocol did not define prolonged labor, which to some extent could explain why we observed longer labors in our study, but they did not.

Acknowledging our own practice patterns should be the first step in the assessment of clinical practice[316]. If we implement a standardized system where labor outcomes are included, we may more easily recognize events and adverse outcomes in the delivery ward[264,317,318]. An improvement of the use of TGCS as a standardized system including labor outcomes was introduced in Paper II. This may be used as a starting point for future studies by other authors. Currently, a national quality assurance project in Norway is taking place in order to define the indications for intrapartum cesarean sections. In Denmark a national quality assurance program called “safe births” was initiated in 2013, with the aim to reduce the number of fetuses born with asphyxia[319]. Oxytocin augmentation has thereby gained focus, and awareness has been raised. It is believed that such projects will contribute to increased quality

of labor management[317]. In the meantime, obstetricians and midwives should collaborate and improve the available assessment tools[293,320]. This approach of sharing already registered information through audits and feedback should be weighted when discussing quality of care in labor and delivery[269]. Audits and feedback have led to only small improvements in clinical care[316]. However, in obstetrics small improvements may have great impact on the consequences for the woman or fetus[306,316].

8.2.4 Postpartum hemorrhage

The observed increase in the incidence of severe PPH in Paper I has been reported by others[219]. The increase of severe PPH is not due to changes in risk factors over time, but to an unexplainable higher incidence of uterine atony[213,218,219]. However, recently previous severe PPH is found to be the strongest independent risk factor in addition to retained placenta tissue on the risk of severe PPH[321]. The increasing rates of abnormal placentation are associated to increasing cesarean section rates affecting the risk of near miss cases and the maternal morbidity[322,323]. Length of labor and oxytocin augmentation is risk factors for atonic uterine response, but the magnitude of the risk varies across studies[212,324]. This is partly explained by confounding factors and variations in study design and population[324]. The incidence of uterine atony was not explored in Paper I, but our findings of increased obstetric intervention might be associated with an increased risk of poor uterine response[324]. One could argue that the observed increase in severe PPH and the associations with obstetric interventions we observed support these findings.

Continuous surveillance of the obstetric population before and during labor is important to prevent further increases in the rates of severe PPH. This may be performed on a national level, a hospital level, and by clinical audits[211,226,325]. The TGCS might be of value when exploring the incidence of severe PPH and could lead to measures that will improve obstetric training and practice.

A reduction in the use of oxytocin augmentation parallel to an increasing incidence of labors >12 hours during the study period was observed in Paper III. Severe PPH rates also increased, but the overall blood transfusion rates were stable. Due to this, the accuracy of the subjective PPH estimation at the SUH may be questioned, even if this would not explain the observed

increase in severe PPH reported in Paper III. Reduced use of oxytocin augmentation has been suggested to reduce the risk of severe PPH in some studies[229]. Other studies that observed a reduced use of oxytocin augmentation did not explore changes in severe PPH[152,280]. Possible associations between reduced use of oxytocin augmentation, longer labors and the risk of severe PPH need to be explored in further studies.

8.2.5 Childbirth satisfaction

A woman's satisfaction with the childbirth experience is an important health outcome and can be viewed as an indicator of the quality of maternal care[326,327]. A fundamental goal for midwives and obstetricians is to support the women during childbirth and avoid medical interventions when they are not indicated[327]. A review of women's satisfaction with the childbirth experience found that support from caregivers, together with self-control and involvement in decision-making during labor were the most important factors[327,328].

One-to-one care was one of the focuses of the protocol implemented in Paper III, but we have no information regarding the possible influence of this factor on childbirth satisfaction. The observed reduced use of oxytocin and longer labors in Paper III correlates. It has been argued that birth experience depends on the length of labor, though the literature on this topic is inconsistent[329,330]. The only systematic review on women's satisfaction of childbirth found that length of labor was not an influencing factor[327]. However, length of labor >18 hours increases the risk of a negative experience by RR 3.6, and prolonged labor is considered to be an important risk factor for negative childbirth experience[330]. Prolonged labor is also the most common indication for acute cesarean section, and unplanned medical interventions are related to poor birth experience[328,330]. Some studies have included birth satisfaction as a secondary outcome. They observed that early intervention, even if it resulted in more obstetric interventions, was associated with better birth satisfaction. In women with prolonged latent phase, the authors suggested that a shorter length of labor contributed to higher satisfaction among nulliparous and multiparous women[331]. A RCT assessing active management of labor and routine care explored maternal satisfaction by a questionnaire 6 weeks postpartum. They found all women in the study reported high satisfaction with labor care[332]. Another RCT assessing early versus postponed oxytocin treatment for slow progression of labor found no

difference in women's perception of childbirth[328]. Still, information on childbirth experience should be included when oxytocin augmentation is evaluated.

8.2.6 Generalizability

An essential question for researchers is the external validity of their studies. In Papers I and III, the unselected population at SUH contribute to a generalization of the associations observed. Due to stratification, by use of the TGCS in Paper III, the effect of confounding is reduced even though the "Hawthorne effect" among the birth attendants still is present. In addition, the clinical and simple method of judicious use of oxytocin augmentation presented should make an implementation, even worldwide, feasible. Due to these arguments we argue that the observed associations can to some extent be generalized and thereby transferred to other countries and units with similar populations and health care systems.

9 Conclusion

The use of oxytocin augmentation has been increasing (Papers I and IV). Implementing judicious use of oxytocin augmentation resulted in a significant reduction in its use. This reduction was associated with an overall reduced incidence of acute cesarean section among women in TGCS groups 1, 2a, 3 and 4a (Paper III). Oxytocin augmentation might benefit women with epidural analgesia, especially those of advanced maternal age if a vaginal delivery is the preferred outcome (Paper IV). This needs further investigation.

An agreed set of labor outcomes to guide obstetric quality should be determined. These can be incorporated in the TGCS and used to increase the awareness of one's own results and possibly guide measures in the labor ward if indicated (Paper II).

10 Future perspectives

Several RCTs have concluded that oxytocin augmentation shortens labor length, has little impact on mode of delivery, and has no significant side effects if used properly and with good surveillance of the fetus. However, in case-control studies, oxytocin augmentation is associated with fetal acidemia due to incautious and suboptimal use.

More studies on structuring the everyday use of oxytocin augmentation in labor wards are needed, as the rates continue to rise. Unwanted incidents due to neglect or mistakes may not be reflected in study protocols and RCT settings. In addition, future studies should explore and validate the possible association between a reduced use of oxytocin augmentation and the implementation of a protocol for the judicious use of oxytocin. Ingrained in-house traditions and routines in combination with predetermined attitudes among health care professionals and delivering women are challenging to influence. However, focus on a prudent use of oxytocin augmentation might be one way to approach these issues. As oxytocin augmentation should be combined with additional surveillance of the mother and fetus, lower rates of oxytocin augmentation could be a benefit in countries where adequate monitoring is challenging or even impossible. Hence, implementation of a protocol that recommends judicious use of oxytocin also applies for labor wards in developing countries, in which the WHO partograph widely is used.

However, the observed association between increased severe PPH and judicious use of oxytocin augmentation needs to be thoroughly investigated before novel recommendations can be made. This applies to developing countries in particular, as PPH is a major contributor to maternal morbidity and mortality in these countries. It would also be of major interest to clarify the effect of changes in dose, length, and timing of oxytocin augmentation, as well as to identify possible associations between labor outcome and judicious use of oxytocin augmentation.

In addition, it would be of interest to investigate how oxytocin augmentation could modulate the risk of epidural analgesia for cesarean section as hypothesized in Paper IV. This might reveal associations with varying use, and could also increase the clinical value of oxytocin augmentation by individualizing the administration among specific groups of women.

11 References

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Paper I

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MAIN RESEARCH ARTICLE

Is there an increase of postpartum hemorrhage, and is severe hemorrhage associated with more frequent use of obstetric interventions?

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Abstract

Objective. To analyze changes in postpartum hemorrhage over a 10-year period from 1998 to 2007, and to explore factors associated with severe hemorrhage. *Design.* Retrospective cohort study, prospectively collected information. *Setting.* Stavanger University Hospital, a secondary referral center, Norway. *Population.* An unselected population of 41,365 women giving birth at the hospital. *Methods.* We analyzed changes over time in mean postpartum hemorrhage, severe postpartum hemorrhage and associated factors. Estimated blood loss >1,000 ml was defined as severe hemorrhage. Data were collected from the hospital's database. *Main outcome measures.* Severe postpartum hemorrhage and obstetric interventions. *Results.* We observed an increase in severe hemorrhage during the study period. After cesarean sections, the risk of severe hemorrhage was twice the risk of severe hemorrhage after vaginal deliveries (5.9%; 95% CI 5.3–6.6 vs. 2.8%; 95% CI 2.6–2.9). The most important factors associated with severe hemorrhage following vaginal deliveries were twin deliveries (OR 6.8), retained placenta (OR 3.9) and inductions of labor (OR 2.2). For cesarean sections, twin deliveries had the strongest association with severe hemorrhage (OR 3.7) followed by general anesthesia (OR 3.0). Obstetric interventions became more frequent; elective cesarean sections increased from 2.4 to 4.9%, acute cesarean sections from 5.5 to 8.9%, operative vaginal deliveries from 9.3 to 12.5%, inductions of labor from 14.3 to 15.8% and augmentations of labor from 5.8 to 29.3%. *Conclusions.* The incidence of severe postpartum hemorrhage increased, and this may be related to more frequent use of obstetric interventions.

Key words: *Multiple pregnancies, cesarean sections, general anesthesia, induction of labor, augmentation of labor*

Introduction

Worldwide, more than 500,000 women die every year from complications related to pregnancies and deliveries (1). As recently highlighted, postpartum hemorrhage remains the leading cause (2). Maternal mortality is low in developed countries, in Norway around 7 per 100,000 (1). However, severe obstetric morbidity must also be recognized, and excessive bleeding can lead to life threatening situations (3,4). The reported incidence and definition of severe hemorrhage vary significantly between hospitals and countries (5), and recent studies have indicated a rising frequency of severe postpartum hemorrhage (5–7).

Obstetric interventions are increasing and causing concerns. Higher rates of cesarean sections, inductions of labor and augmentations of labor have been put forward as reasons for the increasing incidence of severe postpartum hemorrhage (6,8,9). Other factors associated with postpartum hemorrhage are

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multiple pregnancies, bleeding disorders, previous postpartum hemorrhage, placenta previa, prolonged labor, augmentation of labor, operative vaginal deliveries, soft tissue lacerations, macrosomia and retained placenta (10–15). Different factors interrelate, and severe postpartum hemorrhage may, after all, be unpredictable (11,16). Routine prophylactic use of oxytocin (16), active management of the third stage of labor (17) and immediate interventions (18) are recommended. A recent Norwegian population study concluded that most of the factors associated with severe hemorrhage are related to obstetric management and interventions, and are, in the authors' opinion, thus preventable (14).

The aim of this study was to analyze changes in postpartum hemorrhage during a 10-year period, and to explore factors possibly associated with severe postpartum hemorrhage in our population.

Material and methods

The study population included all women with a pregnancy length between 23 and 43 weeks, who delivered a child with a birth weight >300 g at Stavanger University Hospital from January 1998 to December 2007. The pregnancies were dated at a second trimester ultrasound examination. In all 40,468 singleton, 880 twin and 17 triplet deliveries were included. Due to missing information, 49 women were excluded. In the geographical region there is only one delivery department and home births are uncommon. Characteristics of the study population are presented in Table 1. The information related to pregnancies and deliveries were collected prospectively and recorded in a computerized database at the hospital. All analyses were performed retrospectively.

The attending midwife or obstetrician visually estimated the blood loss in ml. Blood cloths were collected and measured, if possible. Estimated blood loss of more than 1,000 ml was defined as severe postpartum hemorrhage.

The delivery department experienced changes in the routine prophylactic use of oxytocin during the study period. From January 1998 until March 2000, oxytocin was not used routinely. From March 2000 until June 2006, 5 international units (IU) oxytocin were given intramuscularly (IM) to all mothers, immediately after delivery of the baby. From June 2006 and onward, standard procedure has been to inject 10 IU oxytocin IM promptly after delivery.

Data were entered into the statistical software package SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Cross-tabulation with a chi-squared test was used for analyzing categorical variables. Differences in mean postpartum hemorrhage were assessed using Student's *t*-test and one-way ANOVA with Bonferroni's correction. The amount of postpartum hemorrhage was not normally distributed, and was therefore log transformed before the analyses.

Table 1. Characteristics of the study population.

Nulliparous (%)	40.4
Maternal age (mean, years)	29.6
Maternal age ≥35 years (%)	19.1
Previous cesarean section (%)	5.7
Ethnicity (other than Caucasian) (%)	5.8
Gestational age (median, weeks)	40.0
Preeclampsia (%)	3.3
Diabetes mellitus (%)	0.2
Elective cesarean section (%)	3.7
Acute cesarean section (%)	7.1
Cesarean section in general anesthesia (%)	16.1
Induction of labor (%)	14.9
Augmentation of labor (%)	22.8
Epidural analgesia, vaginal delivery (%)	31.7
Acupuncture (%)	19.2
Birthweight (mean, g)	3,534
Operative vaginal delivery (%)	10.4
Episiotomy (%)	15.5
Sphincter rupture (%)	3.8
Breech presentation, vaginal delivery (%)	3.6
Occiput posterior position, vaginal delivery (%)	2.7
Retained placenta (%)	2.8

Multivariable logistic regression analyses were used to examine possible factors associated with severe hemorrhage. Postpartum hemorrhage >1,000 ml was used as dependent variable. Included covariates for women with vaginal deliveries were ethnicity, parity, maternal age ≥35 years, multiple pregnancy, previous cesarean section, preeclampsia, diabetes mellitus, preterm delivery (before 37 completed pregnancy weeks), induction of labor, augmentation of labor, duration of first stage of labor >10 hours, duration of second stage of labor >30 minutes, epidural analgesia, use of acupuncture, birthweight ≥4,000 g, operative vaginal delivery, episiotomy, sphincter rupture, breech presentation, occiput posterior position and retained placenta.

Included covariates for women with cesarean section were parity, ethnicity, maternal age ≥35 years, previous cesarean section, diabetes mellitus, preeclampsia, preterm delivery, multiple pregnancy, induction of labor, duration of first stage >10 hours, birthweight ≥4,000 g, breech presentation, occiput posterior position, general anesthesia and emergency cesarean section.

Factors were included in the multivariable logistic regression analyses if the unadjusted estimates had a

p-value of <0.25. A *p*-value of <0.05 was considered significant.

Results

Over the study period, severe postpartum hemorrhage increased. The incidence was 2.5% (95% CI 2.2–2.8) in 1998/99, 2.5% (95% CI 2.2–2.9) in 2000/01, 3.6% (95% CI 3.2–4.0) in 2002/03, 3.6% (95% CI 3.3–4.1) in 2004/05, and in 2006/07 the rate of severe hemorrhage was 3.3% (95% CI 3.0–3.7). The mean postpartum hemorrhage was quite stable during the study period with a slight, but significant decrease from 2004/05 to 2006/07.

Unrelated to the mode of delivery, 2.9% (95% CI 2.7–3.0) of women with singleton pregnancies experienced severe hemorrhage, and for women giving birth to multiples this rate was 14.1% (95% CI 11.9–16.5). The mean hemorrhage after singleton delivery was 381 ml (95% CI 378–384), and for women with multiples the mean hemorrhage was 723 ml (95% CI 686–761).

The mean hemorrhage after vaginal delivery was 373 ml (95% CI 370–376), and 2.8% (95 CI 2.6–2.9) had a hemorrhage of >1,000 ml. After cesarean section, the mean hemorrhage was significantly higher (517 ml; 95% CI 503–530) and more women experienced severe hemorrhage (5.9%; 95% CI 5.3–6.6). A total of 4,164 women with singleton pregnancies were delivered by cesarean section. Table 2 shows the indications for cesarean section and the frequencies of severe postpartum hemorrhage. Over the study period, these indications did not show significant variations.

In Figures 1 and 2, the mean postpartum hemorrhage and the incidence of severe postpartum hemorrhage after vaginal and cesarean deliveries in five different periods are presented. We observed increased mean hemorrhage after cesarean sections. The rate of severe hemorrhage increased significantly after vaginal deliveries; however, the observed increase after cesarean sections did not reach significance ($p = 0.09$).

During the years 2006 and 2007, when 10 IU oxytocin were given routinely after vaginal delivery, the mean hemorrhage was only slightly, nevertheless significantly, lower (362 ml) compared with the period when 5 IU oxytocin were given routinely (377 ml), and with the period without routine use of oxytocin (372 ml). However, the incidence of severe postpartum hemorrhage was not reduced in any of the periods with routine use of oxytocin.

Table 3 presents the results of the multivariable logistic regression analyses for severe postpartum hemorrhage after vaginal deliveries. Diabetes mellitus and the use of acupuncture were not associated with severe postpartum hemorrhage in these analyses. Table 4 shows the results of the multivariable logistic regression analyses for severe postpartum hemorrhage after cesarean delivery. In these analyses, parity, diabetes mellitus, preeclampsia and occiput posterior position did not show any association with severe postpartum hemorrhage.

Over the study period, there were 6,154 inductions of labor, and the induction rate increased from 14.3% in 1998/99 to 15.8% in 2006/07 (Figure 3). Severe hemorrhage occurred more frequently in women with induced labor (5.2%; 95% CI 4.7–5.8), compared to women with spontaneous onset of labor (2.4%; 95% CI 2.3–2.6). The indications for induction of labor in 5,913 singleton pregnancies were pregnancy-induced hypertensive disorders (16.7%), post-term pregnancies (23.2%), maternal request (12.7%), prelabor rupture of membranes (25.7%) and others (21.7%). The incidence of severe hemorrhage related to the various induction indications were 6.1% (95% CI 4.8–7.8), 6.0% (95% CI 4.8–7.4), 5.1% (95% CI 3.7–6.9), 5.3% (95% CI 4.3–6.5) and 4.4% (95% CI 3.4–5.7), respectively. In all, 929 inductions (15.1%) ended with a cesarean section.

We also observed an increased frequency of augmentation of labor from 5.8 to 29.3%, of elective cesarean sections from 2.4 to 4.9%, of emergency cesarean sections from 5.5 to 8.9%, and of operative vaginal delivery from 9.3 to 12.5%. Variations over time and CI intervals are shown in Figure 3. During the study period, 718 cesarean sections (16.1%) were performed under general anesthesia, but this rate did not increase. Further, we observed stable frequencies of twins and children with birthweight ≥4,000 g.

The use of blood transfusions in the postnatal ward increased markedly during the study period, with a

Table 2. Indications for cesarean sections and frequencies of severe postpartum hemorrhage.

	n	Severe hemorrhage (%)	95% CI
Prolonged labor	716	9.2	7.3–11.6
Placenta previa	92	18.5	11.9–27.6
Antepartum hemorrhage	127	18.9	13.0–26.6
Fetal asphyxia	995	4.0	3.0–5.4
Breech/transverse lie	501	3.6	2.3–5.6
Preeclampsia	174	3.5	1.6–7.3
Previous cesarean section	285	3.2	1.7–5.9
Maternal request	510	2.9	1.8–4.8
Other	764	3.4	2.3–4.9

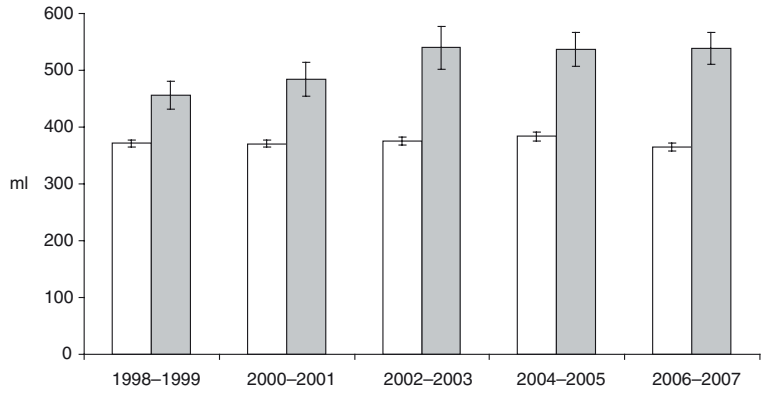

Figure 1. Mean postpartum hemorrhage with 95% CI over a 10-year period. □, vaginal deliveries; ▨, cesarean sections.

frequency of 1.3, 2.1, 2.4, 3.0 and 4.5% of all deliveries in the five 2-year periods, respectively.

Discussion

Over the 10-year study period, severe postpartum hemorrhage increased. We observed a higher rate of severe hemorrhage after cesarean sections than after vaginal deliveries. For women with cesarean sections, twin deliveries and general anesthesia showed the strongest association with severe hemorrhage. The factors most strongly associated with severe hemorrhage after vaginal deliveries were twins, induction of labor and retained placenta.

In other studies, nulliparity, Asian or Hispanic ethnicity, preeclampsia, twins, previous postpartum hemorrhage, induction and augmentation of labor, prolonged labor, amnionitis, epidural analgesia, episiotomy, soft tissue lacerations, operative vaginal deliveries, macrosomia and stillbirth have been found to be factors associated with postpartum hemorrhage after vaginal delivery (10,11). After cesarean section, Asian or Hispanic ethnicity, preeclampsia, leiomyoma, preterm birth, placenta previa, prolonged labor, amnionitis, general anesthesia and macrosomia are factors associated with increased hemorrhage (12,13). Some of these factors, as placenta previa and retained placenta, are independent causes of bleeding, while others are factors that increase the risk of uterine atony, which is the single condition causing most of severe postpartum hemorrhage (5,14).

Studies from Canada, Australia and USA have reported an increase in postpartum hemorrhage (5–7),

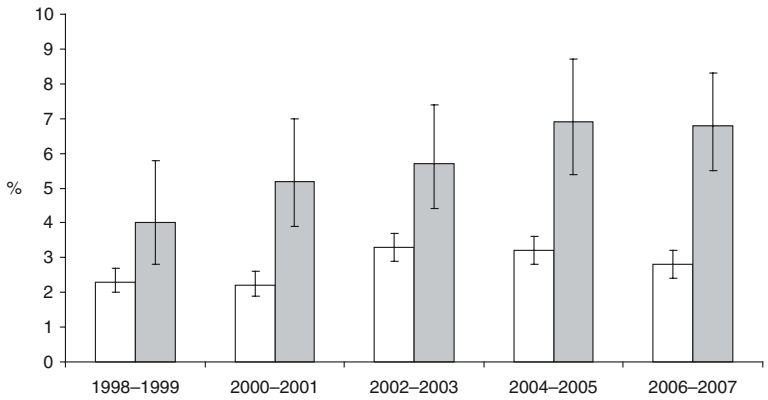

Figure 2. Rates of severe postpartum hemorrhage with 95% CI over a 10-year period. □, vaginal deliveries; ▨, cesarean sections.

Table 3. Logistic regression analyses of associated factors with hemorrhage more than 1,000 ml after vaginal deliveries.

	Unadjusted OR	95% CI	*p*-Value	Adjusted OR	95% CI	*p*-Value
Multiple pregnancy	6.2	4.9–7.9	<0.01	6.8	5.0–9.2	<0.01
Nulliparous	1.4	1.3–1.6	<0.01	1.2	1.0–1.4	0.03
Maternal age ≥35 years	1.2	1.1–1.4	0.01	1.2	1.1–1.5	0.01
Previous cesarean section	1.6	1.1–2.1	<0.01	1.4	1.0–1.9	0.05
Ethnicity (other than Caucasian)	1.4	1.1–1.8	<0.01	1.5	1.2–1.9	<0.01
Preeclampsia	2.4	1.8–3.1	<0.01	1.4	1.0–1.9	0.05
Induction of labor	2.6	2.2–2.9	<0.01	2.2	1.9–2.6	<0.01
Preterm delivery <37 weeks	1.5	1.1–2.0	0.01	0.9	0.6–1.2	0.40
Augmentation of labor	1.5	1.3–1.7	<0.01	1.2	1.0–1.5	0.03
Duration of first stage >10 hours	1.9	1.5–2.4	<0.01	1.4	1.1–1.8	0.02
Duration of second stage >30 minutes	1.7	1.5–1.9	<0.01	1.3	1.1–1.5	0.01
Epidural analgesia	1.8	1.6–2.0	<0.01	1.0	0.9–1.2	0.60
Birthweight ≥4,000 g	1.9	1.7–2.2	<0.01	2.0	1.8–2.4	<0.01
Operative vaginal delivery	1.8	1.5–2.1	<0.01	1.0	0.9–1.3	0.70
Episiotomy	1.6	1.4–1.9	<0.01	1.3	1.1–1.5	0.01
Sphincter rupture	2.1	1.7–2.6	<0.01	1.6	1.2–2.0	<0.01
Breech presentation	1.6	1.1–2.3	0.02	0.9	0.6–1.4	0.65
Occiput posterior position	1.3	0.9–1.9	0.11	1.1	0.6–1.4	0.48
Retained placenta	3.9	3.1–4.9	<0.01	3.9	3.0–4.9	<0.01

and explained it by changes in management and reporting, and not changing of risk factors (6). The observed increasing rate in USA was assumed to be limited to atonic bleeding (5), and further research in other countries is recommended (9). In a British study, the known risk factors associated with primary postpartum hemorrhage were not useful in identifying women who continued bleeding after first-line therapy (19). Peripartum hysterectomies are related to severe maternal morbidity (20), and the incidence has increased over the last 20 years in Denmark, possibly as a consequence of the rising rates of cesarean section (8).

Over the study period, we observed a continuously increasing frequency of cesarean section. However, the relation between the various indications for cesarean section was stable. The incidence of severe hemorrhage after elective cesarean section by the reason for a maternal request was low. Prolonged labor was associated with a high risk of severe hemorrhage. It is worth mentioning that this was as well one of the most frequent indications for cesarean section. Fatigue of the uterine muscle predisposes to uterine atony. More correct diagnoses of prolonged labor and more structured use of oxytocin stimulation have for good reasons been highlighted (21). Furthermore, we observed general anesthesia as a main risk factor for severe postpartum hemorrhage, and regional anesthesia should be preferred whenever possible.

Induction of labor also increased significantly over the study period, and induction on maternal request increased the most. In 2006/07, every fourth induction of labor ensued from a maternal request. Variations in severe postpartum hemorrhage were not significantly related to the indications for induction of labor, even though all inductions, irrespective of

Table 4. Logistic regression analyses of associated factors with hemorrhage more than 1,000 ml after cesarean deliveries.

	Unadjusted OR	95% CI	*p*-Value	Adjusted OR	95% CI	*p*-Value
General anesthesia	3.2	2.5–4.2	<0.01	3.0	2.2–4.3	<0.01
Acute cesarean section	1.7	1.3–2.3	<0.01	1.1	0.8–1.7	0.51
Multiple pregnancy	2.9	2.1–4.1	<0.01	3.7	2.4–5.8	<0.01
Maternal age ≥35 years	1.5	1.1–1.9	0.01	1.7	1.3–2.4	<0.01
Previous cesarean section	0.8	0.6–1.1	0.21	1.0	0.7–1.4	0.83
Ethnicity (other than Caucasian)	1.4	0.9–2.1	0.17	1.3	0.8–2.2	0.30
Induction of labor	1.5	1.1–1.9	0.01	1.3	0.9–1.9	0.13
Preterm delivery <37 weeks	1.3	0.9–1.8	0.16	1.2	0.8–1.9	0.31
Duration of first stage >10 hours	2.1	1.4–3.0	<0.01	1.7	1.0–2.8	0.03
Birthweight ≥4,000 g	1.7	1.3–2.3	<0.01	1.8	1.2–2.6	<0.01
Breech presentation	0.8	0.5–1.1	0.12	0.8	0.5–1.2	0.35

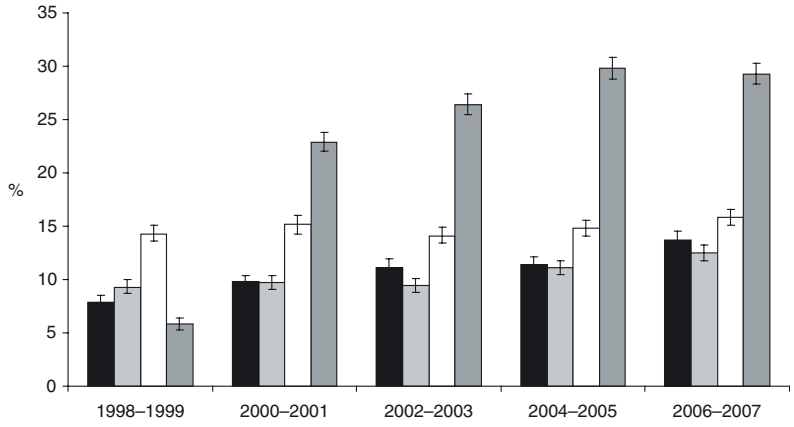

Figure 3. Rates of obstetric interventions with 95% CI over a 10-year period. ■, cesarean sections; ▒, operative vaginal deliveries; □, inductions of labor; ▒, augmentations of labor.

indication, were associated with increased risk of severe hemorrhage. Furthermore, we found augmentation of labor to increase the risk of severe hemorrhage, and we observed substantial rising rates of augmentations over the study period. Another Norwegian study also found a significant increased risk of postpartum hemorrhage associated with obstetric interventions (22).

Multiple pregnancies were the single factor with highest odds ratio for severe hemorrhage. Clinicians, and particularly colleagues working with assisted fertilization, should be aware of this complication. We did not find epidural analgesia to be a risk factor for severe hemorrhage in the adjusted regression analysis, perhaps because many women asking for epidural analgesia in our population have prolonged labor. Beyond that, the results of our regression analyses are in accordance with the results from other studies (10,11). The higher age of primiparas may lead to increased morbidity for the woman as well as for the fetus, and should be of concern (3). We detected rising rates of nulliparous women and women ≥35 years. In addition, there were significantly more nulliparous women (13 vs. 9%) and more women ≥35 years (15 vs. 9%) experiencing cesarean sections. Obesity (BMI >35) is also considered as a risk factor (16). Unfortunately, maternal height and weight were not registered in our database.

Reduction of postpartum hemorrhage was heavily focused in our department during the last 2-year period. Active management of the third stage of labor is recommended as an effective prevention of postpartum hemorrhage (16,17,23,24). Administration of 10 IU of oxytocin soon after birth, early cord clamping and active uterine massage were included in our clinical guidelines. Controlled cord traction is also recommended, but this procedure was not implemented until late 2007. One single intervention might not be effective by itself, but when applied in combination with other procedures, interaction may lead to effectiveness (24). For example, the effect of the oxytocin injection may not be indifferent to the timing. Administration of oxytocin within 1 minute after delivery, as recommended by the International Federation of Gynecology and Obstetrics, may be more effective (24). Hopefully, these changes in routines will reduce the increasing tendency for severe hemorrhage.

In our department, the attending obstetrician is consulted when there is excessive bleeding or estimated blood loss of >1,000 ml. Thorough uterine massage, oxytocin infusion and administration of misoprostol rectally are the first actions. Further options of treatment are manual exploration of the uterine cavity, administration of cyclocapron, injection of prostaglandin in the myometrium, uterine tamponade, uterine artery embolization and hysterectomy.

During the last 2-year period, we also focused on preventing sphincter ruptures by systematically teaching midwives and obstetricians how to always support the perineum (25). A significant reduction of sphincter ruptures has been observed in our department, and this has probably prevented some severe hemorrhage.

More junior obstetricians are now performing cesarean sections, but a consultant is always within reach for assistance. Over time, the surgical technique

has gradually changed and the Joel-Cohen-based technique is now the standard method. 5 IU oxytocin is routinely injected intravenously immediately after cesarean delivery of the baby, but we have not had a standard method for delivering the placenta. The importance of adjusted routines, surgical techniques and duration of operation should be addressed in new studies.

An objective measurement of the magnitude of postpartum hemorrhage is unattainable. In many studies, combinations of hemoglobin and hematocrit, the need for blood transfusion, and medical diagnoses have been used to classify severe hemorrhage (6,7,11). Others, like us, have mainly used the estimated blood loss, realizing the inaccuracy of this approach (10,14,15). However, it remains the only simple routine method available in everyday practice (14,26), where midwives are found to have the most accurate estimations (27). In our department, blood transfusion in the postnatal ward also increased during the study period; this emphasizes the significance of the estimates. The strength of our study is a large and unselected population and the systematic registration of the data as a daily routine.

In conclusion, the upward trend of induction and augmentation of labor and cesarean sections is a cause of concern (8,22,28,29). We observed an increased frequency of severe postpartum hemorrhage, and this finding may, to some extent, be related to more frequent obstetric interventions. Our findings illustrate the need of a medically based indication for interventions during pregnancy and labor.

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Paper II

A method to assess obstetric outcomes using the 10-Group Classification System: a quantitative descriptive study

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ABSTRACT

Objectives: Internationally, the 10-Groups Classification System (TGCS) has been used to report cesarean section rates, but analysis of other outcomes are also recommended. We now aim to present the TGCS as a method to assess outcomes of labor and delivery using routine collection of perinatal information.

Design: A methodological study to describe the use of the TGCS

Setting: Stavanger University Hospital (SUH) Norway, National Maternity Hospital Dublin (NMH) Ireland and Slovenian National Perinatal Database (SLO) Slovenia

Participants: 9848 women from Stavanger University Hospital, Norway, 9250 women from National Maternity Hospital Dublin, Ireland and 106 167 women, from Slovenian National Perinatal Database, Slovenia

Main outcome measures: All women were classified according to the TGCS within which cesarean section, oxytocin augmentation, epidural analgesia, operative vaginal deliveries, episiotomy, sphincter rupture, postpartum hemorrhage, blood transfusion, maternal age>35 years, body mass index >30, Apgar score, umbilical cord pH, hypoxic ischemic encephalopathy, antepartum and perinatal deaths were incorporated.

Results: There were significant differences in the sizes of the groups of women and the incidences of events and outcomes within the TGCS between the three perinatal databases.

Conclusions: The TGCS is a standardized objective classification system where events and outcomes of labor and delivery can be incorporated. Obstetric core events and outcomes should be agreed and defined in order to set standards of care. This method provides continuous and available observations from delivery wards, possibly used for further interpretation, questions and international comparisons. The definition of quality may vary in different units and can only be ascertained when all the necessary information is available and considered together.

Key words:
Cesarean section, quality of care, labor outcome, neonatal outcome, the 10-Group Classification System, core outcome

Abbreviations:

SUH, Stavanger University Hospital; NMH, National Maternity Hospital; SLO, Slovenian National Perinatal Database; TGCS, the 10-Group Classification System; WHO, World Health Organization; FIGO, The International Federation of Gynecology and Obstetrics

Strengths and limitations of this study:

- This study proposes the use of an available method which may elaborate potential trends in delivery units and thus guide labor and delivery management
- Events and outcomes of labor are incorporated in the 10-Group Classification System from three different populations in Europe
- The 10-Group Classification System is limited by unclear definitions of some of the outcomes used and encourage the importance of an agreed set of obstetric core outcomes
- The design as a quantitative descriptive study limits the ability to explore causes of the different prevalence's of outcomes and events observed

INTRODUCTION

Safety, consistency and quality in labor and delivery are key priorities for all labor and delivery units. It is difficult to determine what quality in labor and delivery is, but attempts to develop important outcomes are taking place (1-4). An agreed classification system, incorporating key outcomes that are objective, measurable and relevant to clinical practice is required in order to assess consistency and quality of care.

Clinical practice and guidelines do vary internationally and occasionally also nationally. However, agreeing on a standard classification for assessment of quality of care should be less contentious. It is essential that providers and users of maternity care are aware of events and outcomes in their units and in addition having the ability to compare their results objectively over time and to other units. Only then can assessment of the quality of care take place (5, 6). The emphasis on evidence-based medicine should be supported by prospective databases combined with a multidisciplinary quality audit programme. Acceptance and commitment to this philosophy will provide insight about labor and delivery and importantly ensuring that we are providing safe and quality care (7).

The 10-Group Classification System (TGCS) was first described in 2001 and originally popularized as a method to assess cesarean section rates (8). The intention however, was to introduce a generic perinatal classification to assess all perinatal events and outcomes of which cesarean section is only one. The way the ten groups are structured make them relevant to all clinicians and women themselves and can provide a common language and starting point for any discussion on safety, quality of care and perinatal audit (9). The TGCS is endorsed by the World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FIGO) and increasingly used by labor and delivery units to report their cesarean section rates (10-18). The WHO and FIGO also recommend that other events and outcomes surrounding labor and delivery are analyzed in relation to cesarean section using this classification.

This paper classifies data from three perinatal databases in different countries and explores the usefulness of the TGCS as a method to assess the quality of care. It also discusses the challenges that occur even using a standard classification system.

METHODS

Data related to pregnancies and deliveries were prospectively collected in Stavanger University Hospital (SUH) Norway 2010-2011, National Maternity Hospital Dublin (NMH) Ireland 2011 and Slovenian National Perinatal Database (SLO) Slovenia 2007-2011. The study population included 9848 women in SUH, 9250 women in NMH and 106 167 women in SLO. All women were classified according to the TGCS (Figure 1). Cesarean section was defined as after spontaneous onset, induction or pre-labor. Pre-pregnancy body mass index was calculated as weight in kilograms/height in meters squared. Episiotomies were either lateral or mediolateral and perineal tears affecting the external or the external and internal sphincter were classified as obstetric anal sphincter injuries. The attending midwife or obstetrician visually estimated blood loss and postpartum hemorrhage > 1000 millilitres were registered at SUH and NMH, and postpartum hemorrhage > 500 millilitres in SLO.

Perinatal deaths included all intrauterine deaths after 22 weeks gestational age and within the first week after delivery. Hypoxic ischemic encephalopathy was classified using the Sarnat or modified Sarnat definition as grade I (mild), grade II (moderate) and grade III (severe). All data are presented as descriptive statistic.

Stavanger University Hospital

Stavanger University Hospital has a catchment population of approximately 320 000 and is the regional maternity unit in the west of Norway. It has a tradition of low obstetrical intervention rates. Women with one previous cesarean were encouraged to deliver vaginally. Information related to pregnancies and deliveries was prospectively collected and recorded in an electronic obstetrical journal system (Natus).

The Regional Committee for Medical and Health Research Ethics classified the study as a quality assurance study of routinely recorded data (REK Vest 2012/1522) and the local committee for data protection (2012/41) approved the project.

National Maternity Hospital

The National Maternity Hospital is a tertiary referral maternity hospital in Dublin, Ireland and one of the largest labor and delivery units in Europe delivering over 9000 women a year. It is well known for its Active Management of Labor philosophy on labor (19). This package of care is based on the prevention of prolonged labor and the physical and emotional sequel that follow. Labor and delivery information is collected prospectively on an obstetrical and

neonatal database. The hospital has traditionally for many years completed an Annual Clinical Report detailing each year's results.

Slovenian National Database

Slovenia is a European Union member state in Central Europe with approximately 2.1 million of inhabitants and 20 000 deliveries per year. Health care in Slovenia is a public service provided through the public health service network. Perinatal care is almost entirely covered by compulsory health insurance, which is publicly funded. Slovenia has had a National Perinatal Information System (NPIS) since 1987 and registration into a computerized database by the attending midwife and doctor is mandatory. Data from all 14 country's maternity unit are collected. To assure quality of data collection, controls are built in the computerized system and audited periodically.

RESULTS

The populations contained 43%, 46% and 48% nulliparous women in SUH, NMH and SLO. The overall cesarean section rates were 13.6%, 21.4% and 17.4% in SUH, NMH and SLO, respectively. The highest rate of cesarean in groups 1 and 2a was observed in SLO. NMH presents the lowest rate of cesarean in group 3 and SUH the lowest rate in group 5. Rupture of the uterus was diagnosed in 0.02% (2/9848) women in SUH, no women in NMH and 0.04% (39/106 167) women in SLO during the study period. The relative sizes of the groups and cesarean section rates are presented in Table 1.

The overall pre-pregnant body mass index > 30 was 9.7%, 12.8%, 8.3% and the frequency of maternal age >35 years was 14.9%, 32.2%, 14.9% in SUH, NMH and SLO, respectively. Maternal characteristics stratified according to the TGCS are presented in Table 2.

The overall use of epidural analgesia varied from 35.0% at SUH and 49.0% at NMH to 2.7% in SLO. The overall operative vaginal delivery rate varied from 12.7%, 11.9% and 3.2% in SUH, NMH and SLO, respectively. The overall induction rates were 20.1%, 24.9% and 23.5% and the frequencies of use of oxytocin were 23.6%, 28.3% and 57.3% in SUH, NMH and SLO. The overall rates of episiotomy were 19.7%, 28.7% and 32.0% and the rates of obstetric anal sphincter injuries were 1.5%, 1.5% and 0.3% in SUH, NMH and SLO, respectively. The overall red cell blood transfusion rate was 2.7%, 1.4% and 0.2% in SUH, NMH and SLO. Labor outcomes stratified according to the TGCS group's 1-5 are presented in Table 3 and 4.

Overall perinatal death in SUH was 4.2 per 1000, in NMH 3.9 per 1000 and 5.0 per 1000 (540/108070) in SLO. Perinatal deaths among groups 1 and 2 together were 1.3‰, 1.4‰ and 1.2‰, among groups 3 and 4 together 0.1‰, 0.8‰ and 1.2‰ and among women with previous cesarean (group 5) 5.5‰, 0‰ and 0.9‰ in SUH, NMH and SLO, respectively. Neonatal outcomes stratified according to the TGCS 1-5 are presented in Table 5.

DISCUSSION

Every labor and delivery unit has a responsibility to record and publish their results. The results also need to be presented in a standardized and structured way, as the management and implications will vary in different groups of women. Any one event or outcome cannot be considered on their own without the understanding of any effects on other events, outcomes or complications. Care during labor and delivery has changed dramatically over the last 30 years (20). In particular, the cesarean section rate has risen and a common classification system might be helpful exploring benefits and risks associated to this intervention.

Limitations

Several challenges were discovered writing this manuscript. When comparing maternal, labor and perinatal outcomes between units and countries, objective variables (blood transfusion rates, perinatal deaths) have advantages over subjective assessed outcomes (postpartum hemorrhage, Apgar score <7 and hypoxic ischemic encephalopathy). In addition, some of our outcomes were differently defined and registered such as postpartum hemorrhage .This issue has been recognized and highlighted as a general problem in clinical trials (3, 4, 28). Standardizing and agreeing on which core outcomes to be used to assess quality would not only increase the usefulness of the information collected but also encourage delivery units to use the same definitions. Due to different databases and registration, we only succeeded in completing Table 1 with data from all the 10 groups. Ensuring quality data from national databases may be challenging and the low rates in SLO particularly of obstetric anal sphincter injuries and transfusion rates should have been validated. Even more important is the need for a structured and standardized collection and registration of defined core outcomes in delivery units and in national registers.

We present the use of the TGCS as a method of which possible patterns within the observed population may uncover. By comparing outcomes and events between standardized

groups of women, hypotheses requiring further attention might be suggested. However, to explore causality further studies are needed.

The 10-Group Classification System

To achieve good data quality, proper registration and standardized definitions of outcomes are essential. The ability to classify all deliveries into one of the ten groups is however a quality indicator which many institutions, countries and perinatal databases struggle to do (5). By presenting data using the TGCS, the ability to demonstrate significant differences in smaller units is limited. However, examining even a small number of cases may be helpful to develop local strategies to improve the quality of care (14). Risk is not only the chance of certain events occurring but also the implications if it did occur.

The TGCS presents a method of risk stratification, which visualizes how the cesarean section rate varies between different units and countries. Interpretation of other outcomes in the different groups may be used as a guidance to assess obstetric quality. Cesarean section rates can only be evaluated if perinatal and maternal outcomes are included (14, 21). Using the TGCS, there are only three possible explanations for differences in the sizes of the groups and the events and outcomes within the groups: data quality, significant differences in important epidemiological variables and differences in clinical practice (9).

To improve management in labor and optimizing care, collection and simple interpretation of data are necessary (1). The data quality must be validated and by working together at multiple levels within the unit, improvements and adverse trends can be detected (2). The TGCS is shown to be consistent in size and the different cesarean section rates in the groups together with the size allow an informative interpretation of a given overall cesarean section rate (Table 1). When other epidemiological information, events, outcomes and processes are analyzed within the different groups as opposed to a proportion of the overall population, they increase in relevance. The TGCS do not adjust for risk factors, but by quantifying patient's populations and different practice patterns it allows a comparison of clinical value and may encourage a more in depth analysis of individual groups or sub-groups. Following are some examples of how our observations may be interpreted.

Focusing on the management of both physical and emotional care of nulliparous women (group 1) is important as this will prevent the cesarean rate from a further increase when these women return for a future delivery (22, 23). SLO has an overall lower cesarean section rate than NMH, but a higher cesarean section rate of 10% in group 1 (Table 1). Table

5 shows that lower cesarean section rates at SUH and NMH do not compromise good perinatal outcome.

A greater than a 2:1 ratio of the size of groups 1 and 2 reflects a low intervention rate in term single cephalic nulliparous women (5). This is influenced by culture, obstetric practice and case mix of the particular population. The ratios in our populations were 3.1, 1.7, and 3.3, SUH, NMH, SLO, respectively. The benefits of labor induction must be weighed against the potential maternal and fetal risks associated with the procedure as well as knowledge of the population and the incidence of antenatal stillbirths (22, 24). Maternity care before and in relation to the management of labor will further influence to which group and following risk the woman belongs to in her next pregnancy (group 3, 4 or 5) (10). The rate of cesarean section in the subsequent pregnancy was 5.3%, 3.8%, 5.1% (SUH, NMH, SLO respectively) in women without a previous cesarean (group 3 and 4 combined) compared to 46.0%, 60.5%, 74.7% (SUH, NMH SLO respectively) in women with a previous cesarean (group 5).

As presented in Table 2, the women delivering at NMH were in all groups older than the women delivering at SUH and in SLO. When comparing cesarean section rates (Table 1), the low rate at NMH in group 1 might reflect a certain type of labor management as high maternal age rather is associated with increased incidence of interventions.

SUH has the lowest cesarean section rate and the lowest use of oxytocin. Compared to NMH and their philosophy of prevention of prolonged labor this may lead to more labors that are prolonged. The package of Active Management of Labor with one to one care and its advantages has always been an issue of much debate (25). The role of oxytocin in labor management is essential, but the optimal dose and timing is yet to be revealed (26). In addition, by using the TGCS, a higher rate of obstetric anal sphincter injuries among women in group 2a and 5 at SUH is detected which should encourage closer investigation. The overall rate of severe postpartum hemorrhage at SUH, is relatively at least, high and in addition proportionally higher transfusion rates (27). This highlights the importance of analyzing both subjective (estimated blood loss) outcomes together with objective (transfusion rates) when evaluating obstetric practice (28, 29).

Compared to SUH and NMH, the operative vaginal delivery rate is lower in SLO. The risk of adverse maternal and neonatal outcomes increases with an operative vaginal delivery but if the alternative is a cesarean at full dilatation, the risk benefit ratio must be carefully considered (30). Occurrence of maternal and neonatal complications is, however, similar to SUH and NMH with the exception of lower sphincter rupture rates in all groups.

Conclusion

We present cesarean section rates, maternal characteristics together with labor and fetal outcomes using the TGCS as a starting point. This is a systematic method of assessing the events and outcomes, which may contribute to the judgment of quality of care in labor and delivery. We encourage other labor and delivery wards to make use of the same classification and then by working together and sharing our knowledge we can learn from each other. The first step in providing quality of care is to be aware of your results.

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Legends:

Table 1 The 10-Group Classification System for Stavanger University Hospital, Norway, National Maternity Hospital Dublin, Ireland, Slovenian National Perinatal Database, Slovenia 2007-2011

Table 2 Maternal characteristics stratified in the 10-Group Classification System groups 1-5

Table 3 Labor outcomes stratified in the 10-Group Classification System groups 1-5

Table 4 Labor outcomes stratified in the 10-Group Classification System groups 1-5

Table 5 Neonatal outcomes stratified in the 10-Group Classification System groups 1-5

Figure 1 The 10-Group Classification System

Table 1 The 10-Group Classification System for Stavanger University Hospital, Norway, National Maternity Hospital Dublin, Ireland, Slovenian National Perinatal Database, Slovenia 2007-2011

	Relative size of the group (%)			CD rate in each group **(%)**			Contribution made to overall CD rate (%)		
	SUH	NMH	SLO	SUH	NMH	SLO	SUH	NMH	SLO
Overall				(340/9848)	(1980/9250)	(18454/106167)	CD rate 13.6	CD rate 21.4	CD rate 17.4
Group 1	28.9	25.8	33.2	6.5	7.4	10.0	1.9	1.9	3.3
Group 2	9.3	14.8	10.1	25.7	34.9	30.4	2.4	5.3	3.1
Group 2a	8.6	13.8	9.1	19.6	30.2	23.0	1.7	4.2	2.1
Group 2b	0.5	1.0	1.0	100.0	100.0	100.0	0.5	1.0	1.0
Group 3	37.9	29.8	32.3	1.7	1.1	2.4	0.6	0.3	0.8
Group 4	9.7	9.4	8.8	19.5	12.7	14.9	1.9	1.2	1.3
Group 4a	8.4	8.7	7.9	6.4	5.8	4.2	0.5	0.5	0.3
Group 4b	1.3	0.7	1.0	100.0	100.0	100.0	1.3	0.7	1.0
Group 5	5.5	10.2	4.8	46.0	60.9	74.7	2.5	6.2	3.6
Group 6	1.8	2.4	2.3	79.4	93.2	82.6	1.5	2.2	1.9
Group 7	1.0	1.4	1.1	66.7	85.0	71.7	0.6	1.2	0.8
Group 8	1.7	2.2	1.8	40.8	64.9	54.2	0.7	1.4	1.0
Group 9	0.2	0.4	0.6	100.0	100	92.8	0.2	0.4	0.6
Group 10	4.0	3.7	4.9	31.9	37.6	22.1	1.3	1.4	1.1

SUH, Stavanger University Hospital 2010-2011; NMH, National Maternity Hospital 2011; SLO, Slovenian National Perinatal Database 2007-2011

Table 2: Maternal characteristics stratified in the 10-Group Classification System groups 1-5

	Body mass index > 30 %			Maternal age > 35 years %		
	SUH	NMH	SLO	SUH	NMH	SLO
Group 1	5.3	8.1	5.1	5.2	16.7	6.3
Group 2a	10.3	12.7	11.0	10.7	25.4	8.1
Group 2b	9.8	11.2	11.6	21.7	46.7	23.4
Group 3	6.1	11.4	8.2	18.5	37.3	20.5
Group 4a	12.6	16.1	14.9	23.0	45.9	23.7
Group 4b	16.7	14.3	16.6	32.8	57.1	27.8
Group 5	11.6	19.1	14.8	26.7	46.2	23.8

SUH, Stavanger University Hospital 2010-2011; NMH, National Maternity Hospital 2011; SLO, Slovenian National Perinatal Database 2007-2011

Table 3 Labor outcomes stratified in the 10-Group Classification System groups 1-5

	Episiotomy %			Obstetric anal sphincter injuries %			Duration of labor > 12 hours %			Operative vaginal delivery %		
	SUH	NMH	SLO	SUH	NMH	SLO	SUH	NMH	SLO	SUH	NMH	SLO
Group 1	35.8	56.8	50.9	2.4	2.5	0.4	11.3	2.8	1.2	23.7	24.6	5.9
Group 2a	40.6	46.1	45.8	3.7	2.2	0.4	9.9	5.8	1.6	31.9	23.4	7.2
Group 2b	-	-	-	-	-	-	-	-	-	-	-	-
Group 3	7.3	8.8	20.4	0.6	1.0	0.2	2.5	0.2	0.1	3.5	2.5	0.7
Group 4a	11.8	12.2	21.8	0.6	0.6	0.2	3.4	0.4	0.2	6.7	4.9	1.3
Group 4b	-	-	-	-	-	-	-	-	-	-	-	-
Group 5	17.9	18.7	12.1	2.4	0.6	0.1	10.1	0.1	0.2	13.8	8.3	1.7

SUH, Stavanger University Hospital 2010-2011; NMH, National Maternity Hospital 2011; SLO, Slovenian National Perinatal Database 2007-2011

-; not applicable

Table 4 Labor outcomes stratified in the 10-Groups Classification System groups 1-5

	Acceleration with Oxytocin %			Epidural in labor %			Postpartum hemorrhage > 1000 milliliters %			Transfusions %		
	SUH	NMH	SLO	SUH	NMH	SLO	SUH	NMH	SLO	SUH	NMH	SLO
Group 1	33.2	53.2	69.1	43.7	73.7	4.2	4.5	1.0	x	2.6	1.5	0.2
Group 2a	68.3	69.0	79.4	71.8	76.1	5.3	9.9	3.1	x	2.2	3.1	0.2
Group 2b	-	-	-	-	-	-	17.6	1.1	x	2.0	x	0.4
Group 3	6.7	4.0	43.5	19.2	34.9	1.2	2.5	0.5	x	2.8	0.7	0.1
Group 4a	46.9	25.0	68.5	44.7	48.2	2.6	4.1	1.1	x	3.0	1.0	0.3
Group 4b	-	-	-	-	-	-	5.6	4.8	x	1.6	x	0.6
Group 5	12.7	9.0	23.0	39.8	31.7	1.5	5.7	1.6	x	1.8	2.0	0.2

SUH, Stavanger University Hospital 2010-2011; NMH, National Maternity Hospital 2011; SLO, Slovenian National Perinatal Database 2007-2011

-; not applicable

X; missing data

Table 5 Neonatal outcomes stratified in the 10-Group Classification System groups 1-5

	Apgar score <7 at 5 min %			Umbilical cord pH<7.0 %			Antepartum death ‰			Hypoxic-ischemic encephalopathy ‰			Perinatal death ‰		
	SUH	NMH	SLO	SUH	NMH	SLO	SUH	NMH	SLO	SUH	NMH	SLO	SUH	NMH	SLO
Group 1	0.9	1.1	0.4	0.6	0.5	x	0.7	0	0.5	1.1	3.4	0.8	1.1	0	0.7
Group 2a	2.5	1.6	0.8	0.5	0.3	x	2.4	3.1	3.0	1.1	4.3	1.4	2.4	3.9	3.2
Group 2b	0	x	0.7	0	x	x	0	0	0.9	0	0.1	1.6	0	0	1.9
Group 3	0.4	0.3	0.1	0.2	0	x	0.5	0.4	0.5	0.5	0.4	0.3	0.5	0.4	0.6
Group 4a	0.2	0.9	0.3	0.4	0.9	x	2.4	1.2	3.6	0	0	0.5	2.4	2.3	3.9
Group 4b	0	x	0.8	0	x	x	7.5	0	1.0	0	0.3	0.7	7.5	0	0.1
Group 5	1.3	0.2	0.6	0	0.4	x	5.5	0	0.8	1.8	0	0.6	5.5	0	1.0

SUH, Stavanger University Hospital 2010-2011; NMH, National Maternity Hospital 2011; SLO, Slovenian National Perinatal Database 2007-2011
X; missing data

Figure 1 The 10-Group Classification System

Group	Description
1	Nulliparous, single cephalic, ≥37 weeks, spontaneous labor
2a	Nulliparous, single cephalic, ≥37 weeks, induced labor
2b	Nulliparous, single cephalic, ≥37 weeks, cesarean before labor
3	Multiparous (excluding previous cesareans), single cephalic, ≥37 weeks, spontaneous labor
4a	Multiparous (excluding previous cesareans), single cephalic, ≥37 weeks, induced labor
4b	Multiparous (excluding previous cesareans), single cephalic, ≥37 weeks, cesarean before labor
5	Previous cesarean, single cephalic ≥37 weeks
6	All nulliparous breeches
7	All multiparous breeches (including previous cesareans)
8	All multiple pregnancies (including previous cesareans)
9	All abnormal lies (including previous cesareans)
10	All single cephalic, ≤36 weeks (including previous cesareans)

Paper III

AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

Judicious use of oxytocin augmentation for the management of prolonged labor

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Key words
Oxytocin augmentation, cesarean section, Ten group classification system, prolonged labor, estimated postpartum hemorrhage

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Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

Introduction. A protocol including judicious use of oxytocin augmentation was investigated to determine whether it would change how oxytocin was used and eventually influence labor and fetal outcomes. *Material and methods.* The population of this cohort study comprised 20 227 delivering women with singleton pregnancies ≥37 weeks, cephalic presentation, spontaneous or induced onset of labor, without previous cesarean section. Women delivering from 2009 to 2013 at Stavanger University Hospital, Norway, were included. Data were collected prospectively. Before implementing the protocol in 2010, oxytocin augmentation was used if progression of labor was perceived as slow. After implementation, oxytocin could only be started when the cervical dilation had crossed the 4-h action line in the partograph. *Results.* The overall use of oxytocin augmentation was significantly reduced from 34.9% to 23.1% ($p < 0.01$). The overall frequency of emergency cesarean sections decreased from 6.9% to 5.3% ($p < 0.05$) and the frequency of emergency cesarean sections performed due to fetal distress was reduced from 3.2% to 2.0% ($p = 0.01$). The rate of women with duration of labor over 12 h increased from 4.4% to 8.5% ($p < 0.01$) and more women experienced severe estimated postpartum hemorrhage (2.6% vs. 3.7%; $p = 0.01$). The frequency of children with pH <7.1 in the umbilical artery was reduced from 4.7% to 3.2% ($p < 0.01$). *Conclusions.* The frequency of emergency cesarean section was reduced after implementing judicious use of oxytocin augmentation. Our findings may be of interest in the ongoing discussion of how the balanced use of oxytocin for labor augmentation can best be achieved.

Abbreviations: BMI, body mass index; CS, cesarean section; TGCS, Ten group classification system; WHO, World Health Organization.

Introduction

Oxytocin augmentation has an important role in the management of labor (1). Wide variations in its use between countries and hospitals may reflect the lack of structured guidelines (2–6). Labor augmentation with oxytocin is often administered without a clinical indication and unstructured use is common (7,8). Increased uterine activity may cause fetal distress and intense surveillance is needed in laboring women stimulated with oxytocin (9,10). Incautious use of oxytocin is commonly cited in cases of obstetric malpractice and illustrates the need for further exploration (8,9,11).

Key Message

Implementation of a protocol of judicious use of oxytocin was associated with lower rates of emergency cesarean sections.

A definition of prolonged labor and explicit indications for oxytocin augmentation are warranted (1,7,12). Ideally, labor management should follow clear guidelines that are structured in an easy-to-use system (1,13). The World Health Organization (WHO) and the National Institute for Health and Clinical Excellence (NICE) recommend an active phase partograph with a 4-h action line for monitoring the progress of labor (14,15). Augmentation with oxytocin prior to confirming delay when the cervical dilation crosses the 4-h action line in labor is not recommended (14); however, the level of evidence for the recommendations is low.

The Ten group classification system (TGCS) differentiates women into 10 prospective, clinically relevant groups (13). Originally the system was designed to study cesarean section (CS) rates, but wider use is easy to implement and the differentiation also strengthens data quality when assessing other obstetrical outcomes (13,16).

To guide the use of oxytocin augmentation in our labor ward, a strict protocol was implemented using the WHO partograph. Prolonged labor was defined and augmentation with oxytocin indicated only when the cervical dilation crossed the 4-h action line. The aim of this study was to investigate whether judicious use of oxytocin augmentation would change how it was used and how it might influence labor and fetal outcomes.

Material and methods

Stavanger University Hospital has the only delivery unit in a geographical region that includes a population of 320 000 people. Information related to pregnancies and deliveries was collected prospectively and recorded in an electronic birth journal (Natus). The birth journal consists of structured variables and is continuously maintained for data entry and quality control. The study period was from January 2009 to December 2013. The study was approved by the regional ethics committee in western Norway (REK 2014/1912).

The main outcome was the frequency of emergency CS. Secondary outcomes were use of oxytocin augmentation, emergency CS due to fetal distress or dystocia, operative vaginal delivery, sphincter rupture, estimated postpartum hemorrhage >1000 mL, duration of labor >12 h, Apgar score <7 at 5 min, umbilical cord pH <7.00, and umbilical cord pH <7.10.

The study population comprised all women with singleton, term deliveries and cephalic presentations with a spontaneous onset of labor or induced labor in nulliparous and parous women without a previous CS (Figure 1; TGCS groups 1, 2a, 3, and 4a). CS was defined as a pre-labor or emergency procedure (13). Maternal body mass index (BMI) was based on pre-pregnancy weight.

	Excerpt of the ten group classification system
Group 1	Nulliparous, single, cephalic presentation, ≥37 weeks, in spontaneous labor
Group 2a	Nulliparous, single, cephalic presentation, ≥37 weeks, induced before labor
Group 3	Multiparous (excluding previous cesarean section), single, cephalic presentation, ≥37 weeks, in spontaneous labor
Group 4a	Multiparous (excluding previous cesarean section), single, cephalic presentation, ≥37 weeks, induced before labor

Figure 1. Description of the study population comprising the Ten group classification system, groups 1, 2a, 3 and 4a.

Estimated date of delivery was determined by a second trimester ultrasound scan (eSnurra) (17) or from menstrual data when no ultrasound examination was performed.

Start of labor was determined when the woman experienced regular and painful contractions. In 2009, the WHO partograph was introduced for routine use and start of the active phase of labor was defined as when the woman had regular contractions and the cervix was dilated 4 cm and effaced. A clear definition of prolonged labor did not exist in the Department and the midwives and obstetricians individually used oxytocin for augmentation if they felt that labor was progressing slowly. The new protocol with judicious use of oxytocin was implemented 1 January 2010. Prolonged labor was defined when the cervical dilation crossed the 4-h action line, and only then could augmentation with oxytocin be administered. The protocol did not contain new guidelines for the use of oxytocin in the second stage of labor.

In labors with a spontaneous onset in nulliparous and parous women (groups 1 and 3), oxytocin augmentation was defined as oxytocin used to stimulate contractions after prolonged labor during the first stage of labor. Routine amniotomy was not performed during the active phase of labor, but always prior to oxytocin augmentation. The second stage of labor was defined as when the cervix was fully dilated, and the active phase of the second stage was defined as when maternal effort was added. An operative vaginal delivery was considered if the active second stage of labor exceeded 60 min. Malmström metal cup was the preferred device for operative vaginal delivery. Duration of labor was defined from the start of the active phase of labor until delivery.

Misoprostol 25 μg vaginally every 4 h up to a maximum dose of 100 μg/day over 2 days was used as an induction agent in women with Bishop score <6. In women with Bishop score ≥6, amniotomy was performed and oxytocin added if contractions were not established after 1–3 h. Oxytocin was never used as a primary induction agent. The use of oxytocin in induced labors of

nulliparous and parous women (groups 2a and 4a) included use of oxytocin to stimulate contractions before start of the active phase and/or after prolonged labor was defined in the first stage of labor.

An intravenous infusion of 5 IU (0.01 mg) oxytocin in 500 mL saline was administered. The infusion rate started at 6 mIU/min (30 mL/h), with a dose increment of 3 mIU/min (15 mL/h) every 15 min to a maximum of 40 mIU/min (180 mL/h) until progression in labor or regular contractions at a rate of three to five every 10 min was achieved. A combination of low-dose ropivicaine/fentanyl was used for epidural analgesia. Routinely, active management of the third stage of labor included intramuscular administration of 5 IU of oxytocin. Blood loss was visually estimated, and blood-soaked compresses were collected and measured when possible. Estimated blood loss exceeding 1000 mL was defined as severe postpartum hemorrhage. Sphincter rupture was defined as partial or complete tears of the anal sphincter muscles (grade 3–4 perineal tears).

The linear-by-linear association trend test was used in categorical data analyses, and continuous variables were compared using one-way analysis of variance with Bonferroni correction. Data were analyzed with the statistical software package SPSS statistics version 22.0 (IBM SPSS, Armonk, NY, USA) and p-values <0.05 were considered significant.

Results

In total, 24 134 women delivered at the hospital during the study period. The overall CS rate was 13.8%, of which 8.8% were emergency CS and 5.0% pre-labor CS. The study population comprised 20 227 (83.8%) deliveries: 6897 (28.6%) were nulliparous with spontaneous onset (group 1); 2144 (8.9%) were nulliparous induced (group 2a); 8967 (37.2%) were parous with spontaneous onset (group 3); and 2219 (9.2%) were parous induced (group 4a). The characteristics of the study population are presented in Table 1.

The mean maternal age was higher in 2013 than in 2009 or 2011 ($p < 0.01$) and the mean gestational age was younger in 2012 and 2013 than in 2009, 2010 or 2011 ($p < 0.05$). The frequency of induced labor increased significantly over this period. We did not observe any changes in maternal BMI or infant birthweight.

Changes in the use of oxytocin augmentation during the study period are presented in Table 2 for the total study population and subgroups. The use of oxytocin augmentation was significantly reduced in all groups over the study period.

The overall frequency of emergency CS declined from 6.9% to 5.3% ($p < 0.05$) and emergency CS performed due to fetal distress from 3.2% to 2.0% ($p = 0.01$). In subgroup analyses, the rate of emergency CS among nulliparous women with induced labor (group 2a) declined from 26.5% to 15.7% ($p < 0.01$). Furthermore, there was a trend toward a reduced frequency of CS performed due to fetal distress in all groups, which reached statistical significance among nulliparous women only (groups 1 and 2a). The frequency of CS due to prolonged labor did not change.

Table 2. Use of oxytocin in the study population of singleton, term deliveries and cephalic presentation in each of the four subgroups (Ten group classification system groups 1, 2a, 3 and 4a) from 2009 to 2013.

	%					
Years	2009	2010	2011	2012	2013	*p*-value[a]
Total study population	35.5	25.9	26.5	23.6	23.6	<0.01
Nulliparous, spontaneous (Group 1)	45.9	30.7	35.8	31.2	34.4	<0.01
Nulliparous, induced (Group 2a)	79.1	73.7	64.1	59.0	55.2	<0.01
Parous, spontaneous (Group 3)	12.3	5.8	7.6	5.6	6.7	<0.01
Parous, induced (Group 4a)	62.3	57.6	37.6	34.5	24.0	<0.01

[a]Linear trend analyses.

Table 1. Characteristics of the study population (n = 20 227) from 2009 to 2013.

Years	2009 (n = 3926)	2010 (n = 4144)	2011 (n = 4113)	2012 (n = 4091)	2013 (n = 3953)	*p*-value
Nulliparous women (%)	46.1	44.7	45.0	43.8	44.0	0.04[a]
Maternal age (years)	29.6	29.8	29.6	29.9	30.0	<0.01[b]
Gestational age (days)	282.0	281. 9	281.5	281.4	281.3	<0.01[b]
BMI (kg/m^2)	23.9	24.0	23.8	23.8	23.7	0.07[b]
Infant birthweight (g)	3567	3572	3569	3557	3578	0.30[b]
Induction of labor (%)	18.6	18.9	21.4	24.0	24.9	<0.01[a]

[a]Linear trend analyses.
[b]One-way ANOVA.

The frequency of sphincter rupture decreased among induced nulliparous women (group 2a) from 5.6% to 1.2% ($p < 0.01$). The frequency of women spending more than 12 h in active labor increased from 4.4 to 8.5% ($p < 0.01$). In subgroup analyses, the increase was statistically significant among nulliparous women (groups 1 and 2a). An increase in estimated severe postpartum hemorrhage from 2.6 to 3.7% ($p = 0.01$) was observed in the overall study population. Among women with a vaginal delivery, the frequencies of estimated severe postpartum hemorrhage were 2.2, 2.7, 2.6, 2.8, and 3.2% during each of the 5 years, respectively ($p = 0.1$). The increase in mean estimated hemorrhage was not significant: 354, 352, 352, 359 and 371 mL, respectively. Among women with a CS, the respective frequencies of estimated severe postpartum hemorrhage each year were 8.9, 11.8, 11.4, 9.4, and 13.2% ($p = 0.4$). In women with a CS, the increase in mean estimated hemorrhage was not significant: 625, 651, 630, 621 and 655 mL during each year, respectively. Blood transfusion rates among all deliveries in the delivery unit decreased by 3.4, 3.2, 2.1, 2.4, and 2.7% ($p < 0.01$), respectively, during each year of the study.

Blood samples from the umbilical cord were collected in 60.4, 57.9, 67.8, 65.8 and 73.6% of the study population from 2009 to 2013, respectively. The frequency of infants with pH <7.1 in the umbilical artery was reduced from 4.7% to 3.2% ($p < 0.01$), but the reduction in infants with pH <7.0 did not reach statistical significance ($p = 0.10$). There was a trend toward a reduced frequency of children with umbilical artery pH <7.1 in the pooled group that reached statistical significance in spontaneous, nulliparous women (group 1; $p < 0.05$). Changes in labor and fetal outcomes in the total study population are presented in Table 3. Subgroup analyses are available in Tables S1 and S2.

Table 3. Labor and fetal outcomes in the study population from 2009 to 2013.

	%					
Years	2009	2010	2011	2012	2013	*p*-value[a]
Emergency CS	6.9	5.9	6.0	6.7	5.3	<0.05
CS due to fetal distress	3.2	2.7	2.8	2.4	2.0	0.01
CS due to dystocia	2.2	1.8	2.1	2.5	1.7	0.75
Epidural analgesia	34.3	34.8	36.5	35.2	36.4	0.06
Duration of labor >12 h	4.4	5.8	7.0	8.0	8.5	<0.01
Operative vaginal delivery	14.8	14.0	13.5	14.0	15.5	0.42
Sphincter rupture	2.3	1.4	1.7	2.0	1.5	0.10
PPH >1000 mL	2.6	3.2	3.2	3.3	3.7	0.01
Apgar score after 5 min <7	0.8	0.7	0.8	1.0	1.0	0.17
pH umbilical cord <7.00	0.7	0.8	0.5	0.6	0.4	0.10
pH umbilical cord <7.10	4.7	4.8	4.2	3.5	3.2	<0.01

Duration of labor: from start of active phase of labor until delivery.
CS, cesarean section; PPH, estimated postpartum hemorrhage.
[a]Linear trend analyses.

Discussion

The frequency of labors augmented with oxytocin decreased significantly after implementation of judicious use of oxytocin in the obstetrical department. This change was associated with a reduced overall emergency CS rate and fewer CSs performed due to fetal distress.

Oxytocin is a drug with potential side effects and recent statements have focused on stricter protocols, recommending a medical indication for its use (8,18,19). The increased use of oxytocin is not only due to the rise in induced labor; rates above 50% among nulliparous women in spontaneous labor are reported (7,18). Several delivery units have tried to implement active management of labor with the intention of stopping the observed increase in CS rates and reducing the rate of prolonged labors (20). Importantly, active management of labor includes several elements in addition to active use of oxytocin: one-to-one care during the active stage of labor, routine amniotomy, and restricting the duration of the active stage of labor to 12 h (20). The rising and, at times, incautious use of oxytocin may be caused by too much focus on implementing the active use of oxytocin in obstetrical departments while overlooking the other aspects of active management of labor. Our finding that reduced use of oxytocin augmentation was not associated with an increase in the CS rate differs from earlier findings (2,21,22). This may reflect the complexity of designing and implementing a uniform guideline for the use of oxytocin augmentation during labor (1,3,14).

Changes in both the characteristics of the population, such as higher BMI and older maternal age, and obstetrical practice, such as more use of epidural and more induction of labor, may influence the risk of prolonged labor and CS (23). Our observed decrease in gestational age is probably associated with increased induction rates. More liberal use of induction in high risk women and more women with post-term pregnancies were induced because these guidelines changed during the study period. This implies a change over time in the population of the four TGCS groups studied, which might have biased our results. The role of oxytocin in the management of labor is essential. Still, after 40 years of administration of the drug, its optimal timing and use is yet to be revealed (24).

The importance of precise definitions of labor progression should be stressed (1). Prolonged labor depends on when the start of the active phase of labor is determined. By choosing the definition suggested by WHO, we proceeded to implement a common indication for the use of oxytocin and, subsequently, oxytocin augmentation was administered only when indicated. In advance, we arranged audits for all staff discussing the pros and cons, realizing that implementation of new routines in daily practice is challenging (25). Efforts were made before the protocol was accepted and approved. One midwife was responsible for the follow up of routines and the use of oxytocin was monitored monthly for quality assurance. A reduction in the frequency of women with stimulated labors was observed beginning in the first years after introduction of the new routines. The consistent use of the WHO partograph might have influenced the overall CS rate but would not explain the decreasing trend of CSs performed due to fetal distress. The declining trend in newborns with low umbilical artery pH was not observed until 2012 and 2013. This may be due to an increased vigilance concerning the maximum dose of oxytocin used and reduced overall use of oxytocin, particularly in the second stage of labor (26).

Previous studies have documented that oxytocin augmentation is associated with a shorter duration of labor, which is in accordance with our findings (5,21,24). Childbirth satisfaction is an important health outcome and it may be desirable to avoid long labors (27). However, a systematic review on women's satisfaction with childbirth did not find labor length to be an influencing factor (28). Another study concluded that early oxytocin augmentation for slow labor progression did not appear to be more beneficial than expectant management regarding women's perceptions of childbirth (29). To address this issue further, knowledge of the women′s experiences of childbirth before and after our study would have been of major interest and should be a focus of new studies. Long duration of labor and lower maximal dosing of oxytocin are both associated with an increased risk of postpartum hemorrhage (30). These findings are consistent with our observations and need further attention. However, in subgroup analyses the rate of prolonged labors increased, the difference being significant only among nulliparous women (groups 1 and 2a). The rates of estimated severe postpartum hemorrhage increased significantly only among parous woman (groups 3 and 4a) (data shown in Tables S1 and S2) and the overall transfusion rates in the delivery unit decreased.

Our study design has limitations. We cannot prove causality between oxytocin augmentation and labor outcomes in an observational study. In addition, the use of oxytocin was only recorded as a dichotomized variable; the duration of the augmentation or the maximum doses used were not available for analyses. The use of oxytocin in induced labor (groups 2a and 4a) includes both oxytocin used to stimulate contractions before the start of the active phase and/or after prolonged labor in the first stage of labor. The differentiation between oxytocin used as an induction agent or as an augmentation agent is difficult. Still, the overall decrease in the use of oxytocin was significant in women with induced labor, and we believe that this is a valuable observation. Prolonged labors may affect the frequency of chorioamnionitis, but this information was not recorded. Visual estimates of blood loss are crude, and we realize the inaccuracy of this method. Unfortunately, due to different databases, the blood transfusion rates were not available for subgroup presentation in the TGCS. Arterial blood sampling from the umbilical cord was performed in 67% of the delivering women, with an increased frequency later in the study period. This may have biased our results. Our findings should be generalized with caution because the data were collected from only one hospital. However, the data were checked regularly for quality control. The major strengths of the study were the high number of patients included and the differentiation of the population into subgroups according to the TGCS classification. The hospital serves a nonselected population and this strengthens the credibility of our observations. Continuous monitoring of the new procedure resulted in successful implementation. In this way, we introduced a clearly defined indication for the use of oxytocin augmentation.

In summary, implementation of a protocol clearly defining the start of active labor, prolonged labor, and indications for oxytocin use, was associated with decreased use of oxytocin augmentation. The rate of emergency CS and CS performed due to fetal distress decreased. More women experienced prolonged labor and estimated severe postpartum hemorrhage. Our findings may be of interest in the ongoing discussion of how balanced use of oxytocin for labor augmentation can best be achieved.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Use of oxytocin (%) and labor characteristics in singleton, term deliveries and cephalic presentation among nulliparous women with spontaneous onset of labor (n = 6897; group 1) and induced labor (n = 2144; group 2a) from 2009 to 2013.

Table S2. Use of oxytocin (%) and labor characteristics in singleton, term deliveries and cephalic presentation among parous women with spontaneous onset of labor group 3 (n = 8967; group 3) and induced labor (n = 2199; group 4a) from 2009 to 2013.

Table S1 Use of oxytocin (%) and labor characteristics in singleton, term deliveries and cephalic presentation among nulliparous women with spontaneous onset of labor (N= 6,897; group 1) and induced labor (N=2,144; group 2a) from 2009 to 2013.

Years		2009 %	2010 %	2011 %	2012 %	2013 %	p-value*
Emergency CS							
	Spontaneus	7.5	7.1	7.1	8.3	5.8	0.36
	Induced	26.5	21.3	18.2	20.6	15.7	<0.01
CS due to fetal distress							
	Spontaneus	3.7	2.9	2.9	2.8	2.2	0.02
	Induced	11.7	11.6	8.0	7.2	6.2	<0.01
CS due to dystocia							
	Spontaneus	2.7	2.7	3.1	3.4	2.2	0.95
	Induced	9.8	6.1	6.9	8.3	6.0	0.21
Epidural analgesia							
	Spontaneus	41.9	44.9	42.6	41.7	44.4	0.71
	Induced	69.0	72.9	70.7	66.4	72.1	0.98
Duration of labor >12 hours							
	Spontaneus	7.5	10.7	11.9	14.2	14.9	<0.01
	Induced	6.4	9.1	10.6	15.0	18.3	<0.01
Operative vaginal delivery							
	Spontaneus	26.0	25.3	22.0	24.2	27.0	0.89
	Induced	31.3	31.1	32.6	27.0	36.2	0.37
Sphincter rupture							
	Spontaneus	3.6	2.3	2.4	3.3	2.9	0.76
	Induced	5.6	2.3	4.9	3.3	1.2	<0.01
PPH >1000 ml							
	Spontaneus	3.3	3.9	3.6	3.1	3.5	0.82
	Induced	3.9	7.8	6.7	5.5	8.7	0.07
Apgar score after 5 min <7							
	Spontaneus	0.8	0.9	0.9	1.3	1.3	0.14
	Induced	2.5	1.5	3.1	2.2	2.7	0.65
pH umbilical cord <7.00							
	Spontaneus	1.0	1.2	0.7	1.0	0.4	0.17
	Induced	0.7	1.0	0.3	0.3	0.5	0.41
pH umbilical cord <7.10							
	Spontaneus	6.9	5.5	4.7	4.8	4.4	0.01
	Induced	6.5	6.7	6.4	4.4	4.8	0.17

CS=cesarean section, PPH=estimated postpartum hemorrhage, Duration of labor=from start of active phase of labor until delivery, *=linear trend analyses

Table S2 Use of oxytocin (%) and labor characteristics in singleton, term deliveries and cephalic presentation among parous women with spontaneous onset of labor group 3 (N = 8,967; group 3) and induced labor (N=2,199; group 4a) from 2009 to 2013.

Years		2009 %	2010 %	2011 %	2012 %	2013 %	p-value*
Emergency CS							
	Spontaneus	2.3	1.9	1.9	2.4	2.2	0.79
	Induced	7.0	5.7	7.2	5.3	4.2	0.08
CS due to fetal distress							
	Spontaneus	1.0	0.7	0.9	0.7	0.8	0.58
	Induced	3.5	2.6	5.1	2.8	1.6	0.13
CS due to dystocia							
	Spontaneus	0.5	0.4	0.4	0.7	0.5	0.59
	Induced	1.1	1.0	1.2	0.9	0.8	0.65
Epidural analgesia							
	Spontaneus	18.7	17.4	21.1	19.4	18.3	0.63
	Induced	44.5	42.9	46.6	44.8	43.3	0.91
Duration of labor >12 hours							
	Spontaneus	1.5	2.1	3.1	2.7	2.3	0.05
	Induced	3.5	2.8	3.9	4.4	3.8	0.47
Operative vaginal delivery							
	Spontaneus	3.8	3.0	4.0	4.4	3.9	0.32
	Induced	7.0	7.5	6.0	8.9	6.8	0.77
Sphincter rupture							
	Spontaneus	0.9	0.8	0.4	1.1	0.8	0.90
	Induced	1.3	0.3	0.9	0.9	0.6	0.59
PPH >1000 ml							
	Spontaneus	1.8	1.8	2.1	2.6	2.0	0.24
	Induced	2.7	2.8	2.8	3.8	5.6	0.01
Apgar score after 5 minutes <7							
	Spontaneus	0.3	0.4	0.4	0.3	0.2	0.56
	Induced	1.3	0.3	0.0	1.5	1.0	0.70
pH umbilical cord <7.00							
	Spontaneus	0.4	0.4	0.4	0.4	0.5	0.93
	Induced	0.7	0.3	0.6	0.2	0.3	0.33
pH umbilical cord <7.10							
	Spontaneus	2.7	3.4	3.5	2.1	2.2	0.13
	Induced	2.2	5.2	3.2	3.4	1.5	0.20

CS=cesarean section, PPH=estimated postpartum hemorrhage, Duration of labor=from start of active phase of labor until delivery, *=linear trend analyses

Figure legends:

Table S1 Use of oxytocin (%) and labor characteristics in singleton, cephalic, term deliveries among nulliparous women with spontaneous onset of labor (N= 6,897; group 1) and induced labor (N=2,144; group 2a) from 2009 to 2013.

Table S2 Use of oxytocin (%) and labor characteristics in singleton, cephalic, term deliveries among parous women with spontaneous onset of labor group 3 (N = 8,967; group 3) and induced labor (N=2,199; group 4a) from 2009 to 2013.

Paper IV

May oxytocin augmentation modify the risk of epidural analgesia for cesarean delivery among nulliparous women in spontaneous labor at term? A case-control study

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Key words: Maternal medicine, Cesarean delivery, maternal age, epidural analgesia, oxytocin augmentation, medical management

Abstract

Objective: Maternal age is an established risk factor for Cesarean delivery (CD), whereas epidural analgesia and oxytocin augmentation may modify this relation. We investigated the effects and interactions of epidural analgesia, oxytocin augmentation and maternal age on CD.

Design: A cross-sectional design analyzed as case-control study.

Setting: National birth registry data from Norway and Denmark.

Participants: 416 386 nulliparous women with spontaneous onset of labor, ≥ 37 weeks of gestation, singleton infants in cephalic presentation during 2000–2011.

Methods: Main exposure was maternal age, whereas epidural analgesia, oxytocin augmentation, birth weight and time-period were explanatory variables. Chi-square test and logistic regression were used to estimate associations and interactions.

Main outcome measure: Cesarean delivery

Results: The CD rate increased consistently with maternal age, both overall and in strata of epidural analgesia and use of oxytocin. We observed strong interactions between maternal age, use of oxytocin and epidural analgesia on the risk of CD. Women with epidural generally had a reduced risk of CD when oxytocin was used compared to when not used. In Norway, this applied to all maternal age groups, but in Denmark only for women ≥ 30 years. Among women without epidural, use of oxytocin was associated with an increased risk of CD in Denmark, while no difference was observed in Norway.

Conclusions: Our results suggest that use of oxytocin in nulliparous women with epidural analgesia are associated with a reduced risk of CD in labors with spontaneous onset, but not in nulliparous women without epidural analgesia.

Strengths of this study

- Large sample size from two national birth registries with 100% completeness of case reporting
- Very low numbers of missing variable information throughout the study
- Consistent reporting of proportions of categories within variables over the study period

Limitations of this study

- Lack of details on oxytocin use (early/late, stage of labor, duration, dosage and discontinuation)

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Conflicts of interest

None of the authors have any conflict of interest

Introduction

Oxytocin augmentation (OA) has been the drug of choice to increase the probability of vaginal delivery in women with labor dystocia (1). Possible adverse effects of the widespread and increasing use of oxytocin should be assessed, as more than half of the nulliparous women in spontaneous labor are medicated due to insufficient progress of labor (2–4).

Changes in maternal risk factors and obstetric practice have contributed to a rising cesarean delivery (CD) rate (5). Maternal age at delivery has increased steadily during the last decades, and the risk of CD increases with maternal age (6). Use of epidural analgesia (EA) has escalated, and its use is associated with longer duration of labor, especially among nulliparous women (7). As OA is more prevalent among women who receive EA (2, 7), oxytocin use may modify the association between EA and CD, despite no difference in CD rates between oxytocin-exposed and non-exposed women in two randomized trials (8).

In a case-control design we aimed to investigate the effects and interactions of EA, oxytocin and maternal age on CD among nulliparous women delivering singleton infants with cephalic presentation at term.

MATERIALS AND METHODS

Our study population comprised nulliparous women with spontaneous onset of labor, singleton pregnancies with cephalic presentation, and ≥ 37 weeks of gestation (ten-group classification system (Robson) group 1) (9), giving birth from 2000 to 2011 in Norway and Denmark.

Variables were harmonized across birth registries in the merged database. Maternal age was defined as the difference in completed years between date of delivery and maternal

date of birth, and categorized into six groups (< 20, 20–24, 25–29, 30–34, 35–39, ≥ 40 years). Parity and previous caesarean delivery were defined as the highest number based on information from the registry (linkage of births to their mothers by the unique national identification numbers) or maternal information provided at first delivery. Gestational age was estimated from ultrasound screening in second trimester, but from 2004 and onwards a first trimester scan for combined risk assessment with age, nuchal translucency and biochemical test was performed in Denmark (10). Lie was classified as longitudinal or transverse and presentation as cephalic or breech. Start of delivery was defined as spontaneous onset of birth, induction or CD. Mode of delivery comprised spontaneous vaginal delivery, instrumental vaginal delivery (vacuum extraction or forceps) or caesarean delivery. Emergency CDs encompassed all CDs not reported as planned. Since 1998, the Medical Birth Registry of Norway (MBRN) has gathered information about mothers and their corresponding pregnancies, deliveries and infants, via check boxes supplemented with free text information on the birth notification form. Use of oxytocin and EA are based on check boxes, and a sample of this information was validated against medical records at reporting hospitals by one of the authors (KK). The validation showed a positive predictive value of OA above 98%. For Denmark, information about pregnancy and delivery, including use of OA and EA during labor, was captured from the Danish National Patient Register. We categorized three-year time periods as 2000–02, 2003–05, 2006–08 and 2009–11. Included in the original database were women who delivered after the 22nd gestational week, or, if gestational age was missing, women who gave birth to infants with a birth weight of 500 grams or more.

Statistical analyses

All analyses were done in Statistical Package for Social Sciences (SPSS) version 21. Chi-square test was used to evaluate linear trends, and logistic regression analysis was used to

estimate odds of CD in relation to maternal age, use of EA and oxytocin, when adjusting for potential confounding factors such as birth weight (> 4000 grams: yes/no) and time-period. We tested interactions using multiplicative models. Age standardization was done by the direct method, using the total and age-specific subpopulations of the entire database as reference populations.

Ethics

This study is part of the Nordic Robson Research Group, where the Regional Committee for Medical and Health Research Ethics, South-East C (REK 2010/3256) assessed the Norwegian participation. The Danish Data Protection Agency governed the Danish participation (reference NOH-2016-006, med I-Suite no. 04548).

RESULTS

The merged database comprised all deliveries from January 1st 2000 to December 31st 2011, totaling to 757 257 and 699 754 deliveries in Denmark and Norway, respectively. The proportion of unclassifiable cases due to missing information on variables comprising the Robson ten group classification system increased slightly from the first to the final study period in Denmark (0.4% to 0.9%) but decreased in Norway (1.8% to 0.7%).

The study population comprised 416 386 women, representing 29.8% (225 678/757 257) of all Danish and 29.1% (203 420/699 754) of all Norwegian women giving birth. The study population decreased from 31.8% to 27.4% of all births in Denmark but was stable at around 29% of all births in Norway throughout the study period.

Table 1 displays characteristics of the study population. Maternal age increased in both countries, but Danish parturients were in general older. EA use increased with maternal

age in both countries. Its use also increased during the period but to a larger degree in Denmark, where the overall use was more prevalent. Oxytocin use also increased consistently with maternal age in both countries, but the age-specific use of oxytocin demonstrated generally larger increases over time in Denmark (Table 1). The overall use of oxytocin was more prevalent in Norway than in Denmark.

Among women without EA, the use of oxytocin decreased during the period from 36.4% to 30.8% and 32.1% to 30.2% in Denmark and Norway, respectively (table 2). Among women with EA, oxytocin use was relatively stable from 72% to 75% in Denmark but increased moderately from 62% to 69% in Norway. Oxytocin use increased consistently with rising maternal ages in both countries (Table 2).

In the study period the age-standardized overall CD rate increased from 9.4% to 10.5% in Denmark and from 8.0% to 9.3% in Norway (Table 3). The CD rate in both countries increased consistently with maternal age in strata of EA use and in strata of oxytocin use in all time periods. The increase by age was more apparent when EA was used (Figure 1). In both countries the overall CD rate among women with EA and augmentation with oxytocin was significantly higher than among those exposed to neither EA nor oxytocin (data not shown). Among women with EA, the risk of CD decreased during the study period in Denmark but increased in Norway (Table 3). This fact, in addition to country-specific differences in prevalence of oxytocin use via EA, implies country-specific interactions, from exposure of EA and oxytocin on our primary outcome variable, CD. As a consequence, country-specific stratified analyses were performed.

In both countries, significant interactions between maternal age and use of EA, and between maternal age and use of oxytocin, on CD risk were found. Accordingly, we created a new variable comprising age, use of EA and use of oxytocin. We defined women aged 20–24

years with no use of EA nor oxytocin as the common reference group, as we considered this subset to be the women with lowest risk of CD. For all age groups in Norway, women who received EA and oxytocin had significantly lower CD rates than those who received EA but not oxytocin, while in Denmark this association held for women 30 years or older (Figure 2). For women in Norway who did not receive EA, the risk of CD did not differ significantly by OA in any age groups except for those ≥ 40 years, where women receiving OA had a lower risk of CD compared to women without OA. In Denmark, on the other hand, women who did not receive EA with OA had higher CD risks than women without OA, except in the oldest age group (≥ 40 years), where there was no difference.

In predicting CD among the Norwegian study population, there was minimal confounding of time period on the stratified odds ratios of maternal age, EA and OA (Figure 2). In Denmark, time period had a confounding effect on CD, as EA increased over the time periods, and oxytocin use changed differently by age and use of EA (data not shown).

The overall prevalence of fetal birth weight ≥ 4000 grams decreased during the study period, from 16.1% to 12.7% in Denmark and from 17.0% to 12.4% in Norway. These changes were consistent across maternal age groups in both countries. Among women delivering a fetus with birth weight ≥ 4000 grams, the CD rate increased from 15.8% to 19.5% in Denmark and from 12.6% to 16.2% in Norway during the same period. Furthermore, the CD rate among these women increased with maternal age in all time periods in both countries (data not shown). In both countries, however, birth weight had no confounding effect on the association between oxytocin, maternal age and EA and their effects on CD.

Discussion

The overall use of oxytocin among nulliparous women with spontaneous onset of birth increased and reached 46% in Denmark and 48% in Norway. Stratified by maternal age, use

of oxytocin versus no oxytocin use was associated with a reduced risk of CD among women with epidural analgesia in both countries. In Norway this applied to all maternal age groups, but in Denmark only to women 30 years or older. Among women without EA, oxytocin use showed minimal impact on the risk of CD in Norway, while its use was associated with an increased risk of CD in women less than 40 years old in Denmark.

This study applies a stratified dynamic approach, which reflects the use of EA and use of oxytocin by maternal age in daily clinical obstetric practice. We observed that CD rates increased with maternal age in both Denmark and Norway. However, the use of EA and OA seemed to modify the effects of maternal age on risk of CD in both countries. In Norway use of oxytocin and EA were consistent across the maternal age groups and time periods. In Denmark there was an increase in EA use from the first to the second time period, and oxytocin use varied more by maternal age and EA use, compared to Norway. This may explain the observed interaction between time period and epidural/oxytocin use for Danish data.

We have not found other studies analyzing CD rates stratified by maternal age, use of EA and use of oxytocin. A Cochrane review with data from 27 randomized controlled trials assessed the effect of EA versus non-EA on women in labor, and discovered no difference in the overall risk of CD (risk ratio (RR) 1.10 (95% CI: 0.97–1.25)) (13). The timing of EA, early or late in the first stage of labor, did not influence the risk of CD (RR 1.02 (95% CI: 0.96–1.08), from 9 trials) (14). Use of EA increases the use of oxytocin (13), but use of oxytocin among women with EA is not yet found to reduce the risk of CD (RR 0.95 (95% CI: 0.42–2.12), from 2 trials) (8). A Cochrane review on early augmentation versus expectant management in prevention of delayed labor found that early use of oxytocin was associated with a modest reduction in the risk of CD (RR 0.87 (95% CI: 0.77–0.99), from 11 trials) (15). There was, however, large heterogeneity related to use of EA and oxytocin between the

included studies, an issue the authors did not explore in the discussion (15). Another Cochrane review with data from six trials revealed that active management of labor (defined as strict diagnosis of labor, routine amniotomy, oxytocin for slow progress and one-to-one support in labor) gave a modest, but significant, reduced risk of CD (RR 0.77, 95% (CI: 0.63–0.94)) (16). The authors stated that there were no differences between the groups in use of EA, but this does not rule out a possible effect modification of EA through other variables, as shown in the present study. Furthermore, the authors of this review did not discuss the large variations in oxytocin use in relation to diverging CD rates (16), nor did they consider oxytocin as a possible effect modifier of maternal age and EA, as observed in the present study. In addition, the fact that findings from an observational study diverge from several randomized controlled trials (RCTs) may to some extent be explained by the presence of residual confounding in the observational studies and lack of external validity in RCT studies. Kotaska et al. (17) demonstrated that use of high oxytocin doses compared to low oxytocin doses among women with EA reduces the risk of CD, whereas our associations are related to use or no use of oxytocin.

The effect of maternal age stratified by use of EA and oxytocin has received little attention in the literature. Small sample sizes in most randomized clinical trials may explain this concern. However, pooling of data from randomized trials, as included in the various Cochrane reviews cited above (8, 13–16), will probably still yield an insufficient sample size for analyses, in contrast to studies utilizing large sample sizes from birth registry data.

Other confounders that might have an independent effect on CD – e.g. maternal body mass index and length/arrest of labor were neither available for analysis. However, medicated with oxytocin are women with long duration of labor and/or arrest of labor. Indications for EA and use of oxytocin are occurring before provision of the actual medications. Thus, EA and use of oxytocin capture the indications within the variables themselves (co-linearity).

Therefore, we do not consider lack of this particular information as confounders for the reported associations on CD.

Furthermore, we consider the lack of details on oxytocin use as a major weakness. We have no information on the administration of oxytocin (early/late, stage of labor), duration, dosage or discontinuation. Using a stratified approach, we acknowledge that false assumptions may be created, and causality cannot be claimed in an observational study.

The strength of our study is the large sample size, based on birth registries with long traditions of collecting structured information and with low numbers of missing information, and high consistency of the variables used across the study's timeframe (Table 1). Because of the strong associations observed in our study, we argue that our findings might be plausible and add knowledge on the use of oxytocin on a population level.

In conclusion, we have demonstrated consistent data suggesting that use of oxytocin in women with epidural analgesia might be associated with a reduced risk of CD, especially among the older maternal age groups among nulliparous women with spontaneous onset of labor. This possible effect modifying role of oxytocin use in women with EA on CD needs further investigations.

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Table 1. Study population characteristics, distribution maternal age (in years), and age-specific use of epidural analgesia and oxytocin (%) in Denmark and Norway, 2000-2011

	Denmark N=225 678				**Norway** N=203 420			
Time period	**2000-02** N=61 401	**2003-05** N=57 172	**2006-08** N=57 343	**2009-11** N=49 762	**2000-02** N=49 515	**2003-05** N=49 071	**2006-08** N=51 718	**2009-11** N=53 116
	%	%	%	%	%	%	%	%
Maternal age								
<20	3.5	3.1	3.4	3.4	6.4	5.2	5.5	5.2
20-24	20.8	17.7	18.1	19.1	26.9	25.4	25.5	25.8
25-29	45.6	44.8	42.2	40.7	40.6	38.7	38.0	38.1
30-34	23.6	27.2	28.1	27.3	20.6	24.0	23.7	23.4
35-39	5.7	6.4	7.1	8.3	4.8	6.1	6.5	6.7
≥ 40	0.7	0.8	1.1	1.2	0.6	0.7	0.9	0.9
Use of epidural by maternal age								
<20	8.0	25.6	32.5	37.3	38.5	41.2	45.8	46.4
20-24	8.7	22.2	33.1	36.5	36.9	38.9	43.3	44.6
25-29	8.4	20.7	31.6	34.2	37.1	39.0	41.9	43.5
30-34	10.8	23.2	35.5	37.5	40.6	42.7	46.3	47.8
35-39	14.5	27.1	41.2	40.6	43.9	44.0	49.7	52.6
≥ 40	15.2	32.4	43.3	44.3	44.6	51.2	48.9	53.0
In total*	10.2	23.1	34.8	36.9	39.4	41.2	44.9	46.6
Use of oxytocin by maternal age								
<20	30.0	36.9	34.1	32.0	38.1	38.6	42.6	38.9
20-24	34.9	39.9	41.4	40.5	39.8	43.2	46.0	43.0
25-29	38.8	43.9	46.0	44.8	44.3	47.3	48.4	47.5
30-34	44.1	48.6	51.1	49.5	46.3	51.6	54.9	53.0
35-39	51.6	55.1	56.5	55.4	51.4	54.5	59.0	58.4
≥ 40	50.0	59.4	61.5	58.6	54.1	55.7	55.6	56.7
In total*	41.8	46.6	48.5	47.7	45.4	49.1	51.0	50.1

*Age-standardized

Table 2: Study-population characteristics by use of epidural analgesia (No/Yes) and use of oxytocin augmentation (Yes) stratified by maternal age (in years) and time-period.

		Denmark				Norway			
Time-period		**2000-02**	**2003-05**	**2006-08**	**2009-11**	**2000-02**	**2003-05**	**2006-08**	**2009-11**
		N=61 401	N=57 172	N=57 343	N=49 762	N=49 515	N=49 071	N=51 718	N=53 116
		%	%	%	%	%	%	%	%
No use of epidural:									
Age-specific use of oxytocin:									
Maternal age	< 20	27.0	25.9	20.9	17.5	26.5	21.9	26.1	22.8
	20-24	31.5	30.1	27.1	25.2	29.3	28.2	28.4	26.2
	25-29	36.0	35.3	32.4	30.5	33.1	31.9	32.0	30.6
	30-34	40.3	39.0	36.3	33.8	33.9	35.6	35.0	33.3
	35-39	48.1	45.4	40.0	38.7	39.7	40.5	42.8	39.6
	≥ 40	45.9	51.7	47.3	40.6	44.8	39.0	39.7	39.2
	In total	36.4	35.8	32.7	30.8	32.1	31.8	32.1	30.2
Use of epidural:									
Age-specific use of oxytocin:									
Maternal age	<20	64.5	68.9	61.5	56.3	56.7	62.3	62.2	57.5
	20-24	70.1	73.8	70.4	66.3	57.8	66.7	69.1	63.9
	25-29	70.3	76.9	75.3	72.4	63.3	71.3	71.3	69.5
	30-34	75.9	80.6	78.1	75.6	64.4	73.2	73.7	74.4
	35-39	72.7	81.1	80.0	79.8	66.3	72.4	75.3	75.4
	≥ 40	73.1	75.5	80.1	81.4	65.6	71.5	72.1	72.2
	In total	71.9	77.4	75.3	72.4	61.9	70.2	71.1	69.1

Table 3: Prevalence of Cesarean delivery by maternal age (in years), by epidural (No/Yes) and maternal age, and by oxytocin (No/Yes) and maternal age (%) in Denmark and Norway, 2000-2011.

	Denmark								Norway							
Time-period	2000-02		2003-05		2006-08		2009-11		2000-02		2003-05		2006-08		2009-11	
	%		%		%		%		%		%		%		%	
Maternal age																
<20	3.8		5.1		4.9		6.0		4.0		4.5		3.9		4.7	
20-24	6.0		7.4		7.3		7.1		5.1		5.4		6.1		6.4	
25-29	7.7		8.6		8.8		8.4		6.2		6.7		7.2		8.1	
30-34	10.3		11.5		11.9		11.8		8.7		8.7		10.1		9.5	
35-39	14.8		14.7		15.5		15.2		12.2		11.3		12.8		14.0	
≥40	17.6		22.2		21.6		20.5		18.4		19.0		17.4		18.6	
In total*	9.4		10.5		10.8		10.5		8.0		8.1		8.9		9.3	
Epidural and Maternal age (yrs.)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)
<20	2.8	15.1	3.4	9.9	2.4	10.0	2.2	12.3	1.4	8.3	1.8	8.3	0.8	7.6	1.6	8.3
20-24	5.1	15.8	3.8	19.9	3.1	15.9	3.2	13.9	1.6	11.1	1.4	11.8	1.4	12.3	1.4	12.5
25-29	6.1	24.6	4.8	23.1	3.6	20.1	3.0	18.9	1.6	14.0	1.6	14.8	1.6	15.1	1.7	16.4
30-34	8.1	28.4	6.1	29.3	4.8	24.7	4.3	24.2	2.8	17.3	1.9	17.8	1.9	19.6	1.9	17.7
35-39	11.5	34.2	8.9	30.1	5.6	29.4	5.8	28.9	3.8	23.0	2.7	22.2	2.7	23.0	2.7	24.2
≥40	14.4	35.8	11.1	45.2	12.3	33.7	9.3	34.7	7.4	32.1	3.7	33.7	4.4	31.1	5.1	30.6
In total*	7.5	24.6	6.0	24.5	4.6	18.2	4.2	21.0	2.4	16.2	1.9	16.7	1.9	17.5	1.9	17.5
Oxytocin and Maternal age	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)
<20	2.7	6.5	3.7	7.5	4.0	6.6	4.2	9.7	4.0	4.1	4.1	5.1	2.9	5.3	3.3	6.8
20-24	4.5	8.8	4.9	11.1	4.8	10.9	4.5	10.8	4.5	6.0	4.7	6.4	4.8	7.7	4.9	8.3
25-29	5.5	11.1	5.8	12.1	5.4	12.8	4.9	12.8	5.3	7.3	5.4	8.3	5.4	9.2	5.9	10.5
30-34	7.1	14.3	7.4	15.7	8.4	15.2	7.8	15.8	8.2	9.2	6.8	10.5	7.9	12.1	7.2	11.6
35-39	12.9	16.6	11.1	17.6	11.4	18.6	11.2	18.3	12.4	12.0	11.4	11.2	11.0	14.1	11.2	15.9
≥40	15.4	19.9	20.6	23.2	19.8	22.7	18.0	22.3	22.2	15.1	18.8	19.3	18.6	16.5	19.5	17.9
In total*	7.1	12.7	7.3	14.1	7.5	14.2	7.2	14.6	7.5	8.5	6.9	9.3	7.2	10.7	7.2	11.4

*Age-standardized

Figure 1. Cesarean delivery rates in Robson group 1 stratified by maternal age, use of epidural analgesia (+/-), use of oxytocin augmentation (+/-), country and time periods (2000-02 blue, 2003-05 red, 2006-08 green, 2009-11 black)

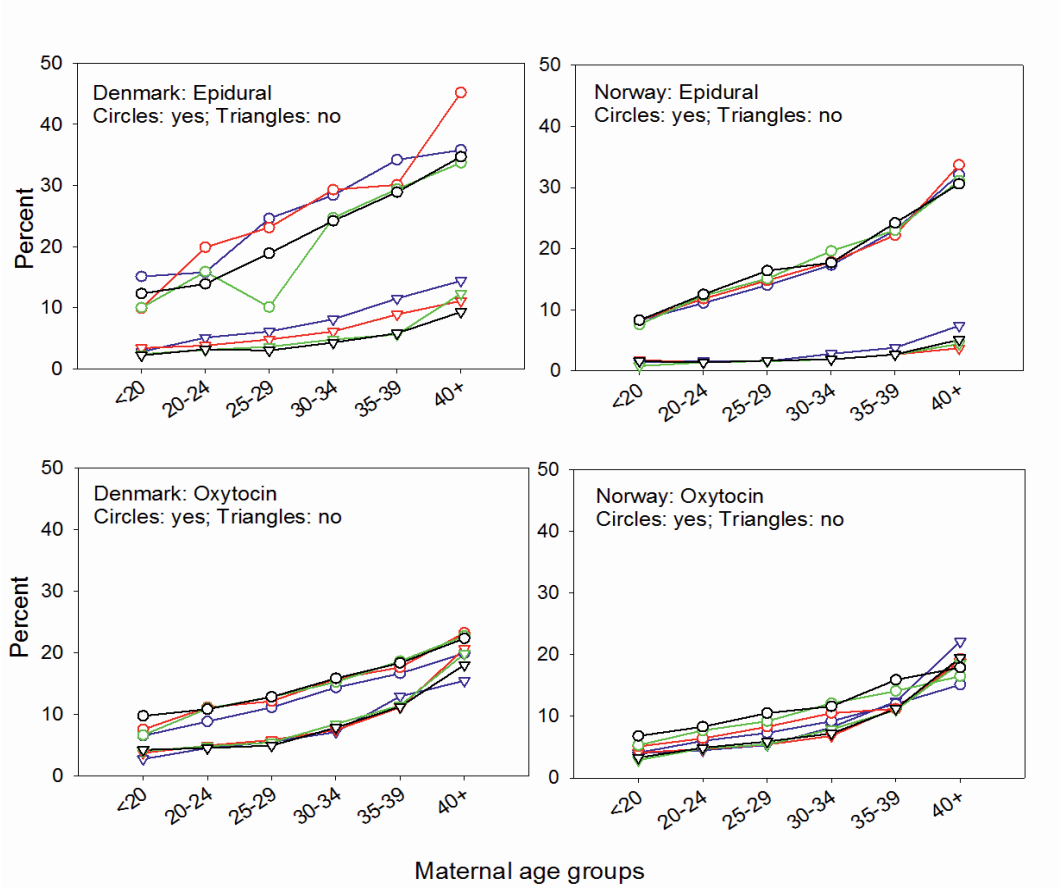

Figure 2. Adjusted odds ratio in logarithmic scale for cesarean delivery in Robson group 1 stratified by maternal age, use of epidural analgesia (+/-) and use of oxytocin augmentation (+/-). Adjusted for time period and birth weight (+/- 4000 grams). Age group 20-24 years, EA (-) and oxytocin (-) used as reference.