The Labour Progression study (LaPS). Assessing labour progression using different guidelines: Maternal and neonatal outcomes

Rebecka Dalbye

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Faculty of Health Sciences
Oslo Metropolitan University, OsloMet

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Universitetsbiblioteket
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Telefon (47) 64 84 90 00

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Summary

Partographs and guidelines are used to assess and monitor labour progression, and they aim to identify slow progress of labour and determine the appropriate management of labour. There is no standardised definition of labour duration or onset of labour, nor is there a consensus to which guideline is best suited for clinical use for assessing labour progression.

Escalation in the global rates of labour interventions, particular caesarean sections and oxytocin augmentation, has strengthen the interests in understanding the labour progression.

Research suggests that some interventions, such as intrapartum caesarean sections (ICS) and oxytocin augmentation, might be performed too soon, according to the prevailing definitions of normal labour progress and labour dystocia. This means that labours in women with slow progress might be misclassified as abnormal and thus increase the chance of unnecessary interventions.

The overall aim was to investigate in what way two different guidelines for assessing labour progress, the WHO partograph and Zhang's guideline, affect maternal and neonatal outcomes related to delivery among nulliparous women with a singleton vertex infant and spontaneous onset of labour at term.

Aims

(I) To investigate the use of intrapartum caesarean sections.
(II) To investigate the use of oxytocin augmentation
(III) To investigate labour duration in different labour phases and stages.

We planned, initiated, and implemented the Labour Progression Study (LaPS) according to the signed protocol. The LaPS was a cluster randomised trial collecting data between December 2014 and January 2017. The LaPs data is the basis of all analyses presented in the three papers included in this thesis. A total of 14 clusters were enrolled in the trial. The obstetric units, acting as clusters, were randomly assigned (1:1) to the control group or to the intervention group. The randomisation was computer generated, stratified by the proportions of previous ICSs and the number of deliveries. Women randomised to the control group, adhered to the WHO partograph and women randomised to the intervention group adhered to the Zhang's guideline.

A total of 11 615 women were considered eligible to participate in the trial, and 7,277 (62.7 %) women with signed consent were included in the analyses. The number of ICS were 271 (6.8 %) in the Zhang group and 196 (5.9 %) in the WHO group, and did not differ between the groups. However, the ICS rates were reduced in both the Zhang and WHO group by 26.5 % and 37.8 %, respectively. Oxytocin augmentation was used in 1658 (41.7 %) women in the Zhang group compared with 1561 (47.2 %) women in the WHO group, with no statistical significant difference between the groups. In the Zhang group 24.1 % of the participants were augmented with oxytocin prior to 6 centimetres of cervical dilatation compared with 28.4 % in the WHO group and 18.5 % of the women in the Zhang group were augmented with oxytocin without being diagnosed with labor dystocia compared with 23.2 % in the WHO group. The adjusted median duration of labour was 7.0 hours in the Zhang group, compared with 6.2 hours in the WHO group; the median difference was 0.84 hours with 95 % confidence interval [CI] (0.2–1.5). The adjusted median duration of the first stage was 5.6 hours in the Zhang group compared with 4.9 hours in the WHO group; the median difference was 0.66 hours with 95 % CI (0.1–1.2). The corresponding adjusted median duration of the second stage was 88 and 77 minutes; the median difference was 0.18 hours with 95 % CI (0.1–0.3). There were no maternal or neonatal deaths identified during the study period.

In conclusion, the results did not demonstrate significant differences in ICS rates or proportion of oxytocin administration between women in the Zhang group compared with women in the WHO group. However, women in the Zhang group were less likely to be augmented with oxytocin prior to six centimetres of cervical dilatation. Furthermore, we found a longer overall duration of labour and duration of first and second stages for women adhering to Zhang's guideline compared with the WHO partograph.

The findings from the LaPS represent important obstetric knowledge when adhering to two different guidelines for assessing labour progression and the results may influence clinical practice of today. The thesis highlights the challenge if standard guidelines in maternity care should be normative and generates thoughts on whether individual variations should be taken into account when assessing labour progression. The thesis contributes with robust information to the worldwide discussion on how to reduce unnecessary interventions.

Oppsummering (Summary in Norwegian)

Partogram og retningslinjer brukes til å vurdere og overvåke fremgang i fødsel, med hensikt om å identifisere langsom fremgang og også bestemme hensiktsmessig behandling. Det er ingen konsensus om en normal fødsels varighet eller start av fødsel og derfor heller ingen konsensus om hvilke retningslinjer som best egner seg til klinisk bruk for å vurdere fremgang av fødsel.

Andelen intervensjoner under fødsel, spesielt akutte keisersnitt og stimulering av rier med oksytocininfusjon er stigende både nasjonalt og internasjonalt og interessen for å forstå fødselsprogresjon har økt markant.

Forskning antyder at noen intervensjoner, som for eksempel akutte keisersnitt og stimulering med oksytocin i fødsel utføres for tidlig i henhold til de retningslinjer som er rådende på fødselsinstitusjonene vedrørende vurdering av progresjon av fødsel. Dette betyr at fødsler som har langsom fremgang potensielt kan bli feilklassifisert som unormal progresjon og dermed øker sjansen at kvinnene blir utsatt for et unødvendig inngrep.

Den overgripende hensikten med studien var å undersøke hvordan to ulike retningslinjer for vurdering av fremgang i fødsel, WHO partogrammet og Zhangs retningslinjer, påvirker maternelle og neonatale kliniske utkomme hos førstegangsfødende kvinner med et barn i hodeleie og spontan start av fødselen ved termin.

Mål

(I) Å undersøke frekvensen av keisersnitt gjort i aktiv fødsel.

(II) Å undersøke frekvensen av ri stimulering med oksytocin.

(III) Å undersøke fødselens varighet i de forskjellig fødselsfasene.

Vi planla, initierte og gjennomførte Fødselsprogresjonsstudien (LaPS) i henhold til signert protokoll. LaPS er en multisenter kluster randomisert studie og datainnsamlingen blev utført fra desember 2014 til januar 2017. Alle dataene som er presentert i de tre artiklene og som utgjør avhandlingen, er basert fra LaPS. Totalt er 14 sykehus inkludert i studien og disse sykehusene danner klusterne og ble randomisert (1: 1) til kontrollgruppe eller til intervensjonsgruppe. Randomiseringen var computer generert og stratifisert av tidligere proporsjonene av keisersnitt og antall fødsler på fødestedene. Kvinnene i kontrollgruppen

forholdt seg til WHO partogrammet og kvinnene i intervensjonsgruppen forholdt seg til Zhangs retningslinjer.

Det var totalt 11 615 mulige deltager, og 7.277 (62.7 %) kvinner hadde et signert samtykke og blev dermed inkludert i analysene. Antall akutte keisersnitt var 271 (6,8 %) i Zhang gruppen og 196 (5,9 %) i WHO gruppen, og det var ingen forskjell mellom de to gruppene. Imidlertid blev det observert en markant reduksjon av akutte keisersnitt i både Zhang og WHO-gruppene med henholdsvis 26,5 % og 37,8 %. Stimulering med oksytocin blev brukt hos 1658 (41.7 %) kvinner i Zhang-gruppen sammenlignet med 1561 (47.2 %) kvinner i WHO-gruppen, uten at det var noen statistisk signifikant forskjell mellom gruppene. I Zhang-gruppen blev 24.1 % av kvinnene stimulert med oksytocin før cervix var dilatert 6 centimeter jamført med 28.4 % i WHO-gruppen og videre blev 18.5 % av kvinnene i Zhang-gruppen og 23.2 % i WHO-gruppen stimulert med oksytocin uten at langsom fremgang var identifisert. Fødselsvarighet i de ulike fasene oppgis i justerte median tider. Tiden i fødsel var 7,0 timer i Zhang-gruppen, sammenlignet med 6,2 timer i WHO-gruppen; medianforskjellen var 0,84 timer med 95 % konfidensintervall [CI] (0,2–1,5). Tiden i første stadium var 5,6 timer i Zhang-gruppen sammenlignet med 4,9 timer i WHO-gruppen; medianforskjellen var 0,66 timer med 95 % CI (0,1–1,2). Den tilsvarende tiden i andre stadium var 88 og 77 minutter; medianforskjellen var 0,18 timer med 95 % CI (0,1–0,3). Det var ikke identifisert noen dødsfall hos mødre eller nyfødte i løpet av studieperioden.

Oppsummert, viste resultatene ingen signifikante forskjeller i andelen av akutte keisersnitt eller stimulering med oksytocin mellom de to studiegruppene. Imidlertid var det mindre sannsynlig at kvinner i Zhang-gruppen ble stimulert med oksytocin før seks centimeter dilatasjon av cervix. Videre blev det også observert en total lengre tid i fødsel, i første og i andre stadium av fødselen hos de kvinnene i Zhang gruppen sammenlignet med WHO gruppens kvinner.

Funnene fra LaPS bidrar med viktig obstetrisk kunnskap vedrørende å forholde seg til to ulike retningslinjer for vurdering av fremgang i fødsel og resultatene kan påvirke dagens kliniske praksis. Avhandlingen fremhever utfordringen om standard retningslinjer for vurdering av fødselsprogresjon skal være normative og videre genererer det tanker om hvorvidt det bør tas hensyn til individuelle variasjoner ved vurdering av fremgang i fødsel. Avhandlingen bidrar med robust informasjon til den nasjonale og internasjonale diskusjonen om hvordan man kan redusere unødvendige intervensjoner.

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Appendices

Appendix I	Information and consent form for the participating women
Appendix II	Signed cooperation agreement forms for all participating obstetric units
Appendix III	Zhang's guideline (paper version) used in the LaPS

List of papers

The thesis is based on the following papers, which will be referred to by their Roman numerals.

Paper I

Bernitz S, **Dalbye R**, Zhang J, Eggebø TM, Frøslie KF, Olsen IC, Blix E, Øian P. The frequency of intrapartum caesarean section use with the WHO partograph versus Zhang's guideline in the Labour Progression Study (LaPS): a multicentre, cluster-randomised controlled trial. Lancet. 2019 Jan 26;393(10169):340-348.
DOI: **https://doi.org/10.1016/S0140-6736(18)31991-3**

Paper II

Dalbye R, Bernitz S, Olsen IC, et al. The Labor Progression Study: The use of oxytocin augmentation during labor following Zhang's guideline and the WHO partograph in a cluster randomized trial. Acta Obstet Gynecol Scand. 2019;98:1187-1194.
DOI: **https://doi.org/10.1111/aogs.13629**

Paper III

Dalbye, R., Blix, E., Frøslie, K. F., Zhang, J., Eggebøe, T. M., Olsen, I. C., Rozsa, D., Øian, P., Bernitz, S. (2020). The Labour Progression Study (LaPS): Duration of labour following Zhang's guideline and the WHO partograph - a cluster randomised trial. *Midwifery, 81*(february 2020), Article 102578.
DOI: **https://doi.org/10.1016/j.midw.2019.102578**

Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
CS	Caesarean Section
ICS	Intrapartum caesarean section
LaPS	The Labour Progression Study
SD	Standard Deviation
TGCS	Ten Group Classification System
Web-CRF	Web- Case Report Form
WHO	World Health Organization

Introduction

Traditionally, the progress of labour is measured by cervical dilatation. However, the expected progression varies between countries and sets of guidelines. There is no standardised definition of labour duration or the onset of labour, nor is there a consensus regarding which guideline is best suited for clinical use (1-3). Escalation in the global rate of labour interventions, particularly caesarean section (CS) and oxytocin augmentation, has increased interest in understanding labour progression. Research suggests that some interventions, such as intrapartum caesarean section (ICS), could be performed too soon according to the prevailing definitions of normal and slow labour progress. This means that women who have slow but normal progression of labour may be misclassified as abnormal, increasing the chance that they will be subjected to unnecessary interventions.

Caesarean section

CSs save lives and improve health outcomes for women and their babies. Ensuring access to CS is an essential part of strategy for meeting the Millennium Development Goals and the forthcoming Sustainable Development Goals by reducing child and maternal mortality (4). However, this surgical procedure is associated with complications for both the mother and neonate, and hence unnecessary CS should be avoided (5). Additionally, the procedure is a global public health concern; it is associated with lower rates of breastfeeding, an increased risk of postpartum depression (6), anaemia, hysterectomy and other complications such as infections and thromboembolism (7). CS also contributes to increased risk of stillbirth, uterine rupture, placental abruption, placenta praevia and abnormally invasive placenta in subsequent pregnancies and deliveries (8). Furthermore, neonates delivered via CS have an increased risk of postpartum respiratory distress (9) and infant asthma and allergies (10).

Worldwide, the incidence of CS has increased dramatically over the past decades, particularly in middle- and high-income countries, for multifaceted reasons (5, 11, 12). Changes in maternal characteristics and professional practice; the increasing pressure of malpractice lawsuits; and economic, organisational, social and cultural factors have affected this trend (11, 13, 14). In many countries, the obstetric population is older and features an increased prevalence of obesity (13, 15). Furthermore, great emphasis has been placed on individual

patients' autonomy. Women are encouraged to decide for themselves which type of care they wish to receive, the providers of this care, the location of delivery and the degree of intervention they wish to receive, and for many, CS is convenient. CS is also a convenient option for obstetricians (11, 13, 15), especially those in countries with private health care systems. Private health insurance companies often require an obstetrician, rather than a midwife, to act as the primary care provider (14). Conflicting demands between work schedules and the need to provide personalised care to private patients may arise, and such conflicts are often resolved through liberal use of CS to efficiently maximise obstetricians time. Additionally, within some health care systems, fears of medical litigation and reduced tolerance for birth complications have led to an increase in the rate of unnecessary CS (13, 14). Research may also have a major impact on obstetric practice. For example, in 2000, Hannah et al. (16) concluded that elective CS resulted in significantly lower perinatal morbidity and mortality than planned vaginal birth in women with term breech presentation. As a result, the American College of Obstetricians and Gynecologists (ACOG) changed their guidelines to recommend CS for these women, and in Scandinavia, the rate of CS for women with breech presentation increased, although at a lower rate in Norway. Cultural factors are more country-specific. For example, in China, the date of a baby's delivery is believed to affect its future, so many parents choose CS (17).

In 1985, the World Health Organization (WHO) expert panel stated, 'There is no justification for any region to have CS rates higher than 10–15 percent' (18). For the past three decades, this percentage was considered the optimal rate of CS (19-24), despite the lack of concrete evidence (15). Recently, however, health care professionals, scientists, epidemiologists and policy-makers have increasingly expressed that there is a need to revisit the 1985 recommendation (25, 26). In 2015, Molina et al. (5) published a large cross-sectional ecological study that estimated the annual CS rates in the 194 WHO member states. The results of this study suggest that national CS rates of up to approximately 19% were associated with lower maternal or neonatal mortality. In 2014, the WHO conducted two studies: a systematic review (27) of available studies that aimed to determine the ideal CS rate within certain countries and an ecological analysis (12) using the latest available data. The two studies concluded that, at the population level, CS rates higher than 10 % were not associated with reductions in maternal and new-born mortality rates (12, 27). Based on these results, the WHO published a new statement (28).

Although many disagree on the appropriate CS rate, the fact that it is increasing indicates that this topic requires urgent attention. To date, several attempts to stop the increase have been made (29, 30).

According to a review published in 2016 by Betran et al. (11), 18.6 % of all global births occur via CS. Latin America and the Caribbean have the highest CS rates (40.5 %), followed by North America (32.3 %), Oceania (31.1 %), Europe (25 %), Asia (19.2 %) and Africa (7.3 %). The countries with the highest CS rates are Brazil (55.6 %) and the Dominican Republic (56.4 %) in Latin America and the Caribbean; Egypt (51.8 %) in Africa; Iran and Turkey in Asia (47.9 % and 47.5 %, respectively); Italy (38.1 %) in Europe; the United States (32.8 %) in North America; and New Zealand (33.4 %) in Oceania. In the Nordic countries, the highest percentages have been reported in Denmark (20.8 %), Iceland (16.2 %) and Sweden (16.2 %), and the lowest rate was reported in Finland (14.7 %) (11). In Norway, the rate of CS increased from 1.8 % in 1967 to 15.9 % in 2018 (31).

Normal birth

‘Normal birth’ is a term that has been used for many years to refer to uncomplicated vaginal birth, irrespective of the interventions that may have preceded or interfered with the physiological process (32-34). However, the terminology that should be used to describe the birth process has been debated. Specifically, the word ‘normal’ has been viewed as problematic because it is dichotomous, implying that birth is abnormal if it is not ‘normal’ (33). Normal birth can be defined as ‘the birth of an infant without obstetric operative intervention’. Although a woman may have a vaginal birth without obstetric operative intervention, such as forceps, ventouse or CS, she might have received multiple interventions throughout the process of labour, such as induction of labour, epidural analgesia, artificial rupture of the membranes, augmentation with oxytocin or episiotomy (35).

The WHO (36) defines normal birth as “spontaneous in onset, low-risk at the start of labour and remaining so throughout labour and delivery. The infant is born spontaneously in a cephalic presentation between 37 and 42 completed weeks of pregnancy. After birth mother and infant are in good condition”. This indicates that the risk status of the pregnancy and the course of labour and delivery need to be taken into consideration when defining normal birth. Furthermore, the WHO’s 2018 recommendation regarding intrapartum care highlights the

importance of a positive childbirth experience, stating that childbirth should not only be safe but also focus on the experience and recognise this as a significant endpoint for all women undergoing labour. It is based on the premise that most women want physiological labour and birth and a sense of personal achievement and control through involvement in decision-making, even when medical interventions are needed or wanted (2).

The International Confederation of Midwives (ICM) (37) defines normal childbirth as a unique dynamic process in which foetal and maternal physiological and psychosocial factors interact. Normal birth occurs when the woman commences, continues and completes labour and the infant is born spontaneously with cephalic presentation at term without any surgical, medical or pharmaceutical intervention.

A Delphi study issued a consensus statement developed by three US midwifery organisations and childbirth advocacy and consumer groups that defined normal labour from a physiological perspective (34). According to the statement, normal physiological labour and birth are characterised by the usual and functional processes of an organism that is powered by the innate human capacity of the woman and foetus.

In Norway, the Norwegian Directorate of Health registers quality indicators (i.e. indirect targets regarding the quality of the area being measured), including those related to birth. Ten indicators concern maternity care and three of them concern interventions (i.e. the rate of CS, the rate of oxytocin augmentation and the rate of inducing labour). In addition, the indicator 'birth without major intervention and complications' is registered. In 2017, this indicator showed that 68.5 % of first-time mothers completed labour without CS, forceps or ventouse; bleeding above 1500 ml or a blood transfusion; grade 3 or 4 perineal tears; or Apgar scores below 7 at five minutes (38). However, this indicator includes augmentation with oxytocin and should be considered when its definition (birth without major intervention and complications) is discussed.

In sum, defining what constitutes a normal duration of labour after spontaneous onset is challenging, as there is no global consensus regarding the definition of onset of the active phase, duration of different stages or prolonged labour.

The labour process

Labour is a continuous process that is divided into several phases and, usually, two stages based on cervical dilatation (Figure I) (39, 40).

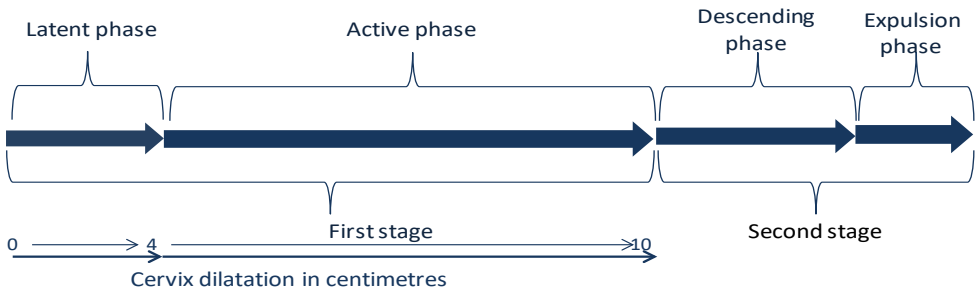


Figure I. Phases and stages of the labour process.

First stage of labour

The first stage of labour is divided into the latent and active phases. The former starts at the onset of labour, which is generally described as the period in which the woman perceives contractions, followed by cervical effacement and dilatation. The latent phase is characterised by irregular and more or less painful contractions as well as slow cervical dilatation. The duration of the latent phase may vary and is generally ill-defined (2). The WHO has stated that a latent phase lasting more than eight hours is prolonged (41), while the International Classification of Diseases, 10th revision (ICD-10) (42) defines a prolonged latent phase as lasting more than 18 hours. Currently, there is a knowledge gap regarding the extent to which the latent phase is of importance in efforts to improve birth outcomes (2). However, this thesis does not study the latent phase in detail, simply viewing the duration of the latent phase as ending at the onset of the active phase.

Defining the time point of transition between the latent phase and the onset of the active phase of labour has been described as one of the most important judgements in maternity care, and it is essential part of monitoring labour progress, both to determine whether interventions are warranted and to avoid unnecessary interventions. According to a review of 62 studies that aimed to report how the onset of the active phase was defined, cervical dilatation and regular, painful contractions are the most commonly applied indicators of labour onset, regardless of

stage or phase (43). However, there is little consensus about the optimal degree of cervical dilatation or regularity of contractions (43). Different guidelines for defining the onset of this phase have been proposed. Some are presented below:

Norwegian Medical Association, Norwegian Society of Obstetrics and Gynaecology (2014 Guidelines)(44).

- Cervical dilatation of 4 cm
- Regular contractions

WHO

- Cervical dilatation of 3 cm (1994 guidelines) (41).
- Cervical dilatation of 4 cm (2000) guidelines) (40).
- Cervical dilatation of 5 cm (2018 guidelines) (2).

National Institute for Health and Clinical Excellence (NICE), United Kingdom (2014 Guidelines) (39).

- Progressive cervical dilatation from 4 cm
- Regular painful contractions

ACOG (2014 Guidelines) (45).

- Cervical dilatation of 6 cm

Most recommendations regarding labour duration and progression have been influenced by Emanuel Friedman's work from the 1950s. He described the active phase of the first stage of labour for nulliparous women as lasting from approximately 2.5 cm of cervical dilatation to complete dilatation (i.e. 10 cm). According to Friedman, this phase is divided into three sub-phases: acceleration, maximum slope and deceleration. The acceleration sub-phase involves a rapid change in the slope of cervical dilatation that occurs over approximately the amount of time needed for the cervix to dilate from 2.5 to 4 cm. The maximum slope sub-phase is characterised by rapid cervical dilatation from approximately 4 to 9 cm. The deceleration sub-phase occurs when the rate of dilatation slows as full dilatation is reached (46-48).

Some studies have found that the transition from the latent to active phase takes place later than previously reported. According to Zhang et al., rapid changes are not observed before cervical dilatation of 6 cm (49). Other studies have also suggested that dilatation of 6 cm is a good point at which to define the transition between the latent and active phases (50, 51). Although some women may be in active labour before 6 cm of cervical dilatation is observed, according to Zhang et al. (51), the standards for active labour progression should not be applied before this dilatation is reached. In 2014, in an effort to decrease the rate of CS by avoiding diagnosis of labour dystocia before 6 cm, the ACOG and the Society for Maternal-Fetal Medicine jointly endorsed defining cervical dilatation of 6 cm as the threshold for onset of active labour for most women (45).

Second stage of labour

The second stage of labour lasts from complete cervical dilatation until the birth of the infant. Like the first stage, it is divided into latent and active phases. The latent phase, also called the descending or passive phase, is the time from full dilatation of the cervix until involuntary expulsive contractions. It can also be described as the period in which the foetal head descends towards the pelvic floor without active pushing. This is followed by the active phase, also known as the expulsion phase, which involves bearing down or pushing the baby out (39, 40). The active phase of the second stage of labour begins when the baby is visible, when expulsive contractions occur or when a women begins voluntarily actively pushing with full dilatation of the cervix (39).

Assessing labour progression

Methods of assessing labour progression and definitions of slow progress remain unclear, mainly due to a lack of consensus regarding the expected progression of labour. This is concerning to some as women may undergo unnecessary interventions because slow labour progress is poorly defined. Furthermore, applying stages and phases to real situations is challenging due to variations in definitions of the onset of labour and transitions between phases and stages. Therefore, it is crucial to understand the normal variation in the duration of labour (43, 49, 50, 52-55).

Emanuel Friedman was the first to describe a comprehensive method of evaluating labour in clinical practice (46, 47). In a landmark series of publications, Friedman presented the relationship between the duration of labour and cervical dilatation as a sigmoid curve. In addition to providing mean estimates of each phase of labour, Friedman included definitions of labour protraction and arrest that still guide practice today (48). He also introduced a graphical tool for monitoring labour progression, called either a partograph or partogram in the literature. This thesis will refer to the tool as a partograph as this is the term accepted by the WHO.

Partographs provide a visual overview of the progression of labour. Midwives and obstetricians use the tool to record cervical dilatation, foetal descent and maternal and foetal wellbeing during labour and delivery. Originally, the partograph was introduced to prevent prolonged labour and improve labour care, especially in developing countries. Use of it during labour enables early detection of abnormal advancement, meaning that obstruction of labour can be detected in a timely manner and necessary interventions can be provided (3).

However, evidence regarding the effects of partograph use is inconclusive (3). The WHO credited partograph use with decreasing the rate of prolonged labour from 6.4 % to 3.4 %, the rate of labours that required augmentation from 20.7 % to 9.1 % and the rate of ICS from 9.9 % to 8.3 % (56). However, a Cochrane review from 2018 suggested that, overall, use of partographs did not significantly affect any primary outcomes, like CS, instrumental vaginal delivery or Apgar score less than seven at five minutes (3) .

Despite this, many birth care units in both high- and low-income settings currently use partographs and have reported benefits regarding the quality of care. These benefits are derived from the fact that it provides a visual overview of labour progression and enables recording of outcomes, auditing of care, training of clinicians, identifying women in need of obstetric intervention and transferring of care (57-59). Additionally, in Australia, the partograph remains a central element of labour management. However, its form has changed; the latent phase and action lines have been omitted. Instead, the emphasis is placed on clinical judgement and individual assessment. The partograph provides a comprehensive picture of labour, and when used correctly, reduces the need for long tedious documentation, facilitates handover and fosters teaching and learning experiences (60).

Despite a lack of evidence regarding its effectiveness, partographs are still recommended by midwifery and obstetrics organisations in high-, middle- and low-income countries (3, 39, 40,

56). The Cochrane review of the tool concludes that it seems reasonable to continue using partographs until stronger evidence is available due to their widespread use and acceptance worldwide (3) .

Partograph designs

Friedman's curve

In 1954, Friedman presented his first publication on labour progression and proposed a progression curve based on data from 100 women in labour. For this publication, he conducted a series of examinations of nulliparous women who delivered at term at one institution during an undefined period. Most women in the sample were admitted while in spontaneous labour and delivered vaginally. Friedman assessed changes in cervical dilatation through frequent rectal examinations, and vaginal examinations were performed when any doubt existed regarding cervical dilatation, particularly when the women had a very soft or thin cervix. To minimise the errors associated with inter-observer variability, Friedman ensured that almost all examinations were performed and recorded by one individual. The examinations were generally performed every one to two hours, depending on the progression of labour and the peaks of contractions. To examine the pattern of labour progression in this population, Friedman graphed each participant's labour and cervical dilatation over time on square-ruled graph paper, such that the slope of the line was defined as cm/h. Based on this assessment, he reported that the curves in all normal cases were S-shaped and varied only in slope (46).

In 1955, Friedman examined data on 500 primiparous women at term (47). He used the same approach as in his preliminary analysis, describing the pattern of labour in greater detail and noting the average values and limits of what he identified as normal labour. He also graphically illustrated the phases and stages of labour (Figure 2). The duration of labour was determined retrospectively, starting from the acceleration of cervical dilatation and ending at complete dilatation (Figure II).

The active phase of first stage was defined as the period from 2.5 cm to 10 cm of cervical dilatation. For nulliparous women, this phase lasted an average of 4.6–4.9 h, although the average time necessary for dilatation from 4 to 10 cm was only 2.6 h and the maximum

duration of the active phase of labour was 11.7 h, with a standard deviation (SD) of 2. Based on these studies, when dilatation is 4–9 cm, nulliparous women dilate at a mean rate of 3.0 cm/h, and the slowest acceptable rate is 1.2 cm/h (47, 61). In the study of nulliparous women, Friedman determined that the mean duration of the second stage of labour was 57 min (47).

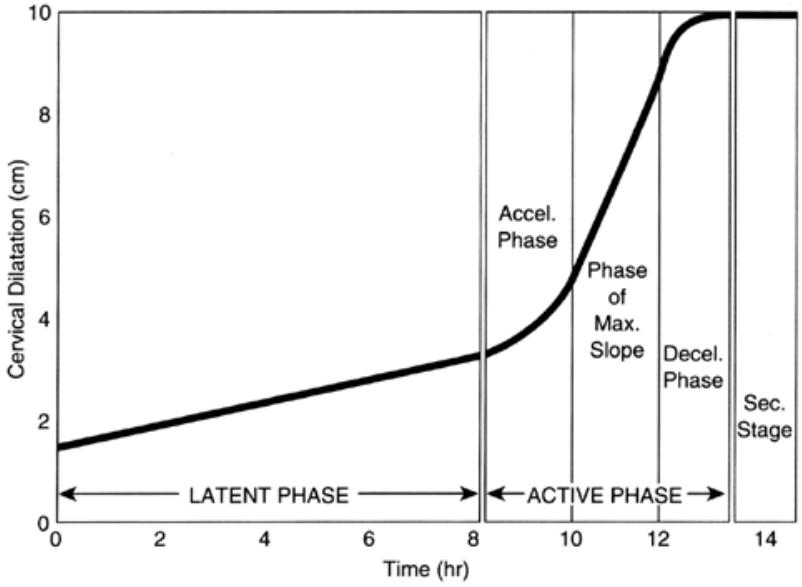


Figure II. Friedman's labour curve (47). Reprinted with permission of Wolters Kluwer Health, Inc.

Philpott's alert and action lines

In the early 1970s, based on Friedman's findings, Philpott et al. developed a guideline for assessing labour progression and detecting abnormal progression using alert and action lines (62, 63). The alert line represents the modified mean rate of cervical dilatation for the slowest 10 % of nulliparous women in the active phase: 1 cm/h (63). The action line is placed parallel to the alert line but begins 2–4 h later. If the action line is crossed, this indicate slow progress of labour (62). In 1994, the WHO presented a partograph (56) based on the work of Friedman (46, 47) and Philpott (62, 63). The partograph is (Figure III) currently used worldwide as part of routine labour care (39, 40).

Figure III. WHO partograph (40) developed based on the findings of Philpott et al. Reprinted from *Managing Complications in Pregnancy and Childbirth: A Guide for Midwives and Doctors* (2000) with permission from the WHO.

The labour scale

The labour scale (Figure IV) (64) is a modified version of the WHO's partograph based on intrapartum care guidelines published by NICE. Uterine contractions, foetal heart rate, membrane status and vital signs are plotted as well as cervical dilatation. This scale allows for more comprehensive reporting on the conditions of labour, including cervical dilatation, degree of effacement on the cervix, cervical consistency and direction of the cervix (i.e. posterior, middle or anterior).

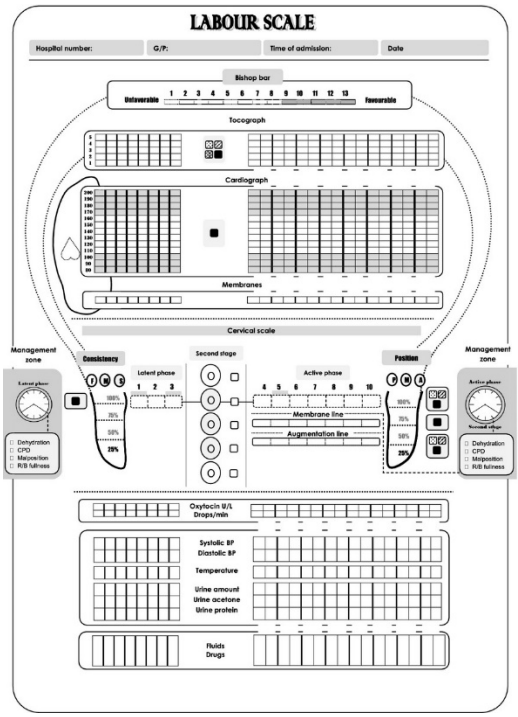


Figure IV. The labour scale (64). Reprinted with the permission of John Wiley and Sons.

Zhang's labour curve

In a retrospective observational study published in 2002, Zhang et al. presented an alternative labour curve based on 1,329 nulliparous women with spontaneous onset of labour and spontaneous vaginal birth. The mean duration of the active phase of the first stage of labour (i.e. from 4 to 10 cm of cervical dilatation) was 5.5 h (49). There was variation among women in this regard; most entered the active phase at dilatations ranging from 3 to 5 cm, but a significant number did not reach the active phase until 6 cm of dilatation (49).

Zhang et al. (51) replicated these findings in a large multi-centre cohort study conducted in 19 hospitals across the United States. In this retrospective study, the duration of labour was analysed for 62,415 parturients of mixed parity with spontaneous labour onset and spontaneous vaginal birth (Figure V). The cohort included 27,170 nulliparous women, each of whom vaginally delivered a singleton foetus with cephalic presentation and normal neonatal outcomes. Epidural analgesia was performed for 84 % of the women, and oxytocin augmentation was performed for 47 % (51).

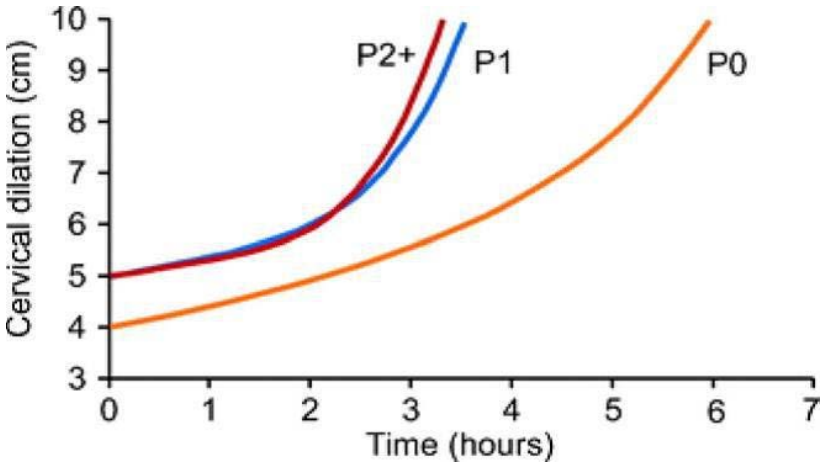


Figure V. Zhang's labour curve (51). Reprinted with permission of Wolters Kluwer Health, Inc.

In Zhang et al.'s cohort, the 95th percentile of active phase dilatation was 0.5–0.7 cm/h for nulliparous women. This indicates that cervix dilatation proceeded more slowly than historically described. The authors also reported that it may take more than 6 h to progress from 4 to 5 cm of dilatation and more than 3 h to progress from 5 to 6 cm (51). Furthermore, the maximal slope of the rate of change of cervical dilatation over time (i.e. the active phase) did not generally start until at least 6 cm of cervical dilatation was observed (51). The median duration of the second stage for nulliparous women without epidural analgesia was 36 min, and the 95th percentile was 2 h and 48 min. For nulliparous women with epidural analgesia, the median duration was 1 h and 6 min, and the 95th percentile was 3 h and 36 min.

Zhang et al. suggested that cervical dilatation was more likely to occur in stepwise, rather than linear, manner, which enables assessment of individuals' labour progression using a more flexible approach that they argued would reduce the incidence of CS in cases of dystocia (51).

Neal and Lowe 's physiologically based partograph

In 2012, Neal and Lowe (65) presented a physiologically based partograph for use in hospitals to assess the labour progression of low-risk, term, nulliparous women with spontaneous labour onset. This partograph (Figure VI) incorporates several evidence-based labour principles and is designed to safely limit diagnoses of dystocia (65).

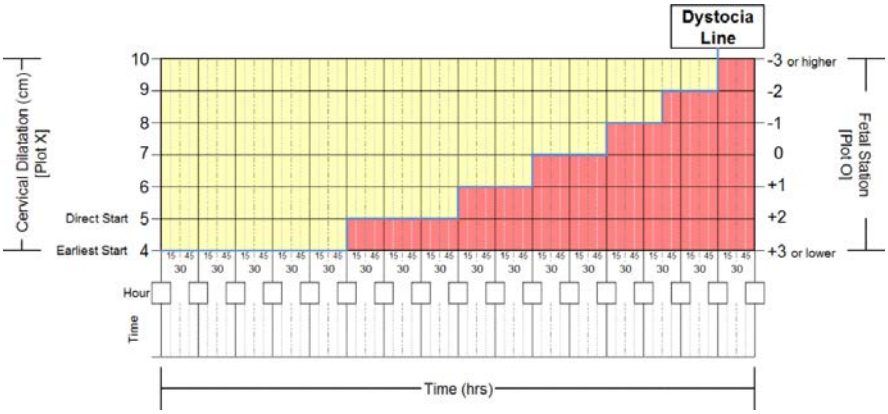


Figure VI. Physiologically based partograph developed by Neal and Lowe (65). Reprinted with the permission of Elsevier and the Copyright Clearance Center.

Studies such as those of Albers (66, 67), Zhang et al. (49) and Jones et al. (68) have found that, normally, the active phase of first stage in nulliparous women lasts longer than previously believed. Understanding the physiological pattern of labour is only the first step towards optimal labour management. The next, and more difficult, step is to define labour abnormality.

Labour dystocia

The term 'dystocia' originates from the Greek word *dystokia*, a combination of *dys* ('difficult') and *tokos* ('childbirth'). Therefore, labour dystocia is defined as slow or difficult

labour or delivery. Clinicians may also use several related terms, inefficient uterine contractions, failure to progress, protracted or arrested labour, prolonged or obstructed labour, dysfunctional labour and protracted or arrested descent.

Labour dystocia is typically diagnosed after a delay in cervical dilatation or foetal descent. It is caused by a combination of factors that are traditionally understood to be related to uterine contraction, the presentation and position of the foetus and the mother's bony pelvis (69). Inefficient uterine contractions—those that are hypotonic (i.e. contractions are synchronous but the pressure during a contraction is insufficiently strong) or hypertonic (i.e. the basal tonus is elevated or contractions occur in a way that does not affect the cervix)—are one of the main causes of labour dystocia (69). However, labour dystocia can also be caused by abnormalities in foetal presentation or position, such as such as foetal head deflection (brow or face presentation) or asynclitism. Macrosomia may also be a cause. The maternal pelvis can also cause labour dystocia. Before the 20th century, the main reason for CS was rickets. Nowadays, a bony pelvis rarely limits vaginal deliveries, even if soft tissue abnormalities in the reproductive tract lead to a contracted pelvis (70). Psychological measures obtained during pregnancy have shown that the mother's fear of childbirth and stress are also associated with delayed labour (69, 71).

Labour dystocia can be diagnosed during the active phase of both the first and second stages of labour, including the descending and expulsive sub-phases. Based on Friedman's studies, the 95th percentile of nulliparous women in the protracted active phase have a cervical dilatation of less than 1.2 cm/h (47). Zhang et al. determined the slowest statistically normal duration of labour for the 95th percentile of nulliparous women, measuring the time required to dilate 1 integer cm to the next: 6.4 h to dilate from 4 to 5 cm, 3.2 h to dilate from 5 cm to 6 cm, 2.2 h to dilate from 6 cm to 7cm, 1.6 h to dilate from 7 cm to 8 cm, 1.4 h to dilate from 8 cm to 9 cm and 1.8 h to dilate from 9 cm to 10 cm. It remains unclear whether the parameters for the 95th or 90th percentile best define abnormal labour progression (51).

Labour dystocia in the second stage of labour can be identified only by the progression of descent of the foetal head. The normal upper limit for the duration of the second stage of labour in nulliparous women was determined to be 2 h (72), due to a landmark 1952 study, the infant mortality rate was reported to increase after 2.5 h, and hence the two-hour rule became the standard (73). Later, Cohen et al.'s work caused the upper limit for the duration of the second stage to be increased by an additional hour when epidural analgesia was applied (74).

Thus, until recently, the normal duration of the second stage of labour for nulliparous women was defined as either 2 or 3 h (75). According to Zhang et al. (51), a prolonged second stage in nulliparous women was defined as 3.6 h for those with epidural analgesia and 2.8 h for those without the intervention (51).

Studies have reported that about 21–44 % of nulliparous women experience a delay in labour (76-81). The exact incidence of dystocia during delivery remains unknown as it is difficult to assess due to the different study populations, definitions and clinical practices applied in relation to the condition. This has led experts to recognise that labour dystocia might be over-diagnosed, and many women with normal labour progression may unnecessarily receive treatment. Neal et al. stated that inconsistent terminology makes it difficult to communicate effectively within and across clinical settings and limit the ability to use research results to improve labour care (82).

Oxytocin

Endogenous oxytocin is a neuropeptide hormone mainly produced in the hypothalamus and pulsatile-released into the circulatory system via the pituitary gland. Oxytocin is essential in human physiology; its role in parturition and lactation is well established, it has been shown to regulate social behaviour (83, 84) and, in the last few decades, researchers have theorised that it is involved in the human stress response. However, studying the nature of the mammalian oxytocin is complicated, and so most of our knowledge about the physiological regulation and secretion of oxytocin during labour is derived from investigations of animals (85), and detailed analysis of oxytocin in plasma has demonstrated wide variations in secretion and concentration during the pregnancy and labour of mammals.

There is overwhelming evidence that oxytocin and oxytocin receptors play a role in the parturition process, but the nature of its involvement and the extent to which it is necessary in pregnancy and labour is still under investigation. Uterine oxytocin receptors are of particular interest in research, as these receptors increase at term in all mammals and oxytocin production dramatically increases, depending on the site of expression (i.e. the myometrium or decidua/uterine epithelium).

Augmentation with oxytocin

In 1954, the American biochemist Vincent du Vigneaud was the first to sequence and biochemically synthesise oxytocin, for which he earned the Nobel Prize in Chemistry one year later (86). Since synthesised oxytocin, known as Syntocinon®, became accessible to birth attendants, it has been increasingly administered during labour to induce the latent phase of the first stage or augment the active phase of the first stage or the entire second stage. During the active phase of the first stage of labour, augmentation is intended to increase the frequency, duration and intensity of contractions in order to shorten labour and prevent adverse outcomes, such as instrumental vaginal delivery or ICS. It can also be administered for prophylaxis and/or treatment of haemorrhage after the baby is born.

In a Cochrane systematic review, Bugg et al. reported an association between oxytocin administration and reduction in the mean duration of labour by approximately 2 h. However, there was no decrease in the rates of CS or improved maternal or foetal birth outcomes (87). Indeed, observational studies have reported that oxytocin augmentation is associated with adverse outcomes for mothers and neonates. Bernitz et al. reported an increased risk of instrumental vaginal delivery and episiotomy for women who received oxytocin during labour without labour dystocia (88). Additionally, in a Swedish population-based register study of 106,755 deliveries, there was a significant association between oxytocin use and operative delivery, ICS and anal sphincter ruptures (89). For neonates, oxytocin administration was associated with low Apgar scores as well as increases in the transfer rate of new-borns to the neonatal intensive care unit (89).

Oxytocin is a potent medication and is included in the list of high-alert medications published by the Institute for Safe Medication Practices in the US (90). High doses of oxytocin can cause sustained tetanic uterine tachysystole (89, 91-95) and highly unfavourable results. Additionally, Jonsson et al. showed that a hyperactive uterine contraction pattern, usually caused by over-stimulation by oxytocin, is strongly associated with foetal distress and academia at birth (91, 93). In a Swedish study, incautious use of oxytocin was determined to be the cause of severe asphyxia in 71 % of cases (95). Further, a high proportion of obstetric malpractice claims in the US (92) and in Norway (96) have been associated with incautious oxytocin use.

To improve the management of labour and reduce adverse neonatal outcomes, checklists and different standardised protocols for oxytocin administration have been recommended (92, 97, 98), with positive results. However, augmentation with oxytocin infusion is still widely used worldwide to treat labour dystocia (31, 99-101). In fact, obstetric interventions during labour have increased in recent decades (31, 101). In 2014, the Norwegian Society of Obstetrics and Gynaecology updated the guidelines for augmentation of labour, as shown below(44).

Oxytocin infusion
• 1 ml (8.3 microgram/ml = 5 IU/ml) of oxytocin should be administered in 500 ml of normal saline. • The infusion rate should start at 6 milliunits/minute (30 ml/h) • Dosage should be increased in intervals of 3 milliunits/minute (15 ml/h) every 15 minutes. • The maximum dose is 40 milliunits/minute (180 ml/h).
Regimen
• Oxytocin augmentation is recommended in women with ineffective contractions. • Amniotomy should be performed before oxytocin augmentation is started. • The doses described above are recommended until progress in labour or regular contractions (3–5 every 10 min) are achieved. • Use of 1 IU (0.2 ml) oxytocin intra muscular (or intra venous) during the final stage of labour should be avoided because of increased risk of hyperstimulation and subsequent foetal distress. In exceptional cases, it might be indicated when the foetal head is supposed to be delivered during the next contraction. • Oxytocin augmentation should not be used in situations with shoulder dystocia.

Aims of the study

The overall aim of this thesis is to investigate the way in which two different guidelines for assessing labour progress (one based on Friedman's and Philpott's research, referred to as the WHO partograph, and one based on Zhang and co-worker's research, referred to as Zhang's guideline), affect maternal and neonatal outcomes related to delivery of a singleton infant among nulliparous women with cephalic presentation and spontaneous onset of labour at term.

Hypothesis and objectives

We hypothesised that adhering to Zhang's guideline would decrease the rate of ICS among low-risk nulliparous women, compared to adhering to the WHO partograph, without jeopardising the outcomes of the mother or neonate. The null hypothesis is that there is no difference in the probability of ICS between the two guidelines.

Specific objectives

- To compare the impacts of adhering to Zhang's guideline for labour progression and the WHO partograph on the rate of ICS in nulliparous women (Paper I).
- To compare the use of oxytocin augmentation during labour in nulliparous women when adhering to Zhang's guideline and to the WHO partograph (Paper II).
- To compare the duration of different phases of labour when adhering to Zhang's guideline and the WHO partograph (Paper III).

Methods

To test the hypothesis, a cluster randomised controlled trial (cRCT) was conducted. We planned, initiated, obtained and terminated the Labour Progression Study (LaPS) according to the signed protocol. All the data presented in the three papers included in this thesis were collected from the LaPS. A detailed description of the study design is presented below.

Study design

A cRCT is one in which intact social units or clusters of individuals, rather than individuals, are randomised to different intervention groups (Figure VII). The cluster randomisation design has become particularly common for evaluating interventions, including educational programmes and innovations in the provision of health care (102). Our choice of randomising on a hospital level rather than the individual level was due to the risk of contamination, which would be particularly high if the mothers who received the control intervention were treated by the same midwife or physician that treated other mothers with the new intervention and vice versa (102).

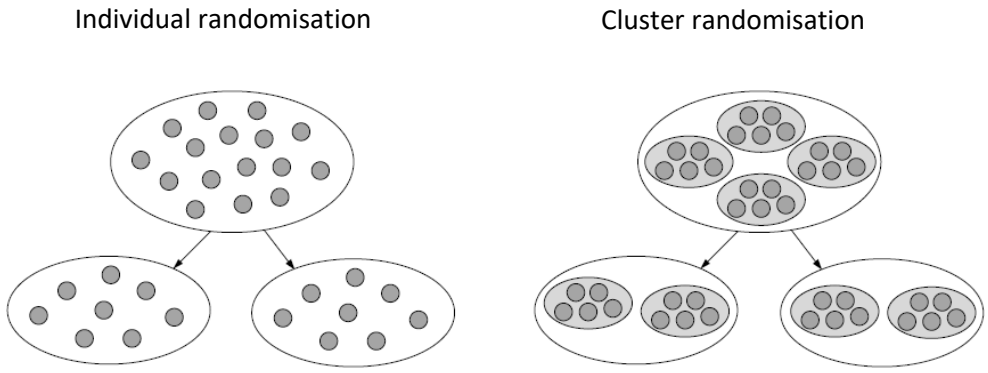


Figure VII. Illustration of individual and cluster randomised controlled trial.

Study setting

Maternity care in Norway is organized so that all women in Norway are offered free health care during pregnancy and delivery. Specifically, they are entitled to antepartum care from a midwife at a maternity and child health care centre (in Norwegian, *helsestasjon*) or from their general practitioner. Approximately 60,000 babies are born annually in Norway. Almost all intrapartum care (more than 99 % of cases) is administered in government-owned institutions, apart from a few independent midwives who offer home birth for low-risk women. Uncomplicated deliveries are supervised by midwives with little involvement from obstetricians, and complicated deliveries are managed by midwives together with obstetricians. According to parliament report (white paper) number 43 (1999–2000), in 2001, the Norwegian Parliament decided to organise national birth care into three levels of institutions: (1) specialised obstetric units in larger hospitals that provide all birth care services and have a neonatal intensive care unit as well as an obstetrician, paediatrician and anaesthesiologist available 24 hours a day; (2) obstetric units in smaller hospitals with an obstetrician and anaesthesiologist on call; and (3) midwife-led units, both alongside within hospitals and free-standing, that provide care for women with a low risk of complications. In case of complications or a change in risk status, women receiving level 3 birth care are transferred to a level 1 or 2 hospital. Norway is divided into four geographic health regions (North, Middle, West and South-East) containing 45 birth institutions of which 24 birth units, has more than 500 deliveries in 2018. All maternity care is free of charge, and doctors and midwives are publicly employed and receive a fixed regular salary.

Power calculation

The ICS rate was used as the basis for calculating power. The sample size (i.e. the number of clusters and individuals) was based on the proportion of ICS (9.2 %) relative to the total number of deliveries in the 24 eligible hospitals at the time of calculation (i.e. 2012). We believed that a 25 % reduction in the ICS rate was possible based on an examination of 100 partographs of women diagnosed with labour dystocia according to the WHO partograph for labour progression who underwent an ICS, although 25 (25 %) would not have been diagnosed with labour dystocia according to Zhang's guideline. To achieve 80 % power to detect a 25 % relative reduction in ICS use with Zhang's guideline, a probability of $p < 0.05$

and a between-cluster variation coefficient of 0.08, we would have to include at least 14 obstetric units and 6,582 participants.

Participating clusters

To perform the study within a reasonable period of time, only obstetric units with more than 500 births annually were included. To ensure representative selection of the obstetric units, all geographical health regions in Norway were included. At the time of inclusion, 24 obstetric units were assessed for eligibility. All units that could adhere to the protocol were considered eligible.

Randomisation, recruitment and inclusion processes

The obstetric units, acting as clusters, were randomly assigned (1:1) to the control group, which adhered to the WHO partograph, or to the intervention group, which adhered to Zhang's guideline. The randomisation was computer-generated, stratified by the proportion of previous ICSs and the number of deliveries and was conducted in the Unit of Biostatistics and Epidemiology at Oslo University Hospital, Oslo, Norway, in September 2014.

After random allocation of the obstetric units and before inclusion of the participants, the staff in all obstetric units completed a programme on the trial protocols. The programme provided information about the trial and thorough instructions regarding the use of the assigned guidelines. Written information about the trial and guidelines were printed on posters and made constantly available to midwives and obstetricians in the units. In each obstetric unit, there was one dedicated person (a local coordinator) who was responsible for the trial, including recruiting and including the participants and entering the required data.

Researchers from the LaPS group revisited the units to ensure consistency and strict adherence to the allocated guidelines. Every Monday during the study period, one of the members of the LaPS research group contacted the local coordinators for a weekly update on the trial and to determine whether they needed assistance or motivation.

Participating individuals

The inclusion criteria for the participating individuals were as follows: nulliparous women delivering a singleton foetus with cephalic presentation and spontaneous onset of active labour at week 37 of gestation or later. The participants were thus within group 1 according to the Ten Group Classification System (TGCS) proposed by Robson (103). The TGCS, also known as the Robson classification, is used as a global standard for assessing, monitoring and comparing CS rates. It classifies women into 10 groups based on their obstetric characteristics, including parity, previous CS, gestational age, onset of labour, foetal presentation and number of foetuses. The categories are totally inclusive and mutually exclusive. The classification system does not take into account pre-pregnancy body mass index (BMI), chronic diseases or complications during pregnancy.

The estimated date of delivery was based on a second-trimester ultrasound scan. At this examination or at the time of admission to the labour ward, eligible women received written information about the trial and a consent form. All TGCS group 1 women adhered to the guideline to which their obstetric unit was assigned. Women who understood the Norwegian language and provided their informed consent were included in the analysis.

Intervention

The LaPS trial investigated the active phase of the first stage of labour and the second stage. Spontaneous onset of active labour was defined as at least 4 cm of cervical dilatation with regular contractions. Seven birth care units were randomised to the intervention group adhering to Zhang's guideline, and seven birth care units were randomised to the control group adhering to the WHO partograph.

For women adhering to Zhang's guideline, labour dystocia was diagnosed if cervical dilatation did not meet the expected progression of dilatation for the 95th percentile. The time limits were as follows: 6 h and 30 min to dilate from 4 to 5 cm, 3 h and 15 min to dilate from 5 to 6 cm, 2 h and 15 min to dilate from 6 to 7 cm, 1 h and 30 min to dilate from 7 to 8 cm, 1 h and 30 min to dilate from 8 to 9 cm, and 1 h and 45 min to dilate from 9 to 10 cm. Labour dystocia in the second stage was diagnosed if the descending phase lasted longer than 1 h and

45 min (2 h and 30 min for women with epidural analgesia) or if the expulsion phase lasted longer than 1 h.

For women adhering to the WHO partograph for labour progression, labour dystocia was diagnosed if cervical dilatation was slower than one centimetre per hour assessed after 4 h, which is after the 4 h action line was crossed. Labour dystocia was diagnosed in the second stage if the descending phase lasted longer than 1 h (2 h for women with epidural analgesia) or if the expulsion phase lasted longer than 1 h.

If labour dystocia was diagnosed, the guideline for treatment of insufficient contractions was followed in all birth care units in both the intervention and control groups. In the 14 included birth care units, oxytocin was administered as an intravenous infusion of 5 IE in 500 ml of saline, and the infusion rate began at 300 mU/hour with a dose increment of 150 mU/hour every 15 min until a satisfactory number of contractions were obtained or until the maximum dose of 1,800 mU/hour was reached, according to the Norwegian guidelines for augmentation of labour (104).

Documentation process

All the clinical outcomes were registered in a web-based case report form (web-CRF) designed by the Unit of Applied Clinical Research at the Norwegian University of Science and Technology (NTNU) to ensure that all variables entered by the local coordinators were equally presented. The system was transparent so that all corrections could be traced with dates and signatures. Local coordinators only had access to their own case report forms, and they were responsible for checking that all the entered data were de-identified, complete and accurate. For quality control, one of the researchers in the LaPS research group checked whether all the required boxes in the case report form contained accurate information. Before closing the database, two of the LaPS research group members conducted a final check of all variables for quality control purposes. When missing data were identified, the local coordinators were contacted and asked to search for the missing data in the patient's medical record. If implausible values were found, the local coordinators were asked to correct or verify the values.

Variables used in each paper

Paper I

Paper I aimed to investigate whether there were differences in clinical consequences for the TGCS group I women adhering to Zhang's guideline (51) and those adhering to the WHO partograph (40) .

The primary outcome was the frequency of ICS use. The secondary outcomes were as follows:

- Operative vaginal delivery
- Artificial rupture of the membranes
- Augmentation with oxytocin
- Epidural analgesia
- Blood transfusion
- Episiotomy
- The degree of obstetric anal sphincter injury (OASIS)
- Apgar score of less than 7 at 5 min
- Arterial umbilical cord pH of less than 7.00

The descriptive statistics measured labour duration, labour dystocia according to the allocated guidelines and labour dystocia as an indicator of ICS.

All of the analyses in paper I were based on all included women, except for the analyses of episiotomy and OASIS, which were restricted to women with vaginal deliveries, and the calculation of labour dystocia as an indicator of ICS, which was restricted to women who received ICS.

Paper II

Paper II aimed to provide detailed knowledge and descriptive statistics about the use of augmentation with synthetic oxytocin during labour in accordance with Zhang's guideline (51) or the WHO partograph (40) . Analyses were conducted to assess the effects of the two different guidelines on nulliparous women.

The following outcomes were measured:

- The proportion of oxytocin augmentation during labour
- Duration of oxytocin augmentation (in minutes)
- Maximum dose of oxytocin (in ml/h)
- Dose when initiating augmentation
- Cervical dilatation when initiating augmentation
- Proportion of cases in which oxytocin was discontinued
- Proportion of cases with labour dystocia according to the allocated guideline
- Cervical dilatation when labour dystocia was diagnosed

All analyses in Paper II were based on all included women, except for the analyses of the duration of oxytocin administration, maximum dose of oxytocin administration and cervical dilatation when initiating oxytocin, which were restricted to women who were treated with oxytocin infusion to augment contractions.

Paper III

Understanding the normal variations in labour duration is important, and these variations should be considered when identifying slow labour progress. Thus, Paper III aimed to investigate the duration of different phases of active labour among women in TGCS group 1 when adhering to Zhang's guideline (51) or the WHO partograph (40) .

The outcomes measured in the paper were:

- The duration of total time in active labour,
- The duration of the active phase of the first stage,
- The duration of the second stage.

The duration of total time in active labour was defined as the time from the first registration of cervical dilatation of at least 4 cm until the delivery of the baby, either vaginally or by ICS. The duration of the active phase of the first stage was defined as the time from the first registration of cervical dilatation of at least 4 cm until the cervix is fully dilated at 10 cm or ICS is performed. The duration of the second stage was defined as the time from full dilatation of the cervix until the baby was born vaginally or via ICS.

The descriptive statistics in median and the 95th percentile from one integer centimetre to the next centimetre of cervical dilatation were presented for each treatment group and subdivided into vaginally delivered and for those with an ICS.

Computing of time variables for the different delivery phases and stages

The length of the active phase of the first stage of labour was re-coded based on cervix dilatation data from the web-CRF. In the web-CRF, dilatation data could be entered for every half hour from the start of partograph registration. If cervix dilatation was not examined, the corresponding data point was not filled in the web-CRF. The duration of the second stage was directly registered in the web-CRF. The total length of active labour was computed as the sum of the length of the active phase of the first stage and the duration of the second stage.

Estimated duration of progression to the next centimetre of dilatation

The duration of progression to the next centimetre of dilatation was estimated. Women with at least two cervical dilatation measurements during active labour were included in these calculations. Progression was estimated as a maximum of six separate time intervals during the first stage of the active phase: 4–5 cm, 5–6 cm, 6–7 cm, 7–8 cm, 8–9 cm and 9–10 cm of cervical dilatation.

The progression depended on each participant's cervical dilatation at admission. That is, women who were admitted at a cervical dilatation of 4 cm and who reached dilatation of 10 cm would progress through six time intervals, while those who were admitted at a dilatation of 5 cm would progress through five time intervals, and so on. For the women who reached full cervical dilatation, the starting point of each time interval is the first registration of a specific centimetre and the end point is the first registration of the consecutive centimetre. If the consecutive centimetre was not observed but advanced cervical dilatation was observed at a later time point, the time to the consecutive centimetre was estimated by linear interpolation between the two consecutive measurements. The starting point of an interval was estimated in the same way if the specific cervical dilatation was not observed but an advanced cervical dilatation was observed at a later time point.

For women who underwent ICS before full cervical dilatation, the last registered cervical dilatation was considered the end point of the last time interval; that is, the time interval was right-censored. These women contributed with the their unique observation time in this interval, which was set to the period from when they entered the interval until ICS was performed.

Statistics

Statistical analyses

In all three papers, the demographic and baseline characteristics of the treatment group were descriptively summarised. All efficacy analyses were based on the size (i.e. point estimate) of the difference between the treatments and the 95 % confidence interval (CI) and p-values of the corresponding statistical hypothesis test as supporting information. A two-tailed p-value of 0.05 or less was considered significant. The adjusted risk ratio, risk difference and mean difference with confidence intervals were estimated using the delta method (105). In addition, the intraclass correlation coefficient (ICC) was estimated by the logistic mixed model. The ICC is a descriptive statistic that can be used when quantitative measurements are performed on units that are organised into groups, and it describes how strongly units in the same group resemble each other (Figure VIII).

$$ICC = \frac{Between\ cluster\ variability}{With\ in\ cluster\ variability + Between\ cluster\ variability}$$

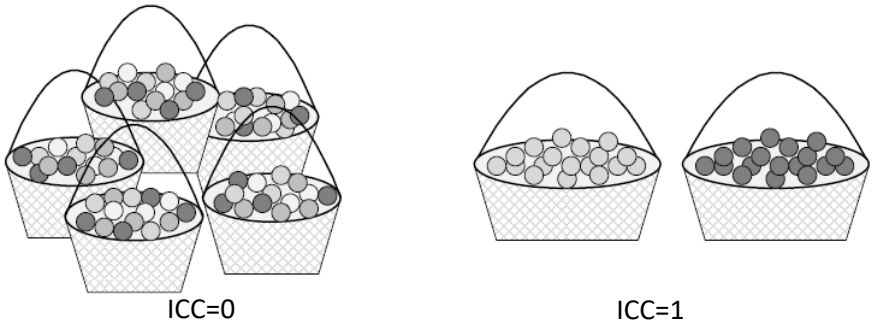


Figure VIII. Illustration of intraclass correlation.

The analyses were conducted according to the intention-to-treat principle and aimed to estimate the effect of the two guidelines. All statistical analyses were performed using Stata, version 15 (2015, Stata Statistical Software, Release 15.1, College Station, TX, USA), except for the analyses of the duration of progression from one centimetre interval to the next, which were analysed using the statistical programme R, version 3.5.0.

Overview of the efficacy analyses

Table 1. Efficacy analyses used in Papers I–III.

Paper	Statistical analyses	
I	Mixed logistic regression model	ICS Operative vaginal delivery Rupture of the membranes Oxytocin Epidural analgesia Blood transfusion Apgar score Umbilical cord pH Episiotomy OASIS Labour dystocia Labour dystocia as an indicator of ICS
II	Mixed logistic regression model	Oxytocin augmentation Cervical dilatation when initiating augmentation with oxytocin Proportion of cases in which oxytocin was discontinued Proportion of cases with labour dystocia according to the allocated guideline Cervical dilatation when labour dystocia is diagnosed
	Generalised linear mixed gamma model	Duration of oxytocin augmentation Maximum dose of oxytocin augmentation Dose of oxytocin when initiating augmentation
III	Parametric survival analysis	Duration of total time in active labour Duration of the active phase in the first stage Duration of second stage

Mixed logistic regression model

The mixed logistic regression model was used in Papers I and II to assess the differences between the dichotomous variable endpoints. Obstetric units were used as a random intercept,

and the treatment strategy was used as a fixed effect. In the model, we adjusted for the stratification variables (annual ICS rates and number of deliveries) and for the predefined covariates that are considered potential risk factors for ICS at an individual level. These predefined covariates were maternal age, BMI, marital status and educational level of the mother. The predefined covariates of the neonates were birthweight and head circumference.

Generalised linear mixed gamma model

A generalised linear mixed gamma model with a logarithmic link function was used for continuous outcomes. In this model, birth care units served as random intercepts and the treatment strategy served as the fixed effect. We adjusted for the stratification variables (annual ICS rates and number of deliveries) and for the following predefined covariates: maternal age, BMI, marital status and educational level of the mother. The predefined covariates of the neonates were birthweight and head circumference.

Parametric survival analysis

The time-to-event variables were analysed using a mixed Weibull regression model with cluster as the random intercept and treatment strategy as the fixed effect. We adjusted for the same covariates as in the mixed logistic regression and generalised linear mixed gamma models in addition to the first registration of cervical dilatation. The analysis results were presented as adjusted estimated group-specific marginal median times and adjusted study group differences. The accelerated delivery time factor was also given. This factor was used to quantify how slow or fast the birth progressed for the women in the intervention group compared to those in the control group.

The aim of survival analysis is to investigate data regarding the time to some event of interest. In some cases, the exact event of interest has not occurred, and hence the time is unknown and thus the individuals are censored. Table 2 presents an overview of the time-to-event variables in Paper III, the events of interest and whether or not censoring was performed for the three variables. Right censoring happened when the event of interest did not occur in an individual during the trial, while left censoring happened when the event had occurred in the individual before the study started.

Table 2. Overview of the time-to-event variables, events of interest and censoring.

	Event of interest	Censoring
Total time in active labour	Delivery	No censoring
Duration of the active phase of the first stage	Cervical dilatation = 10 cm	Censoring for ICS
Duration of the second stage	Delivery	No censoring. ICS cases in first stage were not included

Delivery was defined as the event of interest for the variable 'total time in the active labour'. The total time in active labour, from the first partograph registration (≥ 4 cm) to delivery (either vaginally or via ICS), was registered for all participating women. No unobserved event was found in this analysis, and thus no censoring was performed. The event of interest for the outcome 'duration of the active phase in the first stage' was cervical dilatation of 10 cm. Thus the women with ICS in the first stage were right-censored at the time of ICS. For the outcome 'duration of the second stage', delivery (either vaginally or via ICS), was the event of interest and women with ICS in the first stage of labour were left-censored at the time of ICS and not included in this analysis.

Robustness analyses

Robustness analyses were performed in Paper I. These analyses were conducted on hospital-level covariates in 2013 because of the time gap between assessment of the stratification variables in 2012 and the onset of the study. Additional robustness analyses included non-adjusted models and models adjusted only for hospital-level covariates. Robustness analyses for umbilical cord artery pH variables that were less than 7.0 were performed with imputation of the worst outcome.

Missing data

Assessments of missing data were based on a blind review of the data. All included women were assessed to determine their birth delivery method, and thus there were no missing data for the primary endpoint. Only 0.3 % of observations were missing for the covariate of BMI, and 0.8 % of values were missing for cohabitant status. Given the low rate of missing data, we

decided to use a stochastic linear regression single imputation (106) for BMI and used a cohabitant status of ‘not known’ as a category in addition to ‘cohabitant/married’ and ‘single’.

The secondary outcomes also had no missing data, except for the umbilical cord artery pH variables, for which 33.1 % of values were missing. For this endpoint, the main analyses were imputed with the best outcome. The best outcome for the variable of dichotomous umbilical cord artery pH was a pH value above or equal to 7.0. The choice to perform imputation with the best or worst outcome was discussed in the research group. Imputation was performed with the best outcome given that the study population was generally healthy, and it was expected that fewer new-borns would have low umbilical cord artery pH.

Ethical considerations

The study was performed in accordance with the ethical standards of research and the Helsinki declaration (107). The managers at all participating obstetric units signed a cooperation agreement in which they agreed to adhere to the protocol. The participating women received written information about the trial and were asked to provide informed consent to include their data in the analysis. The participants did not have the opportunity to choose a different guideline since the obstetric units were randomised. However, they were informed about the option to go to another hospital for labour care. Neither the obstetric units nor the participants were compensated financially. The study was approved by the Regional Committee for Medical and Health Research Ethics (no. 2013/1862/REK Sør-Øst) and registered with ClinicalTrials.gov (no. NCT02221427).

Results

In total, 24 obstetric units were eligible to participate in the LaPS. Ten obstetric units were not able to participate in the study. Three hospitals had other ongoing projects, three abstained from participation and four did not participate for other reasons. Between August 2014 and September 2014, a total of 14 clusters were enrolled in the LaPS (Figure IX).

Between December 2014 and January 2017, a total of 11,615 women were considered eligible to participate in the trial. Among these women, 5,421 were assigned to units in the control group and 6,194 were assigned to units in the intervention group. In the control group, 2,100 did not give signed consent to participate and 16 abstained from participation. In the intervention group, 2,181 did not give signed consent to participate and 41 abstained from participation. Thus, 7,277 (62.7 %) of the 11,615 eligible women were included in the trial. The two study groups were well-balanced in relation to their characteristics, except for variations in civil status (Table 3).

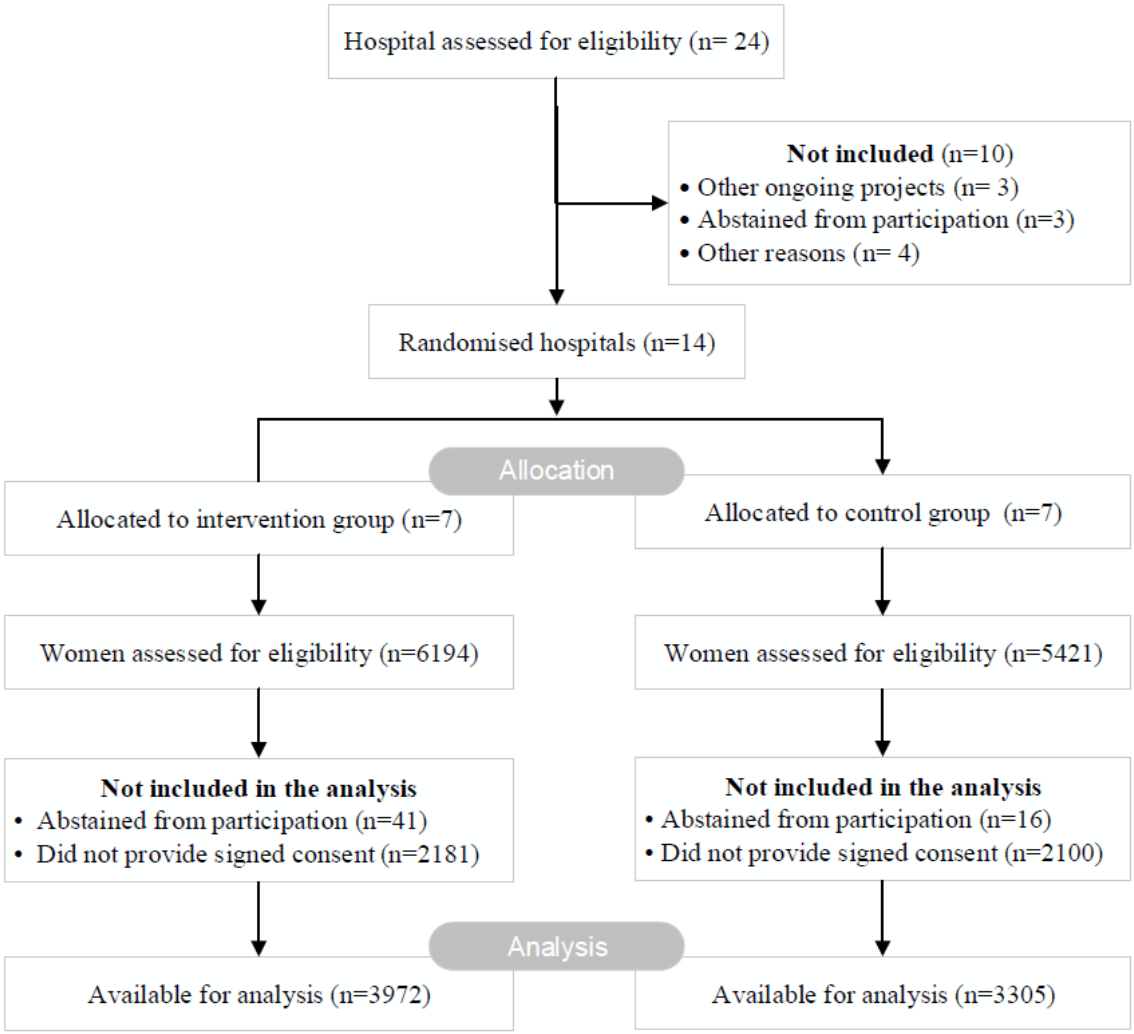


Figure IX. Inclusion of hospitals and participants in the LaPS.

Table 3. Baseline characteristics of included hospitals and participants.

	Zhang group		**WHO group**	
	Hospitals (n=7)	**Participants** (n=3972)	**Hospitals** (n=7)	**Participants** (n=3305)
No. (%) or mean (SD)				
Hospital characteristics				
Deliveries per year				
≥500 to <1000	0	0	1	133 (1.8)
≥1000 to <3000	6	2688 (36.9)	5	2100 (28.8)
≥3000	1	1284 (17.6)	1	1072 (14.7)
Maternal characteristics				
Age at delivery				
<25 (years)		971 (24.4)		784 (23.7)
25–35 (years)		2679 (67.4)		2275 (68.8)
≥35 (years)		322 (8.1)		246 (7.4)
Civil status (Cohabitant or married) **		3741/3946 (94.8)		3137/3271 (95.9)
Higher education ≥12 years		2412 (60.7)		2017 (61.0)
Smoking during first trimester **		230/3963 (5.8)		210/3247 (6.5)
Pre-pregnant BMI †				
Mean **		23.6/3966 (4.3)		23.8/3287 (4.3)
Range				
<18.5		172 (4.3)		142 (4.3)
18.5–24.9		2692 (67.9)		2178 (66.3)
25–29.9		764 (19.3)		688 (20.9)
≥30		338 (8.5)		279 (8.5)
Neonatal characteristics				
Gestational age at onset of active labour (days)		281 (7.0)		281 (8.0)
Birthweight (gram)		3528 (427)		3518 (414)
Head circumference (cm)		35.0 (1.4)		35.0 (1.4)
Sex (female)		1983 (49.9)		1661 (503)

Only women who provided informed consent were included in the analysis. Due to a lack of consent, a total of 4,338 (37.3 %) women were not included in the trial. However, their basic characteristics are presented. The groups showed differences in the proportion of women aged 35 years old or older, those who were cohabitants/married, those who attended higher education and those with low BMI between the included and non-included women during the trial period (Table 4).

Table 4. Comparison of baseline characteristics of the included and non-included women.

	Included women n=7277	Missing	**Non-included women** n=4338	Missing	P-value
Maternal characteristics					
Age at delivery (years)*	28 ± 4		28 ± 5	1	1.0
≤ 25	1755 (24.1)		1026 (23.7)		0.57
25-35	4954 (68.1)		2923 (67.4)		0.44
≥35	568 (7.8)		388 (8.9)		0.03
Cohabitant or married	6878 (94.5)	60	3976 (91.7)	24	<0.001
Higher education ≥ 12 years	4429 (60.9)		2387 (55.0)	70	<0.001
Smoking first trimester	440 (6.0)	67	224 (5.2)	10	0.05
Pre-pregnant BMI *†	24 ± 4	24	24 ± 4	197	1.0
≤ 18.5	314 (4.3)		220 (5.1)		0.06
18.5–24.9	4870 (66.9)		2725 (62.8)		<0.001
25.0–29.9	1452 (20.0)		824 (19.0)		0.2
≥ 30.0	617 (8.5)		372 (8.6)		0.86
Gestational age at onset of active labour (days)*	281 ± 7		281 ± 8	7	1.0

Numbers are provided as no. (%) unless otherwise stated. *Values are means ± SD. †BMI is an individual's weight in kilograms divided by the square of their height in metres.

Main results

As the results are described in detail in each of the papers, only a summary of the main results is provided here.

Paper I

The main outcome measure in this paper was the rate of ICS. In the pre-intervention period, the proportion of ICS among the TGCS group 1 women were 9.3 % and 9.5 % in the intervention (i.e. Zhang) and control (i.e. WHO) groups, respectively. ICS was administered to 271 patients (6.8 %) in the Zhang group and 196 patients (5.9 %) in the WHO group. The adjusted relative risk of ICS in both the Zhang and WHO groups was 1.17 (95 % CI, 0.98–1.40) with an adjusted risk difference of 1.0 % (95 % CI, -0.1–2.1). We did not find any significant differences between the compared groups. There were no differences between the groups in terms of operative vaginal delivery, artificial rupture of membranes, augmentation with oxytocin, epidural analgesia, blood transfusion, episiotomy or anal sphincter injuries. There were also no significant differences in outcomes for the new-borns (i.e. Apgar score after 5 min) or neonates (i.e. umbilical cord artery pH).

Paper II

The objective of this paper was to compare the use of oxytocin augmentation during labour among nulliparous women in the Zhang and WHO groups. Oxytocin was used for 1,658 (42 %) women in the Zhang group and 1,561 (47 %) women in the WHO group. The adjusted relative risk of oxytocin augmentation in the Zhang group was 0.98 % (95 % CI = 0.84–1.15; p = 0.8), while that of the WHO group was −0.8 % (95 % CI = −7.8–6.1). We observed no significant difference in the proportion of oxytocin augmentation between the two study groups. However, there were differences in the use of oxytocin during labour. The participants in the Zhang group were less likely to be administered oxytocin for augmentation prior to cervical dilatation of 6 cm (24 %) compared to participants in the WHO group (28 %), with an adjusted relative risk of 0.84 % (95 % CI = 0.75–0.94; p = 0.003). On average, oxytocin was administered for almost 20 minutes longer in the Zhang group than in the WHO group, with an adjusted mean difference of 17.9 minutes (95 % CI = 2.7–33.1; p = 0.021). In

addition, more women in the WHO group (23 %) than in the Zhang group (19 %) were given oxytocin for augmentation without a diagnosis of labour dystocia.

Paper III

The objective of this paper was to compare the duration of different phases of labour in the Zhang and WHO groups. We found that labour had a longer overall duration, from the first registration of cervical dilatation (≥4 cm) to delivery of the baby, in the Zhang group than in the WHO group. The adjusted median duration of labour was 7.0 h in the Zhang group and 6.2 h in the WHO group (median difference = 0.84 h; 95 % CI = 0.2–1.5). Furthermore, the first and second stages of labour had a longer duration for women in the Zhang group than those in the WHO group. The adjusted median duration of first stage was 5.6 hours in the Zhang group and 4.9 hours in the WHO group (median difference = 0.66 hours; 95 % CI = 0.1–1.2), and the adjusted medians of the second stage were 88 and 77 minutes for the two groups, respectively (median difference = 0.18 hours; 95 % CI = 0.1–0.3).

Discussion

This thesis consists of three original papers, all of which are based on data collected in a cRCT. The main aim of the trial was to investigate the way in which two different guidelines for assessing labour progress affect maternal and neonatal outcomes related to delivery. This chapter compares and discusses the main results of the three papers in relation to previous studies. Furthermore, the methodological strengths and limitations of the papers are discussed to illuminate the extent to which limitations may have influenced the findings.

Discussion of results in Papers I–III

Paper I

The main aim of this paper was to investigate whether the frequency of ICS differed when adhering to the WHO partograph or Zhang's guidelines for assessing labour progression based on real-world evidence. We observed that the frequency was reduced in both the Zhang and WHO groups by 26.5 % and 37.8 %, respectively.

Consortium on Safe Labor was a multicentre retrospective study included 228,668 deliveries performed between 2002 and 2008, which abstracted detailed labour and delivery information from electronic medical records in 19 hospitals across the United States. (45). Based on data from the Consortium on Safe Labor, Zhang et al. (51, 108) published their research on labour progression in 2010. In 2014, the ACOG and the Society for Maternal-Fetal Medicine published recommendations regarding safe clinical strategies to prevent primary CS. After these works, there was controversy regarding whether the new curves and recommendations should be adopted (50, 109-111) as observational studies with different designs produced inconsistent results.

In 2014, Thuillier et al. conducted a before-and-after study (112) by implementing the new ACOG consensus recommendations (45) at Poissy-Saint Germain Hospital in France. The guidelines changed the cut-off point between the latent and active phases of the first stage of labour from 4 to >6 cm. The authors found a decrease in the rate of ICS after implementation of new recommendations from 9.4 % in the pre-guideline period to 6.9 % in the post-guideline period (112). A similar study conducted by Wilson-Leedy et al. in Pennsylvania

(113) examined the adoption of new labour guidelines for nulliparous women. Within the small retrospective cohort, the rate of CS decreased from 26.9 % to 18.8 % and the frequency of CS cases performed to arrest dilatation dropped from 7.1 % to 1.1 % after the new guidelines were implemented (113). It is worth noting that no formal guidelines regarding labour management existed at the hospital before the new recommendations were adopted. Both Thuillier et al. and Wilson-Leedy et al. (112, 113) demonstrated a reduction in the rate of CS (in order to arrest dilatation at <6 cm and in the second stage of labour, respectively). However, the studies were not sufficiently powered or designed to assess the effect size of such reductions for a large population of low-risk women.

Between 2010 and 2014, Rosenbloom et al. conducted a prospective cohort study (114) of 7,845 labouring patients at or beyond 37 weeks of gestation at the Washington University School of Medicine. His study was one of the first to examine the impact of the new ACOG labour guidelines at the hospital level. Rosenbloom et al. did not demonstrate a reduction in ICS use, despite significant changes in labour management over the first few years, after the new labour curves and associated guidelines were published (114). However, he did find an increase in maternal and neonatal morbidity after implementation of the new recommendations (114).

As stated previously, the LaPS is the first trial to compare Zhang's guideline and the WHO partograph with a robust study design (i.e., a cRCT), as the importance of conducting a RCT was requested by researchers (3, 114, 115).

In the LaPS, we found no statistically significant difference in the rate of ICS between the two groups. However, the overall reduction in ICS rate suggests that focusing on interventions might have more of an impact on the rate of ICS rates than use of the guidelines, is in accordance with another cRCT (30). If the LaPS was designed and conducted as a before-and-after study, there might have been a similar reduction after introducing Zhang's guideline. However, the results could be interpreted as favouring the new guideline. This highlights the importance of conducting trials with a robust design to draw accurate conclusions.

In 2018, a Cochrane review (3) was performed to determine the effectiveness and safety of partograph use and which partograph design is most effective for perinatal and maternal morbidity and mortality outcomes and eleven studies with different partographs were

reviewed,. A pilot study that featured the most similar design to Zhang's guideline—a partograph with a stepped dystocia line—compared this design with a traditional partograph containing a two-hour action line among 99 women in Australia (116). There was no clear difference in CS rate between the groups. A different small study compared a labour scale versus the traditional WHO partograph using a sample of 122 women (64). The labour scale resulted in fewer CSs caused by a delay in labour, but it did not produce any clear differences in the overall CS rate or duration of the first stage of labour compared to the WHO partograph. All other studies compared partographs with different hours to action line, and there was no clear difference in the reduction in CS rate when two, three or four hour action lines were used (3).

In 2018, the WHO published a new guideline regarding intrapartum care for a positive childbirth experience. This was a consolidated set of new and existing recommendations for essential labour and childbirth practices that should be provided to all pregnant women and their babies during labour and childbirth. The WHO identified a knowledge gap regarding which guidelines, if any, are preferable for assessing labour progression when aiming to reduce unnecessary interventions such as CS (2). According to the guideline, there is not enough research to recommend a particular paper-based or digital tool for monitoring labour and guiding decision-making to improve birth outcomes (2).

The results of the LaPS are an important contribution to the discussion about whether implementation of Zhangs's guideline is beneficial. In the study, implementation resulted in a statistically and clinically significant decrease in the rate of CS in both groups. However, we did not find any difference between the groups regarding the use of ICS due to diagnosis of labour dystocia. Previous research (117) suggests that a universal standard for an expected linear labour progression curves is not applicable to current physiological labour patterns; one could question whether standard guidelines are applicable to all women if the guidelines do not account for normal and individual variations in labour progression (118).

During the period in which the LaPS was conducted, a Breakthrough project (concept developed by the Institute for Healthcare Improvement, US) was conducted in Norway. This project focused on limiting CS to those for whom it was medically indicated. Of the 14 birth care units included in the LaPS, 13 were also included in the Breakthrough project. In all 13, there was a significant decrease in the rate of ICS during the period of the LaPS. Thus, the extent to which the Breakthrough project affected our results is of interest. However, among

the birth care units with more than 500 deliveries per year that participated in the Breakthrough project but not the LaPS, there was a limited decrease or no decrease in the rate of ICS. Hence, it is likely that the Breakthrough project had little or no impact on the results of the LaPS.

Paper II

The medicalisation of labour and increasing use of interventions, especially oxytocin, in contemporary birth care is a common subject of discussion (119). For example, reduction of unnecessary interventions, including oxytocin, is highlighted in the new guideline for intrapartum care published by the WHO (2). Two of the objectives of the LaPS were to provide detailed knowledge about the use of oxytocin augmentation during labour and to investigate whether there were differences in oxytocin augmentation between the two groups.

The results of the 2018 Cochrane review aiming to determine the effectiveness and safety of partograph use (3) are difficult to interpret and compare due to the use of different partograph designs. Windrim et al. (120) reported no clear differences between groups in an oxytocin augmentation investigation that utilised a partograph vs. no partograph design. In a comparison of partographs with different action line placements (i.e. two, three and four hours), women with a two-hour action line were more likely to receive oxytocin augmentation (3). However, a pilot study of 99 women from Australia, which compared a partograph with a two-hour action line and a partograph with a stepped dystocia line, found that fewer women received oxytocin augmentation in the stepped dystocia line group but there were no clear differences in secondary maternal or neonatal outcomes (116). In a different study comparing a labour scale to the traditional WHO partograph, oxytocin augmentation was found to be reduced in the labour scale group and there were no clear differences in any of the other outcomes (64). The study was small, including only 122 women randomised into the groups, and the results were inconsistent with those of the LaPS, which found no significant difference in the proportion of oxytocin augmentation between the two study groups was observed. However, the LaPS did find differences between the two study groups regarding how oxytocin was used during labour; women in the Zhang group were less likely to receive oxytocin augmentation prior to cervical dilatation of 6 cm than those in the WHO group.

A Swedish trial of early or delayed oxytocin augmentation found no differences in obstetric and neonatal outcomes when oxytocin was used as a single agent, apart from a reduction in labour duration (121), in accordance with the results of systematic reviews (87). Other Scandinavian studies revealed a high rate of oxytocin use among nulliparous women, often without apparent indication (76, 88), consistent with the findings of the LaPS. In the LaPS, a total of 21 % of women underwent oxytocin augmentation without a diagnosis of labour dystocia. More women were augmented in the WHO group (23 %) than in the Zhang group (19 %) without being diagnosed with labour dystocia. In Norwegian hospitals, midwives are, to a significant extent, responsible for determining when labour does not progress as expected and thus initiating oxytocin infusion for low-risk women. However, the high rate of oxytocin intervention is inconsistent with midwives' goal of facilitating normal childbirth. According to Clark et al. (92), the use of checklist-based protocols may be one way to optimise the safety of oxytocin administration. Other studies have also shown that using checklists or standardised protocols for oxytocin use reduces the rate of augmentation with oxytocin (97) and increases the documentation of indications (122).

Oxytocin administration has been associated with adverse neonatal outcomes, typically due to hyperactive uterine contraction patterns caused by overstimulation, as described in the background section (89, 92-95). In the LaPS, 41 neonates with umbilical cord artery pH of less than 7.0 were identified, with no difference between the study groups. Furthermore, we did not find a difference in the frequency of Apgar scores of < 7 after 5 min between the two groups.

Our findings align with previous research, which identified a high rate of oxytocin augmentation without improved birth outcomes for the mother or baby (87-89). For example, a large population-based cohort study including nearly half a million healthy pregnant women and their children showed that children born by spontaneous vaginal birth had fewer short- and long-term health problems than those born after interventions. This also suggests that, when examining labour interventions, researchers need to pay attention to use of oxytocin administration and perform long-term follow-up (123).

Paper III

Understanding normal variations in the duration of labour is important and should be the basis for identifying truly slow labour progress that necessitates interventions (49, 50, 53-55). The purpose of Paper III was to compare the duration of labour from cervical dilatation of 4 cm to delivery when practitioners adhered to Zhang's guideline and the WHO partograph.

Reporting labour duration is challenging due to the selection of participants included in the analysis. Women that deliver via CS may experience different labour progression patterns and durations than those that deliver vaginally. Thus, excluding women who deliver via CS during the first stage of labour will inevitably affect the reported duration. In contrast to prior analyses (51, 118), the analysis conducted as part of the LaPS included all participating women, regardless of their interventions and mode of delivery. As LaPS was performed using a pragmatic approach in real-life clinical situations, labour duration was recorded for all women. This meant that each woman could contribute to the duration of labour with their unique time-to-event, and the analysis could be based on real-life scenarios without significant inclusion and exclusion variables.

Synthetic oxytocin is known to shorten the duration of labour (87). Epidural analgesia may also affect the duration of labour (124, 125), but its impact on labour duration in the first stage remains unclear (126). In the LaPS, more women in the WHO group received augmentation with synthetic oxytocin compared with the Zhang group (47.2 % vs. 41.7 %). The rate of epidural analgesia was similar in the Zhang and WHO groups (48.2 % vs. 50.0 %) and, therefore, the intervention probably had a limited impact on labour duration.

We also found that women who adhered to Zhang's guideline for labour progression had longer overall labour duration (measured from cervical dilatation of 4 cm until delivery), compared to women adhering to the WHO partograph. The unadjusted median duration of labour was 6.6 h in the Zhang group and 6.1 h in the WHO group. The 5th and 95th percentiles in the Zhang group were 1.4 h and 16.0 h, respectively and those in the WHO group were 1.3 and 13.8, respectively.

The unadjusted median duration of the first stage was 5.0 h in the Zhang group and 4.5 h in the WHO group. Previous studies (50, 51, 118) reported median durations of the active phase (from 4 cm until cervical dilatation of 10 cm) ranging from 3.7 h to 5.9 h. Our study is

consistent with these durations, but unlike the LaPS, the other studies included only women who had experienced vaginal births and births with no adverse outcomes.

For women in the LaPS, the 5th and 95th percentiles of durations of the first stage of labour were 0.5 and 15.0 h, respectively, in the Zhang group and 0.5 and 12.5 h, respectively, in the WHO group. The findings of the LaPS support other primary studies, which observed that the dilatation rate in healthy pregnant women could be slower than 1 cm/h (50, 51, 67, 118). Although these studies included women who did not receive obstetric interventions (66, 67), Oladapo's trial (118) included women with no epidural analgesia, but 40 % were administered oxytocin. Two trials performed by Zhang (50, 51) revealed an epidural analgesia rate of 8 % and an oxytocin rate of 20–47 %.

In the LaPS, the 95th percentile of the unadjusted duration of the second stage was considerably longer than that reported by Abalos et al. (52), whose review revealed a median duration in nulliparous women ranging from 14 to 66 min (49, 51, 118). Two studies (49, 51) in this review reported epidural use of 48 % and 100 % and reported relatively longer median durations (53–66 min). The 95th percentile reached 216 minutes in one study (51), while in the LaPS, the adjusted median was 88 min in the Zhang group and 77 min in the WHO group.

In general, the median and 95th percentile durations required to advance from one centimetre of dilatation to the next were longer for women in the Zhang group than those in the WHO group. Among those who delivered vaginally, the 95th percentile durations were 6 h and 4.5 h for the Zhang and WHO groups, respectively. The differences in the unadjusted median hours decreased as labour advanced, and from cervical dilatation of 8 cm onwards, the intervals were equal for the two groups. These findings are in accordance with the labour durations reported in contemporary research presented in a recent systematic review (117). One exception is the study performed by Suzuki et al. (127), who reported slower labour progression from one centimetre to the next. This study reported oxytocin administration of 6.5 % and no use of epidural analgesia (127).

Several trials (49-51, 127, 128) reported that the pooled median time required to dilate 1 cm among nulliparous women was longer than 1 h until dilatation of 5 cm was reached. The 95th percentiles reported by individual studies suggest that it was not uncommon for women to spend more than 4 h dilating from 4 to 5 cm. As labour progressed, the 95th percentiles of different studies showed wide variability around the median for each level of cervical dilatation. One review (52) and the LaPS confirm that there are wide individual variations in

labour patterns, illustrating the importance of assessing labour progression on an individual basis. As such, it is reasonable to use the 95th percentile of the distribution of normal labour duration to define abnormal labour, as this distribution takes the wide individual variation into account. Additionally, for the 5 % of women in the Zhang group who took 6 h or longer to progress from 4 cm to 5 cm of cervical dilatation and those in Suzuki's study (127) who took 15 h or longer to achieve the same progression, labour resulted in vaginal delivery. This highlights the complexity of assessing labour progression.

Methodological considerations

This thesis applies a cluster randomised controlled design. The research quality of cRCT is evaluated in terms of both internal and external validity.

Cluster randomised controlled design

RCT is considered the gold standard design for assessing the effects of treatment, as it provides the most reliable evidence regarding the efficacy of health interventions. However, a cRCT may also be an efficient strategy when an intervention is difficult to implement at the individual level without risk of contamination, such as in the case of interventions that affect environments (102). An cRCT was chosen over an individual RCT for the LaPS because of the former's ability to control for contamination. The risk of contamination associated with individual randomisation would have been particularly high if the mothers who received the control intervention were treated by a midwife or physician who also treated mothers with the new intervention (102).

The disadvantages of cRCT compared to individual RCT include greater complexity in design and analysis, the need to include more participants to achieve the same statistical power (129) and the need for access to an adequate number of groups. Conducting a cRCT with 30 or more clusters can be expensive, although the costs can sometimes be mitigated if data can be accessed from electronic health records or other available resources. In a cRCT, the members of clusters serve as the individual units that are observed and measured. Typically, a small

number of groups are randomised to each condition because the groups often contain a large number of members. However, a small number of randomised groups introduces a greater potential for threats to internal validity because it is less likely to control for potential bias. Thus, this is a major disadvantage of cluster randomised trials. Some of these threats can be decreased by utilising appropriate analytic strategies, adhering to strictly design strategies and anticipating and measuring potential confounding variables. These measures were taken in the LaPS.

Real-life pragmatic approach

A pragmatic RCT aims to test an intervention within a whole-spectrum clinical setting, thereby enabling generalisation (130). With this approach, the LaPS was able to investigate the effectiveness of Zhang's guideline in real-life clinical practice. In contrast, explanatory approaches seek to investigate how an intervention works, typically in well-defined and controlled settings with strict inclusion and exclusion criteria (130).

The decision-making process related to performing an ICS consists of several interacting components. It depends on the individual skills and experiences of both obstetricians and midwives and reflects the real-life clinical context (131). The two main indications for ICS are labour dystocia and non-reassuring foetal heart rate. It may be difficult to define the main indication for an intervention because slow progress is an indication for oxytocin augmentation, even though this increases the risk of foetal distress. Therefore, we used the overall rate of ICS as the main endpoint. When assessing labour dystocia in clinical practice, different practitioners will inevitably choose different approaches, regardless of the labour progression guideline to which they adhere. In Paper I, we presented the total number of ICS cases according to the allocated guidelines (132).

Masking

Masking is considered an important methodological factor for ensuring high internal validity within an RCT. In the LaPS, we were not able to mask the participants or the health care providers. However, to avoid bias in Paper I, the investigators who analysed the data were masked in relation to group allocation (i.e. which clusters belonged to the same intervention)

(132). Before locking the database, a plan for statistical analysis in Paper I was written and approved and all the analyses to be conducted were pre-specified. After random allocation and signing of the statistical analysis plan, the group allocation was revealed.

We also wrote specific statistical plans for Papers II and III, making an effort to keep the decisions for these papers as unbiased as possible by not performing any group comparison analyses prior to finalisation of the documents and thus avoiding result-driven analyses.

Selection bias

Another limitation to be considered is selection bias. When selection bias occurs, the obtained sample is not representative of the defined population of interest and thus is a threat to validity. To ensure representative selection of obstetric units, all geographical health regions in Norway were included. At the time of inclusion, 24 obstetric units were assessed for eligibility. It is possible that selection bias introduced a threat to internal validity since there were ten obstetric units that did not participate in the study, as explained earlier. However, when using a central randomisation system, selection bias is considered to be a low risk. The randomisation process in the LaPS was computer-generated and stratified by the proportion of previous ICSs and the number of deliveries.

Informed consent

Obtaining individuals' informed consent when conducting a cRCT poses several challenges, and the importance of doing so varies. Donner and Klar (102) and Eldridge et al. (133) suggested that the need to seek informed consent from cluster members depends on the type of experimental intervention being evaluated in a particular cRCT. In studies with cluster-level experimental interventions, interventions may be difficult for cluster members to avoid, effectively making refusal to provide consent meaningless. In such studies, it has been suggested that consent need not be sought. Conversely, in studies with patient-level experimental interventions that use a cRCT design for logistical reasons or to avoid treatment contamination, consent should be sought as it would in individually randomised trials. In the LaPS, it was decided that signed consent should be obtained from each woman before using their data. In total, 4,338 women did not provide signed consent and thus their data could not

be used, even though their treatment adhered to one of the guidelines. The Regional Committee for Medical and Health Research Ethics provided permission (2013/1862/REK) for us to retrieve basic characteristics from these women in order to assess whether the population in the LaPS was representative of the general population of TGCS group I women and whether there were differences between the included and non-included women.

Intervention

The intervention included a labour progression guideline from 2010 based on a cohort of 27,000 first-time mothers (51). After random allocation of the obstetric units to the clusters and before inclusion of participants, the staff of all obstetric units underwent a comprehensive programme about the trial protocols.

The intervention has some limitations that must be discussed. First, the intervention group used and monitored labour progress using a paper version of the guideline, whereas the control group used an electronic version. It can be difficult to measure minutes and hours and determine the current time for diagnosis of labour dystocia in a new, not familiar paper version. This process might be easier for midwives in the control group that were familiar with the guideline and electronic format. Second, the LaPS investigated the active phase of labour and defined the onset of active labour as at least 4 cm of cervical dilatation. However, this definition does not align with the original guideline proposed by Zhang; rather, it is rooted in the Norwegian obstetric management and could have affected the results. In a perfect design, the onset of active labour would have been different for the two study groups since the definition of onset in the two guidelines differs.

Treatment compliance

Treatment compliance during labour management is known to be a challenge. We strived to ensure thorough implementation of the trial, as described in the method section. However, we cannot guarantee that all health care providers adhered to the guideline in all cases. Although we lack knowledge about the extent to which the units adhered to the allocated guidelines, we made an effort to guide them and promote adherence when we revisited the units. Also, we assumed that the rate of non-compliance would be the same in both groups. However, when

analysing the data regarding oxytocin use, we found that application of this intervention did not always align with the guidelines; some women underwent oxytocin augmentation without being diagnosed with labour dystocia. It would have been possible to create a random control of adherence to the guidelines by comparing the differences between groups and then adjusting for possible differences, but we did not do this since it is part of the nature of a RCT.

Hawthorne effect

The Hawthorne effect occurs when research participants are influenced by the knowledge that they are being studied (134). The traditional example of this stems from research at the Hawthorne Works, a factory at which researchers discovered that workers were more productive when working conditions (such as lighting) changed, regardless of how they changed. The reason for this increased productivity was that the workers put in extra effort when the researchers were present, and hence all new changes in working conditions seemed to work. In the LaPS, we observed that ICS use was reduced in both the control group (by 37.8 %) and the intervention group (by 26.5 %) relative to the frequency of ICS use in 2012, before the start of the study. The intense focus on assessing labour progression in the study period might have led to optimisation of labour management and an overall decrease in ICS use, which could be explained as the Hawthorn effect.

Statistical considerations

There are multiple methods of analysis that can be used in cluster randomised trials (102, 135). Generally, they can be divided into cluster-level and individual-level methods. Cluster-level methods are based on aggregated data and involve a standard method, such as a t-test or analysis of covariance. The analyses might be weighted by cluster size if there are enough clusters for estimation of the ICC. However, the method might be under-powered when the number of clusters is small and it is not possible to adjust for covariates at the individual level. Individual-level methods are based on individual observations, with the analyses adjusted for clustering effects. Simple methods for adjusting chi-square estimates exist (102), as do model-based approaches, such as marginal generalised estimating equations and

conditional logistic mixed models. Of the two latter types of models, the logistic mixed model seems more robust when fewer than 40 clusters are analysed (135). Compared to simple methods, model-based methods allow for both cluster- and individual-specific covariates. Note that there is a difference in the interpretation of estimated treatment effects between the marginal and conditional models. The marginal model effect measures are interpreted based on the population average, while the conditional model estimates are interpreted based on the average effect for individual hospitals. Due to the low number of clusters in the LaPS, we believed that a conditional mixed model approach was the most robust for analysis.

The choice of a mixed logistic regression model as the main statistical method in the LaPS allowed for inclusion of both individual- and cluster-level covariates and estimation of the ICC. The adjustments for covariates increased the precision of estimates after adjusting for imbalances in the baseline characteristics of the treatment groups.

Survival analysis

While Weibull regression analysis relies on a two-parametric model for distribution of survival times, the Cox model does not impose a parametric form on the distribution. Both methods allow for covariates and adjustment for cluster effects. In line with the analysis of binary data in the original Statistical Analysis Plan, we use a parametric mixed model (i.e. Weibull's) due to its good performance (136, 137).

In the primary analysis, delivery was defined as the event of interest. Since the total duration of active phase of labour (first and second stage), from the first partograph registration (≥4 cm) until delivery (either vaginally or via ICS) was registered for all included women, there were no unobserved events to be analysed and, consequently, no censoring.

In the secondary analyses, the event of interest for duration of the active phase of the first stage of labour was 'cervical dilatation = 10 cm'. Not all women experienced the event of interest, and the event was not observed. In traditional survival analysis, the registered time to an event, if the event does not occur during the observation period (e.g. if the patient is lost to follow-up), is often considered to be censored. This was the case for this variable in the LaPS. However, treating observation times as censored requires assumptions of independent and non-informative censoring (138). If the time to an event is not observed because an event either hinders observation of the event of interest or modifies the chance that this event will

occur, data should ideally be treated as competing events (i.e. competing risk analysis should be performed) and not as censored (139). Although some statistical methods for analysis of competing risk in clustered data have been recently developed (140, 141), these do not cover all models, and we therefore chose to perform traditional survival analyses with censoring of ICS, also due to the low rate of ICS in the study.

Intraclass correlation coefficient

The ICC is a descriptive statistic that can be used when quantitative measurements are performed for units that are organised into groups. It describes how strongly units in the same group resemble each other. Cluster randomised designs introduce dependence (or clustering) between the sampled individual units. For example, in the LaPS, when comparing differences in outcomes achieved under Zhang's guideline, we had to account for the fact that two women sampled from a single birth care unit are more likely to be similar (in terms of outcomes) than two women sampled from different birth care units. A cluster randomised design therefore requires more complex analysis that involves, for example, adjustment for the ICC (129). In our study, the ICC for the primary outcome was small (i.e. less than 0.001), which indicated that the variation in the outcome that could be attributed to clusters was small.

Robustness analyses

We performed several robustness analyses to strengthen internal validity by assessing the effects of different assumptions and choices (142). This was done by checking several additional prespecified analysis models, including unadjusted models, hospital-level only adjusted models, cluster-level analysis models and standard logistic regression. Ignoring the cluster design in the analyses resulted in lower p-values and narrower CIs. This indicates the importance of not ignoring the cluster effect. The results of the LaPS were consistent for all analyses adjusted for cluster effects, suggesting that the findings are valid. The cluster design was incorporated into power calculations to ensure an adequate sample size from the clusters.

Conclusions

The three studies in this thesis provide knowledge about the impact of using two labour progression guidelines on clinical maternal and neonatal outcomes. They serve as important contributions to the literature on different labour progression guidelines and, as they feature robust study designs, provide a strong basis for guiding clinical practice on how to reduce unnecessary interventions.

Paper I

This paper found no significant difference in the frequency of ICS among nulliparous women between obstetric units that adhered to the WHO partograph and those that adhered to Zhang's guideline. Increased focus on assessment of labour progression might have a stronger effect on ICS use than the guidelines themselves.

Paper II

Although no significant difference in the proportion of oxytocin augmentation was observed between the two study groups, there were differences in how oxytocin was used. Women in the Zhang group were less likely to be augmented with oxytocin prior to cervical dilatation of 6 cm. Also, the duration of augmentation with oxytocin was longer in the Zhang group than in the WHO group.

Paper III

Women in obstetric units adhering to Zhang's guideline, compared those in units adhering to the WHO partograph, had a longer total duration of labour, duration of the active phase of the first stage and duration of the second stage.

Future implications

The overall aim of the LaPS was to compare the ways in which the WHO partograph and Zhang's guideline for assessing labour progress affect maternal and neonatal outcomes. The results showed no statistically significant difference in the rate of ICS between the two groups. However, they represent an important contribution to the discussion regarding whether implementation of the new guidelines is beneficial and why RCTs investigating this topic should be performed.

We observed that ICS use was reduced in both the control and intervention groups relative to the frequency of ICS use before our study started. The decrease in the frequency of ICS use in both groups suggests that the global challenge of increases in ICS use can be addressed by focusing on interventions. In Norway, where the frequency of ICS use is low, we found a substantial reduction in ICS use. Further studies should be conducted in countries with more frequent ICS use than in Norway and investigate the extent to which a reduction might eventually occur when the focus on labour progression is increased. Additionally, our findings were restricted to women in TGCS group 1, and thus future studies should use the guidelines to improve birth care and reduce interventions for other subgroups.

Although no significant difference in the proportion of oxytocin augmentation was observed between the two study groups, there were differences in how oxytocin was used. More women were augmented with oxytocin without a labour dystocia diagnosis in the WHO group than in the Zhang group. To use the guideline/partograph as intended, identification of risk, action or intervention only when needed and the capacity to act in accordance with the required interventions are crucial (143).

Additionally, in a recent diagnostic accuracy study, researchers concluded that labour is an extremely variable phenomenon and suggested that current assessments of cervical dilatation over time, including partographs, showed poor diagnostic accuracy in terms of identifying women at risk of severe adverse birth outcomes during labour (55). Being aware of the complexity of labour curves could question whether it is possible or meaningful to adhere to a median labour curve for all women. In the future, personalised labour progression monitoring and care could be provided in settings with many resources via monitoring programmes designed with artificial intelligence techniques (143). Improvements in the quality of care will improve women's satisfaction and perceived quality of the birth experience.

References

1. Vahratian A, Troendle JF, Siega-Riz AM, Zhang J. Methodological challenges in studying labour progression in contemporary practice. Paediatr Perinat Epidemiol. 2006;20(1):72-8.
2. World Health Organization. WHO recommendations: Intrapartum care for a positive childbirth experience [Internet]. Geneva: WHO; 2018 [cited 2019 Aug 29]. Available from: http://apps.who.int/iris/bitstream/handle/10665/260178/9789241550215-eng.pdf;jsessionid=F1F5397399F448885328491174AC61C6?sequence=1.
3. Lavender T, Cuthbert A, Smyth RM. Effect of partograph use on outcomes for women in spontaneous labour at term and their babies. Cochrane Database Syst Rev. 2018;8:CD005461.
4. United Nations. Millennium development goals and beyond 2015. [Internet]. [cited 2019 Aug 28]. Available from: https://www.un.org/millenniumgoals/.
5. Molina G, Weiser TG, Lipsitz SR, Esquivel MM, Uribe-Leitz T, Azad T, et al. Relationship Between Cesarean Delivery Rate and Maternal and Neonatal Mortality. JAMA. 2015;314(21):2263-70.
6. Lobel M, DeLuca RS. Psychosocial sequelae of cesarean delivery: review and analysis of their causes and implications. Soc Sci Med. 2007;64(11):2272-84.
7. Jackson S, Fleege L, Fridman M, Gregory K, Zelop C, Olsen J. Morbidity following primary cesarean delivery in the Danish National Birth Cohort. Am J Obstet Gynecol. 2012;206(2):139 e1-5.
8. Smith GC, Pell JP, Dobbie R. Caesarean section and risk of unexplained stillbirth in subsequent pregnancy. Lancet. 2003;362(9398):1779-84.
9. Levine EM, Ghai V, Barton JJ, Strom CM. Mode of delivery and risk of respiratory diseases in newborns. Obstet Gynecol. 2001;97(3):439-42.
10. Renz-Polster H, David MR, Buist AS, Vollmer WM, O'Connor EA, Frazier EA, et al. Caesarean section delivery and the risk of allergic disorders in childhood. Clin Exp Allergy. 2005;35(11):1466-72.
11. Betran AP, Ye J, Moller AB, Zhang J, Gulmezoglu AM, Torloni MR. The Increasing Trend in Caesarean Section Rates: Global, Regional and National Estimates: 1990-2014. PLoS One. 2016;11(2):e0148343.
12. Ye J, Zhang J, Mikolajczyk R, Torloni MR, Gulmezoglu AM, Betran AP. Association between rates of caesarean section and maternal and neonatal mortality in the 21st century: a worldwide population-based ecological study with longitudinal data. BJOG. 2016;123(5):745-53.
13. Robson MS. Can we reduce the caesarean section rate? Best Pract Res Clin Obstet Gynaecol. 2001;15(1):179-94.
14. Murray SF. Relation between private health insurance and high rates of caesarean section in Chile: qualitative and quantitative study. BMJ. 2000;321(7275):1501-5.
15. Ye J, Betran AP, Guerrero Vela M, Souza JP, Zhang J. Searching for the optimal rate of medically necessary cesarean delivery. Birth. 2014;41(3):237-44.
16. Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. Lancet. 2000;356(9239):1375-83.
17. Mi J, Liu F. Rate of caesarean section is alarming in China. Lancet. 2014;383(9927):1463-4.
18. Appropriate technology for birth. Lancet. 1985;2(8452):436-7.
19. Villar J, Valladares E, Wojdyla D, Zavaleta N, Carroli G, Velazco A, et al. Caesarean delivery rates and pregnancy outcomes: the 2005 WHO global survey on maternal and perinatal health in Latin America. Lancet. 2006;367(9525):1819-29.
20. Althabe F, Sosa C, Belizan JM, Gibbons L, Jacquerioz F, Bergel E. Cesarean section rates and maternal and neonatal mortality in low-, medium-, and high-income countries: an ecological study. Birth. 2006;33(4):270-7.

21. Betran AP, Merialdi M, Lauer JA, Bing-Shun W, Thomas J, Van Look P, et al. Rates of caesarean section: analysis of global, regional and national estimates. Paediatr Perinat Epidemiol. 2007;21(2):98-113.
22. Lumbiganon P, Laopaiboon M, Gulmezoglu AM, Souza JP, Taneepanichskul S, Ruyan P, et al. Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007-08. Lancet. 2010;375(9713):490-9.
23. Belizan JM, Althabe F, Cafferata ML. Health consequences of the increasing caesarean section rates. Epidemiology. 2007;18(4):485-6.
24. Baldo MH. Caesarean section in countries of the Eastern Mediterranean Region. East Mediterr Health J. 2008;14(2):470-88.
25. Victora CG, Barros FC. Beware: unnecessary caesarean sections may be hazardous. Lancet. 2006;367(9525):1796-7.
26. What is the right number of caesarean sections? Lancet. 1997;349(9055):815.
27. Betran AP, Torloni MR, Zhang J, Ye J, Mikolajczyk R, Deneux-Tharaux C, et al. What is the optimal rate of caesarean section at population level? A systematic review of ecologic studies. Reprod Health. 2015;12:57.
28. World Health Organization. Statement on Caesarean Section Rates [Internet]. Geneva: WHO

2015 [cited 2019 Aug 28]. Available from: http://apps.who.int/iris/bitstream/10665/161442/1/WHO_RHR_15.02_eng.pdf.
29. Althabe F, Belizan JM, Villar J, Alexander S, Bergel E, Ramos S, et al. Mandatory second opinion to reduce rates of unnecessary caesarean sections in Latin America: a cluster randomised controlled trial. Lancet. 2004;363(9425):1934-40.
30. Chaillet N, Dumont A, Abrahamowicz M, Pasquier JC, Audibert F, Monnier P, et al. A cluster-randomized trial to reduce cesarean delivery rates in Quebec. N Engl J Med. 2015;372(18):1710-21.
31. Norwegian Birth Registry of Norway [Internet]. Norwegian Institute of Public Health; 2018 [cited 2019 Aug 28]. Available from: https://www.fhi.no/en/hn/health-registries/medical-birth-registry-of-norway/.
32. Anderson G. A concept analysis of normal birth. Evidence Based Midwifery. 2003;1(2):48-54.
33. Kennedy HP, Cheyney M, Lawlor M, Myers S, Schuiling K, Tanner T, et al. The development of a consensus statement on normal physiologic birth: a modified Delphi study. J Midwifery Womens Health. 2015;60(2):140-5.
34. American College of N-M, Midwives Alliance of North A, National Association of Certified Professional M. Supporting healthy and normal physiologic childbirth: a consensus statement by the American College of Nurse-Midwives, Midwives Alliance of North America, and the National Association of Certified Professional Midwives. J Midwifery Womens Health. 2012;57(5):529-32.
35. Downe S. Is there a future for normal birth? Who knows what 'normal birth' really means today? Pract Midwife. 2001;4(6):10-2.
36. Care in normal birth: a practical guide. Technical Working Group, World Health Organization. Birth. 1997;24(2):121-3.
37. International Confederation of Midwives. Keeping Birth Normal [Internet]. The Netherlands2014 [cited 2019 Aug 28]. Available from: https://www.internationalmidwives.org/assets/files/statement-files/2018/04/keeping-birth-normal-eng.pdf.
38. The Norwegian Directorate of health. National Quality indicators [Internet]. Oslo: The Norwegian Directorate of health 2017 [cited 2019 Aug 28]. Available from: https://www.helsedirektoratet.no/statistikk/statistikk/kvalitetsindikatorer/graviditet-og-fodsel/f%C3%B8dsler-uten-st%C3%B8rre-inngrep-og-komplikasjoner.
39. NICE guidelines. Intrapartum care [Internet]. National Institute for Health and Clinical Excellence 2014 [updated 2017; cited 2019 Aug 28]. Available from: https://www.nice.org.uk/guidance/cg190.

40. World Health Organization. Managing complications in pregnancy and childbirth: a guide for midwives and doctors [Internet]. Geneva: WHO; 2000 [updated 2007; cited 2019 Aug 28]. Available from: http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf.
41. World Health Organization. Preventing prolonged labour : a practical guide : the partograph. Maternal Health and Safe Motherhood Programme. Report no. WHO/FHE/MSM/93.8-11 [Internet]. Geneva: WHO; 1994 [cited 2019 Aug 28]. Available from: https://apps.who.int/iris/handle/10665/58903.
42. World Health Organization. International Classification of Diseases. The global standard for diagnostic health information [Internet]. Geneva: WHO; 2018 [cited 2019 Aug 28]. Available from: https://icd.who.int/en/.
43. Hanley GE, Munro S, Greyson D, Gross MM, Hundley V, Spiby H, et al. Diagnosing onset of labor: a systematic review of definitions in the research literature. BMC Pregnancy Childbirth. 2016;16:71.
44. Norwegian Society of Gynecology and Obstetrics. National guidelines in Obstetrics 2014 [Internet]2014 [cited 2018 Aug 28]. Available from: https://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veiledere/Veileder-i-fodselshjelp-2014/.
45. Caughey AB, Cahill AG, Guise JM, Rouse DJ. Safe prevention of the primary cesarean delivery. Am J Obstet Gynecol. 2014;210(3):179-93.
46. Friedman E. The graphic analysis of labor. Am J Obstet Gynecol. 1954;68(6):1568-75.
47. Friedman EA. Primigravid labor; a graphicostatistical analysis. Obstet Gynecol. 1955;6(6):567-89.
48. Friedman EA. Evolution of graphic analysis of labor. Am J Obstet Gynecol. 1978;132(7):824-7.
49. Zhang J, Troendle JF, Yancey MK. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol. 2002;187(4):824-8.
50. Zhang J, Troendle J, Mikolajczyk R, Sundaram R, Beaver J, Fraser W. The natural history of the normal first stage of labor. Obstet Gynecol. 2010;115(4):705-10.
51. Zhang J, Landy HJ, Branch DW, Burkman R, Haberman S, Gregory KD, et al. Contemporary patterns of spontaneous labor with normal neonatal outcomes. Obstet Gynecol. 2010;116(6):1281-7.
52. Abalos E, Oladapo OT, Chamillard M, Diaz V, Pasquale J, Bonet M, et al. Duration of spontaneous labour in 'low-risk' women with 'normal' perinatal outcomes: A systematic review. Eur J Obstet Gynecol Reprod Biol. 2018;223:123-32.
53. Neal JL, Lowe NK, Patrick TE, Cabbage LA, Corwin EJ. What is the slowest-yet-normal cervical dilation rate among nulliparous women with spontaneous labor onset? J Obstet Gynecol Neonatal Nurs. 2010;39(4):361-9.
54. Neal JL, Lowe NK, Schorn MN, Holley SL, Ryan SL, Buxton M, et al. Labor Dystocia: A Common Approach to Diagnosis. J Midwifery Womens Health. 2015;60(5):499-509.
55. Souza JP, Oladapo OT, Fawole B, Mugerwa K, Reis R, Barbosa-Junior F, et al. Cervical dilatation over time is a poor predictor of severe adverse birth outcomes: a diagnostic accuracy study. BJOG. 2018;125(8):991-1000.
56. World Health Organization. World Health Organization partograph in management of labour. World Health Organization Maternal Health and Safe Motherhood Programme. Lancet. 1994;343(8910):1399-404.
57. Lavender T, Lugina H, Smith H. The partograph: a life-saving tool for African midwives. Trop Doct. 2007;37(3):191-2.
58. Bosse G, Massawe S, Jahn A. The partograph in daily practice: it's quality that matters. Int J Gynaecol Obstet. 2002;77(3):243-4.
59. Bedwell C, Levin K, Pett C, Lavender DT. A realist review of the partograph: when and how does it work for labour monitoring? BMC Pregnancy Childbirth. 2017;17(1):31.
60. Groeschel N, Glover P. The partograph. Used daily but rarely questioned. Aust J Midwifery. 2001;14(3):22-7.
61. Friedman E. Labor: clinical evaluation and management. New York, USA: Appleton-Century-Crofts; 1978.

62. Philpott RH, Castle WM. Cervicographs in the management of labour in primigravidae. II. The action line and treatment of abnormal labour. J Obstet Gynaecol Br Commonw. 1972;79(7):599-602.
63. Philpott RH, Castle WM. Cervicographs in the management of labour in primigravidae. I. The alert line for detecting abnormal labour. J Obstet Gynaecol Br Commonw. 1972;79(7):592-8.
64. Shazly SA, Embaby LH, Ali SS. The labour scale--assessment of the validity of a novel labour chart: a pilot study. Aust N Z J Obstet Gynaecol. 2014;54(4):322-6.
65. Neal JL, Lowe NK. Physiologic partograph to improve birth safety and outcomes among low-risk, nulliparous women with spontaneous labor onset. Med Hypotheses. 2012;78(2):319-26.
66. Albers LL, Schiff M, Gorwoda JG. The length of active labor in normal pregnancies. Obstet Gynecol. 1996;87(3):355-9.
67. Albers LL. The duration of labor in healthy women. J Perinatol. 1999;19(2):114-9.
68. Jones M, Larson E. Length of normal labor in women of Hispanic origin. J Midwifery Womens Health. 2003;48(1):2-9.
69. Lowe NK. A review of factors associated with dystocia and cesarean section in nulliparous women. J Midwifery Womens Health. 2007;52(3):216-28.
70. Gary Cunningham KJL, Steven L. Bloom, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Catherine Y. Spong. . Williams Obstetrics. 25 ed2018.
71. Adams SS, Eberhard-Gran M, Eskild A. Fear of childbirth and duration of labour: a study of 2206 women with intended vaginal delivery. BJOG. 2012;119(10):1238-46.
72. Leveno KJ, Nelson DB, McIntire DD. Second-stage labor: how long is too long? Am J Obstet Gynecol. 2016;214(4):484-9.
73. Hellman LM, Prystowsky H. The duration of the second stage of labor. Am J Obstet Gynecol. 1952;63(6):1223-33.
74. Cohen WR. Influence of the duration of second stage labor on perinatal outcome and puerperal morbidity. Obstet Gynecol. 1977;49(3):266-9.
75. American College of O, Gynecology Committee on Practice B-O. ACOG Practice Bulletin Number 49, December 2003: Dystocia and augmentation of labor. Obstet Gynecol. 2003;102(6):1445-54.
76. Selin L, Almstrom E, Wallin G, Berg M. Use and abuse of oxytocin for augmentation of labor. Acta Obstet Gynecol Scand. 2009;88(12):1352-7.
77. Selin L, Wallin G, Berg M. Dystocia in labour - risk factors, management and outcome: a retrospective observational study in a Swedish setting. Acta Obstet Gynecol Scand. 2008;87(2):216-21.
78. Kjaergaard H, Olsen J, Ottesen B, Dykes AK. Incidence and outcomes of dystocia in the active phase of labor in term nulliparous women with spontaneous labor onset. Acta Obstet Gynecol Scand. 2009;88(4):402-7.
79. Zhu BP, Grigorescu V, Le T, Lin M, Copeland G, Barone M, et al. Labor dystocia and its association with interpregnancy interval. Am J Obstet Gynecol. 2006;195(1):121-8.
80. Nystedt A, Hildingsson I. Diverse definitions of prolonged labour and its consequences with sometimes subsequent inappropriate treatment. BMC Pregnancy Childbirth. 2014;14:233.
81. Lavender T, Alfirevic Z, Walkinshaw S. Partogram action line study: a randomised trial. Br J Obstet Gynaecol. 1998;105(9):976-80.
82. Neal JL, Ryan SL, Lowe NK, Schorn MN, Buxton M, Holley SL, et al. Labor Dystocia: Uses of Related Nomenclature. J Midwifery Womens Health. 2015;60(5):485-98.
83. Argiolas A, Gessa GL. Central functions of oxytocin. Neurosci Biobehav Rev. 1991;15(2):217-31.
84. Neumann ID. Brain oxytocin: a key regulator of emotional and social behaviours in both females and males. J Neuroendocrinol. 2008;20(6):858-65.
85. Blanks AM, Thornton S. The role of oxytocin in parturition. BJOG. 2003;110 Suppl 20:46-51.
86. Ragnarsson U. The Nobel trail of Vincent du Vigneaud. J Pept Sci. 2007;13(7):431-3.

87. Bugg GJ, Siddiqui F, Thornton JG. Oxytocin versus no treatment or delayed treatment for slow progress in the first stage of spontaneous labour. Cochrane Database Syst Rev. 2013;6:Cd007123.
88. Bernitz S, Oian P, Rolland R, Sandvik L, Blix E. Oxytocin and dystocia as risk factors for adverse birth outcomes: a cohort of low-risk nulliparous women. Midwifery. 2014;30(3):364-70.
89. Oscarsson ME, Amer-Wahlin I, Rydhstroem H, Kallen K. Outcome in obstetric care related to oxytocin use. A population-based study. Acta Obstet Gynecol Scand. 2006;85(9):1094-8.
90. Institute for Safe Medical Practices. List of High-Alert Medications in Acute Care Settings [Internet]. 2014 [cited 2019 Aug 28]. Available from: http://www.ismp.org/Tools/institutionalhighAlert.asp.
91. Jonsson M, Norden-Lindeberg S, Ostlund I, Hanson U. Metabolic acidosis at birth and suboptimal care--illustration of the gap between knowledge and clinical practice. BJOG. 2009;116(11):1453-60.
92. Clark S, Belfort M, Saade G, Hankins G, Miller D, Frye D, et al. Implementation of a conservative checklist-based protocol for oxytocin administration: maternal and newborn outcomes. Am J Obstet Gynecol. 2007;197(5):480 e1-5.
93. Jonsson M, Norden-Lindeberg S, Ostlund I, Hanson U. Acidemia at birth, related to obstetric characteristics and to oxytocin use, during the last two hours of labor. Acta Obstet Gynecol Scand. 2008;87(7):745-50.
94. Simpson KR, James DC. Effects of oxytocin-induced uterine hyperstimulation during labor on fetal oxygen status and fetal heart rate patterns. Am J Obstet Gynecol. 2008;199(1):34 e1-5.
95. Berglund S, Grunewald C, Pettersson H, Cnattingius S. Risk factors for asphyxia associated with substandard care during labor. Acta Obstet Gynecol Scand. 2010;89(1):39-48.
96. Andreasen S, Backe B, Jorstad RG, Oian P. A nationwide descriptive study of obstetric claims for compensation in Norway. Acta Obstet Gynecol Scand. 2012;91(10):1191-5.
97. Nesheim BI. Low-risk labor - outcomes after introduction of special guidelines combined with increased awareness of risk category. Acta Obstet Gynecol Scand. 2012;91(4):476-82.
98. Hayes EJ, Weinstein L. Improving patient safety and uniformity of care by a standardized regimen for the use of oxytocin. Am J Obstet Gynecol. 2008;198(6):622 e1-7.
99. Rhoades JS, Cahill AG. Defining and Managing Normal and Abnormal First Stage of Labor. Obstet Gynecol Clin North Am. 2017;44(4):535-45.
100. Osterman M.; Martin J. Changes in cesarean delivery rates by gestational age: United States, 1996–2011. NCHS Data Brief. 2013;Jun(124):1-8.
101. NHS Maternity Statistics, England, 2013-14 [Internet]. Health and Social Care Information Centre Hospital Episode Statistics; 2015 [cited 2019 Aug 28]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2013-14.
102. Donner A, Klar, N. Design and Analysis of Cluster Randomization Trials in Health Research. 1 st ed. New York, USA: John Wiley & sons; ; 2010.
103. Robson M, Murphy M, Byrne F. Quality assurance: The 10-Group Classification System (Robson classification), induction of labor, and cesarean delivery. Int J Gynaecol Obstet. 2015;131 Suppl 1:S23-7.
104. Norwegian Medical Association. Augmentation of labor: Norwegian Society in Obstetrics and Gynecology; 2014 [Available from: http://www.nfog.org/files/guidelines/34%20NGF%20Obst%20Augmentation%20of%20labour%20Eggeb%C3%B8.pdf.
105. Reeve R. Confidence interval of difference of proportions in logistic regression in presence of covariates. Stat Methods Med Res. 2018;27(2):451-65.
106. Buuren S. Flexible Imputation of Missing Data [Internet]. New York, USA: Chapman and Hall/CRC; 2012 [cited 2019 Aug 28]. Available from: http://doi.org/10.1201/b11826.
107. The World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [Internet]. 2018 [cited 2019 Aug 28]. Available from:

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.
108. Zhang J, Troendle J, Reddy UM, Laughon SK, Branch DW, Burkman R, et al. Contemporary cesarean delivery practice in the United States. Am J Obstet Gynecol. 2010;203(4):326 e1- e10.
109. Cohen WR, Friedman EA. Misguided guidelines for managing labor. Am J Obstet Gynecol. 2015;212(6):753 e1-3.
110. Cohen WR, Friedman EA. Perils of the new labor management guidelines. Am J Obstet Gynecol. 2015;212(4):420-7.
111. Laughon SK, Branch DW, Beaver J, Zhang J. Changes in labor patterns over 50 years. Am J Obstet Gynecol. 2012;206(5):419 e1-9.
112. Thuillier C, Roy S, Peyronnet V, Quibel T, Nlandu A, Rozenberg P. Impact of recommended changes in labor management for prevention of the primary cesarean delivery. Am J Obstet Gynecol. 2018;218(3):341 e1- e9.
113. Wilson-Leedy JG, DiSilvestro AJ, Repke JT, Pauli JM. Reduction in the Cesarean Delivery Rate After Obstetric Care Consensus Guideline Implementation. Obstet Gynecol. 2016;128(1):145-52.
114. Rosenbloom JI, Stout MJ, Tuuli MG, Woolfolk CL, Lopez JD, Macones GA, et al. New labor management guidelines and changes in cesarean delivery patterns. Am J Obstet Gynecol. 2017;217(6):689 e1- e8.
115. Cohen WR, Friedman EA. Obstetric practice guidelines: labor's love lost? J Matern Fetal Neonatal Med. 2019;32(9):1567-70.
116. Lee NJ, Neal J, Lowe NK, Kildea SV. Comparing Different Partograph Designs for Use in Standard Labor Care: A Pilot Randomized Trial. Matern Child Health J. 2018;22(3):355-63.
117. Oladapo OT, Diaz V, Bonet M, Abalos E, Thwin SS, Souza H, et al. Cervical dilatation patterns of 'low-risk' women with spontaneous labour and normal perinatal outcomes: a systematic review. BJOG. 2017;125(8):944-54.
118. Oladapo OT, Souza JP, Fawole B, Mugerwa K, Perdona G, Alves D, et al. Progression of the first stage of spontaneous labour: A prospective cohort study in two sub-Saharan African countries. PLoS Med. 2018;15(1):e1002492.
119. Albers LL. Overtreatment of normal childbirth in U.S. hospitals. Birth. 2005;32(1):67-8.
120. Windrim R, Seaward PG, Hodnett E, Akoury H, Kingdom J, Salenieks ME, et al. A randomized controlled trial of a bedside partogram in the active management of primiparous labour. J Obstet Gynaecol Can. 2007;29(1):27-34.
121. Dencker A, Berg M, Bergqvist L, Ladfors L, Thorsen LS, Lilja H. Early versus delayed oxytocin augmentation in nulliparous women with prolonged labour--a randomised controlled trial. BJOG. 2009;116(4):530-6.
122. Holmgren S, Silfver KG, Lind C, Nordstrom L. Oxytocin augmentation during labor: how to implement medical guidelines into clinical practice. Sex Reprod Healthc. 2011;2(4):149-52.
123. Peters LL, Thornton C, de Jonge A, Khashan A, Tracy M, Downe S, et al. The effect of medical and operative birth interventions on child health outcomes in the first 28 days and up to 5 years of age: A linked data population-based cohort study. Birth. 2018;45(4):347-57.
124. Anim-Somuah M, Smyth RM, Jones L. Epidural versus non-epidural or no analgesia in labour. Cochrane Database Syst Rev. 2011(12):CD000331.
125. Grant EN, Tao W, Craig M, McIntire D, Leveno K. Neuraxial analgesia effects on labour progression: facts, fallacies, uncertainties and the future. BJOG. 2015;122(3):288-93.
126. Sng BL, Leong WL, Zeng Y, Siddiqui FJ, Assam PN, Lim Y, et al. Early versus late initiation of epidural analgesia for labour. Cochrane Database Syst Rev. 2014(10):CD007238.
127. Suzuki R, Horiuchi S, Ohtsu H. Evaluation of the labor curve in nulliparous Japanese women. Am J Obstet Gynecol. 2010;203(3):226 e1-6.
128. Shi Q, Tan XQ, Liu XR, Tian XB, Qi HB. Labour patterns in Chinese women in Chongqing. BJOG. 2016;123 Suppl 3:57-63.
129. Campbell MK, Piaggio G, Elbourne DR, Altman DG, Group C. Consort 2010 statement: extension to cluster randomised trials. BMJ. 2012;345:e5661.

130. Patsopoulos NA. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci. 2011;13(2):217-24.
131. Ford I, Norrie J. Pragmatic Trials. N Engl J Med. 2016;375(5):454-63.
132. Bernitz S, Dalbye R, Zhang J, Eggebø TM, Frøslie KF, Olsen IC, et al. The frequency of intrapartum caesarean section use with the WHO partograph versus Zhang's guideline in the Labour Progression Study (LaPS): a multicentre, cluster-randomised controlled trial. The Lancet. 2019;393(10169):340-8.
133. Eldridge SM, Ashby D, Feder GS. Informed patient consent to participation in cluster randomized trials: an empirical exploration of trials in primary care. Clin Trials. 2005;2(2):91-8.
134. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. J Clin Epidemiol. 2014;67(3):267-77.
135. Murray DM, Varnell SP, Blitstein JL. Design and analysis of group-randomized trials: a review of recent methodological developments. Am J Public Health. 2004;94(3):423-32.
136. Stedman MR, Lew RA, Losina E, Gagnon DR, Solomon DH, Brookhart MA. A comparison of statistical approaches for physician-randomized trials with survival outcomes. Contemp Clin Trials. 2012;33(1):104-15.
137. Crumer AM. Comparison between Weibull and Cox proportional hazards models [Internet]. Kansas, USA: Kansas State University; 2011 [cited 2019 Aug 28]. Available from: https://krex.k-state.edu/dspace/bitstream/handle/2097/8787/AngelaCrumer2011.pdf.
138. Kleinbaum DG; Klein M. Survival analysis: A self-learning text. 3 rd ed. New York, USA: Springer; 2012.
139. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant. 2013;28(11):2670-7.
140. Zhou B, Fine J, Latouche A, Labopin M. Competing risks regression for clustered data. Biostatistics. 2012;13(3):371-83.
141. Familusi MA. Analysis of Clustered Competing Risks with Application to a Multicentre Clinical Trial [Master thesis]. Cape Town, South Africa: University of Cape Town; 2016.
142. Eldridge S, Ashby D, Bennett C, Wakelin M, Feder G. Internal and external validity of cluster randomised trials: systematic review of recent trials. BMJ. 2008;336(7649):876-80.
143. Oladapo OT, Souza JP, Bohren MA, Tuncalp O, Vogel JP, Fawole B, et al. WHO Better Outcomes in Labour Difficulty (BOLD) project: innovating to improve quality of care around the time of childbirth. Reprod Health. 2015;12:48.

Appendices

Appendix I

Forespørsel om å få bruke avidentifiserte opplysninger fra din fødsel i et forskningsprosjekt

Dette er et spørsmål til deg om å få benytte opplysninger registrert rutinemessig i forbindelse med din fødsel i et forskningsprosjekt.

Bakgrunnen for forskningsprosjektet er at fødeavdelinger, både i Norge og i utlandet, bruker forskjellige retningslinjer for forventet fremgang i fødsel. I det forskningsprosjektet vi nå gjennomfører vil vi se på effekten ved bruk av to forskjellige retningslinjer.

Forskningsprosjektet foregår på 14 fødeinstitusjoner i Norge. Xxxxxx sjukehus er med i prosjektet og er tilfeldig valgt (randomisert) til å forholde seg til en av to retningslinjer for forventet fremgang i fødsel for alle førstegangsfødende der fødselen starter naturlig. Uansett hvilken retningslinje ditt fødested bruker, medfører det ikke noen risiko for deg og barnet ditt. Du vil følges nøye og trygt opp under fødselen.

Opplysningene vi ønsker å registrere er de samme som vi registrerer ved alle fødsler, for eksempel fremgang i fødselen, hvilke medikamenter som eventuelt brukes, oppfølging, inngrep og opplysninger om barnet etter fødsel som vekt og lengde. I tillegg vil vi be deg om å svare på et spørreskjema som omhandler din opplevelse av fødselen ca. fire uker etter at du har født.

Dersom du tillater oss å bruke opplysninger fra din fødsel i forskningsprosjektet, undertegner du nederst på dette arket. Alle opplysninger vil bli fortrolig behandlet og avidentifisert, før de blir analysert. Det vil ikke være mulig å identifisere enkeltpersoner når data skal publiseres. Om du avstår fra å være med i studien, vil det ikke påvirke ditt opphold ved føde-barselavdelingen på noen måte.

Har du spørsmål angående prosjektet er du velkommen til å ta kontakt med *Stine Bernitz* på e-post: stine.bernitz@so-hf.no eller telefon 909 44 715.

Ta med deg dette skjemaet når du kommer til fødeavdelingen.

Jeg har lest informasjonen og samtykker til at avidentifiserte opplysninger i forbindelse med min fødsel kan benyttes i studien.

Fødselsdato: _____ Navn: _____
(BLOKKBOKSTAVER)

E-postadresse: _____

Dato: _____ Signatur: _____

Prosjektansvarlig ved fødestedet

Navn: Xxxx Xxxxx

Tittel: Xxxxxxxxxxxxx

For LAPS

Navn: Stine Bernitz

Tittel: Jordmor, PhD, Sykehuset Østfold

Fritt sykehusvalg. I Norge gjelder "Fritt sykehusvalg" dette innebærer at du selv kan velge hvilket sykehus som skal undersøke og/eller behandle deg. Ordningen med fritt sykehusvalg omfatter alle sykehus forutsatt at institusjonen eies av et regionalt helseforetak eller har avtale med et regionalt helseforetak (www.frittsykehusvalg.no).

Appendix II

THE LABOUR PROGRESSION STUDY

EN MULTI-SENTER CLUSTERRANDOMISERT STUDIE

Samarbeidsavtale mellom _____ **og**

LAPS

Det planlegges for tiden en studie omhandlende retningslinjer for fødselsprogresjon for Robson gruppe I kvinner (førstegangsfødende med et barn i hodeleie som går spontant i fødsel fra svangerskapsuke 37, hvilket utgjør ca 28 % av fødepopulasjonen). Studien er forankret ved Sykehuset Østfold og Universitetssykehuset Nord-Norge.

Langsom fremgang i fødsel er den hyppigste årsaken til akutte keisersnitt, spesielt hos førstegangsfødende, og derfor en stor utfordring innen fødselshjelpen. Utfordringene forsterkes ytterligere ved at et tidligere keisersnitt i 50 % av tilfellene fører til nytt keisersnitt i neste graviditet. Det er ingen konsensus om en normal fødsels varighet og derfor heller ingen konsensus om definisjon av langsom fremgang.

I Norge er det vanlig å bruke en lineær progresjonskurve utarbeidet på bakgrunn av Friedmans kurve som bygger på et lite materiale fra 1950 tallet. I 2002 publiserte Jim Zhang en studie hvor han undersøkte 1329 lavrisikokvinner med spontan fødselsstart og fant at fødselsforløpene var av lenger varighet tidlig i åpningsfasen for så å akselerere raskere enn tidligere antatt mot slutten av åpningsfasen (1). Funnene ble bekreftet i en større studie som inkluderte 26.838 kvinner publisert i 2010 (2).

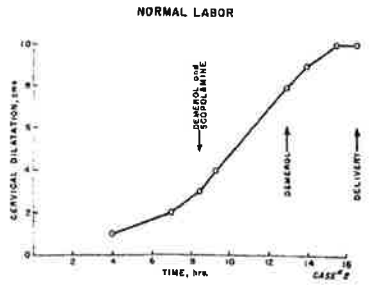
Hovedformålet med denne studien er å undersøke kliniske konsekvenser ved bruk to ulike definisjoner av forventet progresjon i fødselens aktive fase, en basert på fortolkning av Friedmans progresjonskurve og en basert på Zhang progresjonskurve. Det primære endepunktet er akutt keisersnitt, sekundære endepunkt er bruk av oxytocin, dystoci, amniotomi, fosterovervåking, smertelindring, operativ vaginal forløsning, episiotomi, perinealrupturer, post partum blødning, apgar score, navlesnors pH, overflytting til nyfødtintensiv avdeling og kvinners opplevelse av fødselen.

To retningslinjer for normal fødselsprogresjon F (Friedman) og Z (Zhang)

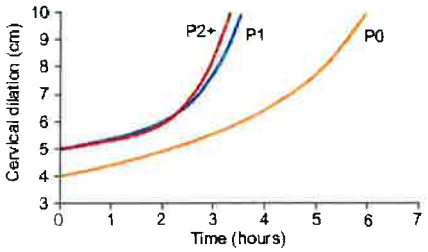
F = Retningslinje for normal progresjon: Normal framgang defineres som at cervix utvider seg minst 1 centimeter per time vurdert etter 4 timer, også kjent som 4-timers action line. Langsom fremgang defineres dersom progresjonen er langsommere enn dette i den aktive fasen av åpningsfasen. Langsom fremgang fra 10 cm til aktiv trykking defineres dersom varigheten overstiger en time, to timer for kvinner med epidural. Langsom fremgang defineres også dersom trykkefasen varer lenger enn 60 minutter. Denne definisjonen på progresjon i fødsel er basert på en tolkning av Friedmans forventete progresjon (figur I).

Z = Retningslinje for normal progresjon som tar hensyn til cervix' åpning ved innleggelse. Det er angitt en maksimal tid fra centimeter til centimeter som blir kortere jo lenger ut i fødselsforløpet kvinnen kommer. Langsom fremgang defineres dersom den angitte

maksimaltiden fra centimeter til centimeter overstiges i den aktive fasen av åpningsfasen. Langsom fremgang fra 10 cm til aktiv trykking defineres dersom varigheten overstiger en timer og 45 minutter, to timer og 30 minutter for kvinner med epidural. Langsom fremgang defineres også dersom trykkefasen varer lenger enn 60 minutter. Denne definisjonen på progresjon i fødsel er basert på forskning på fødsels progresjon av Zhang (figur II).



Figur I: Friedmans kurve



Figur II: Zhangs kurve

Vi benytter et cluster randomisert design hvilket innebærer at alle kvinner som tilhører Robson gruppe I behandles i følge den retningslinjen som hennes fødested er randomisert til i studieperioden (dvs at halvparten av avdelingene som er med i studien vil bruke retningslinje F og halvparten av avdelingene vil bruke retningslinje Z).

Styrkeberegningen baserer seg på en 25 % reduksjon av hovedendepunktet; akutt keisersnitt, fra en gjennomsnittsfrekvens på ca 9.2 % til en gjennomsnittsfrekvens på 6.9 %. En test styrke på 80 % og et signifikansnivå på 0,05 tilsier en inklusjon av 14 clustere og minimum 6582 individer i analysene. For mer detaljert informasjon, se vedlagt studieprotokoll.

Omfang av denne avtalen
Denne samarbeidsavtalen regulerer forholdet mellom
og LAPS ved Sykehuset Østfold for denne studien.

Hvert inkluderte fødested er ansvarlig for gjennomføringen av studien på det respektive sted hvilket innebærer inklusjon av pasienter etter retningslinjer beskrevet i protokollen og i henhold til gjeldende etiske retningslinjer. Videre forplikter det enkelte fødestedet å forholde seg til allokert retningslinje for alle fødekvinner i Robson gruppe I i studieperioden og til å fylle ut den web-baserte elektroniske databasen for alle individer som har gitt sitt samtykke til at dataene kan benyttes i studien.

Undervisning
Det planlegges oppstart av studien andre del av 2014. En studiekoordinator oppnevnes ved hvert enkelt fødested, denne vil drifte studien lokalt og ha tett samarbeid med studieansvarlig og forskergruppen for øvrig. Studieansvarlig vil sørge for instruksjon i bruk av retningslinjene og sammen med studiekoordinator tilse at opplæring av ansatte ved fødestedet gis før oppstart av studien. Inkluderingsperioden er antatt å vare i ca ett år.

Dataeierskap

Dataene dokumentert ved fødestedet eies av det enkelte foretaket. Prosjektgruppen har styringsrett over avidentifiserte data, samlet inn i den web-baserte elektroniske databasen

designet for denne studien ved NTNU. Denne avtalen er ikke til hinder for at det enkelte foretaket kan publisere egne data etter at hovedartiklene er publisert forutsatt at det ikke er i konflikt med hovedpublikasjoner. Dersom krav til medforfatterskap fylles (jfr. Vancouver reglene), åpnes det for at en medforfatter fra hvert fødested kan delta på en av studiens planlagte artikler. Prosjektgruppen har som mål å publisere resultater så raskt og effektivt som mulig.

Forskningsgruppen

Forskningsgruppen består av Stine Bernitz, jordmor, PhD ved Sykehuset Østfold (principal investigator) og førsteamanuensis ved Høgskolen i Oslo og Akershus, Ellen Blix, jordmor, professor ved Høgskolen i Oslo og Akershus, Pål Øian, obstetriker ved Universitetssykehuset Nord-Norge og professor ved Universitetet i Tromsø og Torbjørn Moe Eggebø, obstetriker ved St. Olavs Hospital og førsteamanuensis ved Norges Naturvitenskapelige Universitet.

Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS

Navn og signatur for LAPS:

Ellen Blix:... Ellen Blix ...

Stine Bernitz: ... [signature] ...

Pål Øian: ... P. Øian ...

Torbjørn Moe Eggebø: ... Torbjørn Moe Eggebø ...

Sted/dato:...

Navn, tittel og signatur på ansvarlig for studien ved

...

E-post adresse: ...

Navn på oppnevnt lokal koordinator: ...

E-post adresse... ...

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
2. Zhang J. et al. Contemporary Patterns of Spontaneous Labor With Normal Neonatal Outcomes. Obstet Gynecol 2010;116:1281-1287.

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Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og Molde sjukehus

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: P Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: Molde 1/10-14

Navn, tittel og signatur på ansvarlig for studien ved Molde sjukehus
Grete Teigland, Avdelingssjef

E-post adresse: grete.teigland@helse-mr.no

Navn på oppnevnt lokal koordinator: Berit Fiksdal

E-post adresse: berit.fiksdal@helse-mr.no

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
2. Zhang J. et al. Contemporary Patterns of Spontaneous Labor With Normal Neonatal Outcomes. Obstet Gynecol 2010;116:1281-1287.

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Med vennlig hilsen LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og sykehuset Elverum

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: P Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: Elverum 11/7-14

Navn, tittel og signatur på ansvarlig for studien ved sykehuset Elverum
ANNE BIRTHE LØMO, AVD.SJEF/AVD.OVERLEGE GYN/FØDE

E-post adresse: anne.birthe.lomo@sykehuset-innlandet.no

Navn på oppnevnt lokal koordinator: ANNE GRO KLOKKEHAUG - jm

E-post adresse: annklo@sykehuset-innlandet.no

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
2. Zhang J. et al. Contemporary Patterns of Spontaneous Labor With Normal Neonatal Outcomes. Obstet Gynecol 2010;116:1281-1287.

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Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og Nordlandssykehuset Bodø

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: P Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: Bodø 1/11 - 14

Navn, tittel og signatur på ansvarlig for studien ved Nordlandssykehuset Bodø: DR. HEIDI FROSTAD SIVERTSEN, AVD. OVERLEGE

E-post adresse: HEIDI.FROSTAD.SIVERTSEN@NLSH.NO

Navn på oppnevnt lokal koordinator: MARIT MATHISEN

E-post adresse: MARIT.MATHISEN@NLSH.NO

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
2. Zhang J. et al. Contemporary Patterns of Spontaneous Labor With Normal Neonatal Outcomes. Obstet Gynecol 2010;116:1281-1287.

3/11-14 Anita Kvarsnes
Klinikksjef Kvinne Barn NLSH

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Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og Sørlandet sykehus Arendal

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: P Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: Arendal 5/1-15

Navn, tittel og signatur på ansvarlig for studien ved Sørlandet sykehus Arendal

Overlege, ID-nr.: 2123 592
OLE-GEORG TORJUSEN
Sørlandet Sykehus HF, Arendal
Gyn./obst.avd.

E-post adresse: OLE-GEORG.TORJUSEN@sshf.no

Navn på oppnevnt lokal koordinator: SINDRE GRINDHEIM

E-post adresse: SINDRE.GRINDHEIM@sshf.no

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
2. Zhang J. et al. Contemporary Patterns of Spontaneous Labor With Normal Neonatal Outcomes. Obstet Gynecol 2010;116:1281-1287.

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Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og Lillehammer sykehus

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: P. Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: LHMR 12/6-14

Navn, tittel og signatur på ansvarlig for studien ved Lillehammer sykehus
AVD.SJEF./AVD.OVERLEGE STIAN WESTAD

E-post adresse: stian.westad@sykehuset-innlandet.no

Navn på oppnevnt lokal koordinator: TOVE RAGNHILD JOHNSEN

E-post adresse: tove.ragnhild.johnsen@sykehuset-innlandet.no

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
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Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og Universitetssykehuset i Nord Norge

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix ....

Stine Bernitz: ....

Pål Øian: ....

Torbjørn Moe Eggebø: ....

Sted/dato: Tromsø 11.06.2014 ....

Navn, tittel og signatur på ansvarlig for studien ved Universitetssykehuset i Nord Norge
Gunnel Adelsson ... GUNNEL ADELSSON SEKSJONSLEDER

E-post adresse: gunnel.adelsson@unn.no ....

Navn på oppnevnt lokal koordinator: Gunnbjørg Andreassen ... GUNNBJØRG ANDREASSEN

E-post adresse... gunnbjorg.andreassen@unn.no ....

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
2. Zhang J. et al. Contemporary Patterns of Spontaneous Labor With Normal Neonatal Outcomes. Obstet Gynecol 2010;116:1281-1287.

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Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og Ålesund sykehus

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: P. Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: Ålesund 1/7 - 2014

Navn, tittel og signatur på ansvarlig for studien ved Ålesund sykehus
Janita Skogerø, Avdelingssjef

E-post adresse: janita.skogerø@helse-mr.no

Navn på oppnevnt lokal koordinator: Sissel Hjelle, Seksjonsoverlege

E-post adresse: sissel.hjelle@helse-mr.no

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
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Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og Bærum sykehus

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: P Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: 20/8 14 BÆRUM SYKEHUS

Navn, tittel og signatur på ansvarlig for studien ved Bærum sykehus
INGERID H. HERSTAD NYGAARD

E-post adresse: INYGAA@vestviken.no

Navn på oppnevnt lokal koordinator: BIRGITTE D.A. JANSON

E-post adresse: bijans@vestviken.no

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
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Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og Sykehuset Telemark

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: [signature]

Pål Øian: P. Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: Skien 30/6-14

Navn, tittel og signatur på ansvarlig for studien ved Sykehuset Telemark

Åse Karin Kringlåk, Seksjonsleder, føde og barsel

E-post adresse: kna@sthf.no

Navn på oppnevnt lokal koordinator: Kjersti Helberg Skoe

E-post adresse: kjhf@sthf.no

1 Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
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Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og Sykehuset i Vestfold

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: P Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: Tønsberg 29/08-14

Navn, tittel og signatur på ansvarlig for studien ved Sykehuset i Vestfold
Linn Takheim Nistov Seksjonsoverlege Linn T Nistov

E-post adresse: linnis@siv.no

Navn på oppnevnt lokal koordinator: Irene Jensen

E-post adresse: irene.jensen@siv.no

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
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Med vennlig hilsen for **LAPS - THE LABOUR PROGRESSION STUDY**

Godkjenning av samarbeidsavtalen mellom **LAPS** ved Sykehuset Østfold og Drammen sykehus

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: P Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: Drammen 18.06.14

Marieke Claessen
Avdelingssjef/avdelingsoverlege
Avdeling for Gynekologi og Fødselshjelp
Drammen sykehus
HPR-nr.: 8661197

Navn, tittel og signatur på ansvarlig for studien ved Drammen sykehus
AVD. SJEF MARIEKE CLAESSEN (AVD. OVERLEGE)

E-post adresse: MARIEKE.CLAESSEN@VESTREVIKEN.NO

Navn på oppnevnt lokal koordinator: Seksjonsoverlege Dr. Margit Rosenberg

E-post adresse: MARGIT.ROSENBERG@VESTREVIKEN.NO.

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
2. Zhang J. et al. Contemporary Patterns of Spontaneous Labor With Normal Neonatal Outcomes. Obstet Gynecol 2010;116:1281-1287.

Signert 18/6 Marieke Claessen

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Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og Sykehuset Østfold

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: P Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: FREDRIKSTAD

Navn, tittel og signatur på ansvarlig for studien ved Sykehuset Østfold
HILDE HEIA, AVDELINGSSJEF KK, SØ

E-post adresse: ...

Navn på oppnevnt lokal koordinator: STINE BERNITZ, KATRINE D SJØBORG

E-post adresse: stine.bernitz@so-hf.no / katsjo@so-hf.no

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
2. Zhang J. et al. Contemporary Patterns of Spontaneous Labor With Normal Neonatal Outcomes. Obstet Gynecol 2010;116:1281-1287.

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Forskningsgruppen
Forskningsgruppen består av Stine Bernitz, jordmor, PhD ved Sykehuset Østfold (principal investigator) og førsteamanuensis ved Høgskolen i Oslo og Akershus, Ellen Blix, jordmor, professor ved Høgskolen i Oslo og Akershus, Pål Øian, obstetriker ved Universitetssykehuset Nord-Norge og professor ved Universitetet i Tromsø og Torbjørn Moe Eggebø, obstetriker ved St. Olavs Hospital og førsteamanuensis ved Norges Naturvitenskapelige Universitet.

Med vennlig hilsen for LAPS - THE LABOUR PROGRESSION STUDY

Godkjenning av samarbeidsavtalen mellom LAPS ved Sykehuset Østfold og St. Olavs Hospital

---

Navn og signatur for LAPS:

Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: P Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: M Trondheim 18/6-14

Navn, tittel og signatur på ansvarlig for studien ved St. Olavs Hospital
MARIT MARKVISEN, seksjonsoverlege Kvinne St. Olav

E-post adresse: marit.markvisen@st.olav.no

Navn på oppnevnt lokal koordinator: ennå ikke oppnevnt.

E-post adresse...

1. Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
2. Zhang J. et al. Contemporary Patterns of Spontaneous Labor With Normal Neonatal Outcomes. Obstet Gynecol 2010;116:1281-1287.

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Ellen Blix: Ellen Blix

Stine Bernitz: Stine Bernitz

Pål Øian: Pål Øian

Torbjørn Moe Eggebø: Torbjørn Moe Eggebø

Sted/dato: SUS / 17/7-2014

Navn, tittel og signatur på ansvarlig for studien ved Stavanger Universitetssykehus
Philip von Brandis, seks. overlege

E-post adresse: brph@sus.no

Navn på oppnevnt lokal koordinator: Daniella Rozsa, overlege

E-post adresse daniella.judit.rozsa@sus.no

1 Zhang J. et al. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol 2002;187:824-828.
2 Zhang J. et al. Contemporary Patterns of Spontaneous Labor With Normal Neonatal Outcomes. Obstet Gynecol 2010;116:1281-1287.

Appendix III

Zhang's guideline (paper version) used for the birth care units randomised to the intervention group

Time/hour		15	30	45		15	30	45		15	30	45		15	30	45		15	30	45		15	30	45		15	30	45		15	30	45		15	30	45	
Head level 4																																						
Head level 3																																						
Head level 2																																						
Head level 1																																						
Head level 0																																						
Partus																																						
Cm 10																																						
Cm 9																																						
Cm 8																																						
Cm 7																																						
Cm 6																																						
Cm 5																																						
Cm 4																																						
Cervix	**4 ► 5 cm**				**5 ► 6 cm**				**6 ►7 cm**				**7 ► 8 cm**				**8 ► 9 cm**				**9 ►10 cm**				**Descending phase without EDA**				**Descending phase with EDA**				**Active pushing**				**Baby born:**	
Max	6 hours + 30 min				3 hours + 15 min				2 hours + 15 min				1 hour + 30 min				1 hour + 30 min				1 hour + 45 min				1 hours + 45 min				2 hours + 30 min				60 min					
Latest																																						
Relevant																																						

Paper I

Bernitz, S., Dalbye, R., Zhang, J., Eggebøe, T. M., Frøslie, K. F., Olsen, I. C., Blix, E., Øian, P. (2018). The frequency of intrapartum caesarean section use with the WHO partograph versus Zhang's guideline in the Labour Progression Study (LaPS): a multicentre, cluster-randomised controlled trial. *The Lancet, 393*(10169).

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The frequency of intrapartum caesarean section use with the WHO partograph versus Zhang's guideline in the Labour Progression Study (LaPS): a multicentre, cluster-randomised controlled trial

Stine Bernitz, Rebecka Dalbye*, Jun Zhang, Torbjørn M Eggebø, Kathrine F Frøslie, Inge Christoffer Olsen, Ellen Blix†, Pål Øian†*

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*Contributed equally as first authors

†Contributed equally as senior authors

Department of Obstetrics and Gynaecology, Østfold Hospital Trust, Grålum, Norway (S Bernitz PhD, R Dalbye MSc); **Department of Nursing and Health Promotion, Faculty of Health Sciences, Oslo Metropolitan University (OsloMet), Oslo, Norway** (S Bernitz, R Dalbye, Prof E Blix DrPH); **Xinhua Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China** (Prof J Zhang PhD); **National Centre for Fetal Medicine, St Olavs University Hospital, Trondheim, Norway** (Prof T M Eggebø PhD); **Department of Obstetrics and Gynaecology, Stavanger University Hospital, Stavanger, Norway** (Prof T M Eggebø); **Norwegian National Advisory Unit on Women's Health** (K F Frøslie PhD) **and Research Support Services, Clinical Trial Unit** (I C Olsen PhD), **Oslo University Hospital, Oslo, Norway; Department of Obstetrics and Gynaecology, University Hospital of North Norway, Norway** (Prof P Øian PhD); **and Department of Clinical Medicine, Faculty of Health Sciences, The Arctic University of Norway (UiT), Tromsø, Norway** (Prof P Øian)

Correspondence to: Dr Stine Bernitz, Department of Obstetrics and Gynaecology, Østfold Hospital Trust, 1714 Grålum, Norway **stine.bernitz@so-hf.no**

Summary

Background There is an ongoing debate concerning which guidelines and monitoring tools are most beneficial for assessing labour progression, to help prevent use of intrapartum caesarean section (ICS). The WHO partograph has been used for decades with the assumption of a linear labour progression; however, in 2010, Zhang introduced a new guideline suggesting a more dynamic labour progression. We aimed to investigate whether the frequency of ICS use differed when adhering to the WHO partograph versus Zhang's guideline for labour progression.

Methods We did a multicentre, cluster-randomised controlled trial at obstetric units in Norway, and each site was required to deliver more than 500 fetuses per year to be eligible for inclusion. The participants were nulliparous women who had a singleton, full-term fetus with cephalic presentation, and who entered spontaneous active labour. The obstetric units were treated as clusters, and women treated within these clusters were all given the same treatment. We stratified these clusters by size and number of previous caesarean sections. The clusters containing the obstetric units were then randomly assigned (1:1) to the control group, which adhered to the WHO partograph, or to the intervention group, which adhered to Zhang's guideline. The randomisation was computer-generated and was done in the Unit of Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway, and investigators in this unit had no further involvement in the trial. Our study design did not enable masking of participants or health-care providers, but the investigators who were analysing the data were masked to group allocation. The primary outcome was use of ICS during active labour (cervical dilatation of 4–10 cm) in all participating women. The Labour Progression Study (LaPS) is registered with ClinicalTrials.gov, number NCT02221427.

Findings Between Aug 1, 2014, and Sept 1, 2014, 14 clusters were enrolled in the LaPS trial, and on Sept 11, 2014, seven obstetric units were randomly assigned to the control group (adhering to the WHO partograph) and seven obstetric units were randomly assigned to the intervention group (adhering to Zhang's guideline). Between Dec 1, 2014, and Jan 31, 2017, 11 615 women were judged to be eligible for recruitment in the trial, which comprised 5421 (46·7%) women in the control group units and 6194 (53·3%) women in the intervention group units. In the control group, 2100 (38·7%) of 5421 women did not give signed consent to participate and 16 (0·3%) women abstained from participation. In the intervention group, 2181 (35·2%) of 6194 women did not give signed consent to participate and 41 (0·7%) women abstained from participation. 7277 (62·7%) of 11 615 eligible women were therefore included in the analysis of the primary endpoint. Of these women, 3305 (45·4%) participants were in an obstetric unit that was randomly assigned to the control group (adhering to the WHO partograph) and 3972 (54·6%) participants were in an obstetric unit that was randomly assigned to the intervention group (adhering to Zhang's guideline). No women dropped out during the trial. Before the start of the trial, ICS was used in 9·5% of deliveries in the control group obstetric units and in 9·3% of intervention group obstetric units. During our trial, there were 196 (5·9%) ICS deliveries in women in the control group (WHO partograph) and 271 (6·8%) ICS deliveries in women in the intervention group (Zhang's guideline), and the frequency of ICS use did not differ between the groups (adjusted relative risk 1·17, 95% CI 0·98–1·40; p=0·08; adjusted risk difference 1·00%, 95% CI –0·1 to 2·1). We identified no maternal or neonatal deaths during our study.

Interpretation We did not find any significant difference in the frequency of ICS use between the obstetric units assigned to adhere to the WHO partograph and those assigned to adhere to Zhang's guideline. The overall decrease in ICS use that we observed relative to the previous frequency of ICS use noted in these obstetric units might be explained by the close focus on assessing labour progression more than use of the guidelines. Our results represent an important contribution to the discussion on implementation of the new guideline.

Funding Østfold Hospital Trust.

Research in context

Evidence before this study

Partographs and guidelines are used to assess and monitor labour progression, and they aim to identify labour dystocia and, consequently, enable appropriate labour management, including augmentation and intrapartum caesarean section (ICS). The WHO partograph from 1994 was based on research from 1953 and has been used to assess labour progression on an international level for many years. In 2010, a new guideline was presented, Zhang's guideline, which was based on research that suggested a more dynamic approach to labour progression. Before our study started, we searched PubMed for papers published before Aug 1, 2014, with the search terms "labour progression", "labour guidelines", labour curve", and "partograph". We also searched the reference lists of published articles that we found on the topic. We identified no randomised trials that investigated the effects of adherence to the WHO partograph or Zhang's guideline on maternal and neonatal birth outcomes.

Added value of this study

Our study addresses the important issue of whether the frequency of ICS use differs with adherence to the WHO partograph compared with adherence to Zhang's guideline for labour progression. To our knowledge, this is the first study to compare the WHO partograph with the Zhang guideline that has a robust cluster-randomised design, to ensure valid results, and large number of participants. We found no significant difference in ICS use between the group adhering to the WHO partograph and those adhering to Zhang's guideline. However, the frequency of ICS use was reduced in both the WHO partograph group (by 37·8%) and the Zhang's guideline group (by 26·5%) relative to ICS use in 2012.

Implications of all the available evidence

Our findings suggest that a focus on labour progression might affect the frequency of ICS use, and this effect could be seen on an even larger scale in countries with more frequent ICS use than Norway. This study is an important contribution to the discussion on whether implementation of a new guideline is beneficial.

Introduction

Access to safe caesarean section saves lives and improves health outcomes for women and their babies. However caesarean sections that are not medically indicated should be avoided. The rate of caesarean sections is increasing worldwide and is a great concern because of its association with adverse outcomes for mothers and babies, the more than 50% risk for a subsequent caesarean section, and the increase in costs of labour care.[1–4] Assessment of labour progression and identification of prolonged labour, denoted as true labour dystocia and often caused by inadequate contractions or obstructed labour, have profound effects on labour management and intrapartum caesarean section (ICS) use, since labour dystocia is the main indication for an ICS.[5] Partographs and guidelines are used to assess and monitor labour progression, and they aim to identify labour dystocia and its causes and to determine the appropriate management of labour.[6] For more than 60 years, labour progression has been assessed on the basis of Friedman's work, who first published a graphicostatistical analysis of labour and presented the cervical dilatation for nulliparous women as a sigmoid labour curve.[7] In the early 1970s, Philpott and colleagues[8,9] developed guidelines to assess labour progression on the basis of Friedman's findings. These guidelines consisted of alert and action lines to detect abnormal labour progress. In 1994, the WHO partograph was presented, which was based on Philpott's work.[10]

Because of a substantial change in labour management over the past 50 years and an increase in women's body-mass index and childbearing age, questions have been raised on the appropriateness of the recommendations and the expected cervical dilatation during labour.[5,11–13] In 2010, Zhang and colleagues[12] presented a hyperbolic labour curve that was based on a large contemporary cohort, which was markedly different from Friedman's curve. They found that labour seems to progress more slowly than previously expected, especially before reaching 6 cm of cervical dilatation, and they found that cervical dilatation accelerates as labour advances. This finding implies that following Zhang's guideline allows more time early in labour before labour dystocia is diagnosed. Zhang and colleagues[12,13] suggested that some caesareans might be used too early, based on prevailing definitions of prolonged labour, and they presented a new guideline for labour progression.

This guideline has been implemented in some settings, under the assumption that they would lead to fewer ICSs,[14] without being tested in robust clinical trials.[15] There is an ongoing debate concerning which guidelines and partographs are most beneficial for assessing labour progression. We therefore aimed to investigate whether the frequency of ICS use for nulliparous women in active labour differed when adhering to the WHO partograph compared with Zhang's guideline for labour progression, without jeopardising the safety of the mother or the baby.

Methods

Study design and participants

The Labour Progression Study (LaPS) was a multicentre, cluster-randomised controlled trial in obstetric units in Norway, and it was enabled by the comprehensive, well coordinated midwife delivery system in Norway.

Intrapartum care in Norway is given in government-owned institutions and is free of charge. At all obstetric units, midwives are present at all labours and deliveries; they are responsible for normal labours and deliveries, and obstetricians are only involved when medical assistance is required. Approximately 60 000 babies are born annually at 46 birth institutions in Norway, and 24 of these 46 institutions are each responsible for more than 500 deliveries per year. Norway is divided into geographic health regions (north, central, west, and southeast) and birth care is organised into three levels: level one includes specialised obstetric units in larger hospitals that provide all birth care services, including an obstetrician, paediatrician, and anaesthesiologist, who are available 24 h a day, and a neonatal intensive care unit; level two includes obstetric units in smaller hospitals that have an on-call obstetrician and anaesthesiologist available; and level three includes midwife-led units, both within hospitals and freestanding, that provide care for women with a low risk of complications.[16] In case of complications or change in risk status of women being treated in level three units, the woman is transferred to a level one or two unit.

For the **Medical Birth Registry of Norway** see https://www.fhi.no/en/hn/health-registries/medical-birth-registry-of-norway/

See Online for appendix

To restrain this study to a reasonable time limit, we restricted the potential obstetric units to be included to those with more than 500 births annually. To create a representative selection of obstetric units in Norway, units from all geographical health regions were included. All obstetric units that were able to adhere to the protocol were considered eligible. To secure a thorough implementation of the trial, the management at all participating obstetric units signed a cooperation agreement in which they agreed to adhere to the protocol.

The Ten Group Classification System (TGCS), also known as the Robson classification,[17] is used as a global standard for assessing, monitoring, and comparing caesarean section frequencies. The system classifies women into ten mutually exclusive groups on the basis of their obstetric characteristics (namely parity, number of previous caesarean sections, gestational age, onset of labour, fetal presentation, and number of fetuses). Nulliparous women with a singleton term fetus with cephalic presentation and spontaneous onset of labour at gestational week 37 or greater, are denoted group 1 in the TGCS.[17] This group accounts for approximately 30% of the annual birth population in Norway. For inclusion in our study, participants had to be in TGCS group 1 during active labour (defined as at least 4 cm of cervical dilatation with regular contractions) and able to understand Norwegian and to give written consent. The estimated date of delivery was based on a second-trimester ultrasound scan. At this examination or at the time of admission to the labour ward, eligible women received written information about the trial and were asked to sign an informed consent form. All TGCS group 1 women adhered to the guideline that their obstetric unit was assigned to. However, only eligible women who provided informed consent were included in the analysis.

Ethical approval was obtained by the Regional Committee for Medical and Health Research Ethics (no. 2013/1862/REK Sør-Øst). The study protocol[18] was published in 2017, to present the trial design and methods.

Randomisation and masking

Before random assignment to groups and commencement of the trial, staff at all sites received the same written information about the LaPS. Each obstetric unit provided one dedicated person, a local coordinator, who was responsible for the trial, including recruitment and inclusion of participants and entering the required data. The obstetric units, acting as clusters, were randomly assigned (1:1) to adhere to the WHO partograph (control group) or to Zhang's guideline (intervention group) on the basis of a computer-generated allocation list that was stratified by the proportions of previous ICSs and number of deliveries. The randomisation was computer-generated and was done in the Unit of Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway, and investigators in this unit had no further involvement in the trial (appendix). After random allocation of obstetric units to clusters and before inclusion of participants, a strict programme regarding trial protocols was taught to the staff at all obstetric units. The programme consisted of information about the trial and thorough instructions in use of the assigned guidelines. Written information about the trial and the guidelines was printed on posters and made visible and constantly available for midwives and obstetricians at the units. Researchers from the LaPS group revisited the units, to ensure consistency and rigorous adherence to the allocated guidelines. Every Monday during the study period, one of the steering group members was in contact with the local coordinators for a weekly update of inclusion and for assistance and motivation.

Our study design did not enable masking of participants or health-care providers, but the investigators who were analysing the data were masked to group allocation (appendix). The masked review and prespecification of analyses were done without any knowledge of group allocation or which clusters belonged to the same intervention. After random allocation and signing of the statistical analysis plan, the group allocation was revealed to the units.

Procedures

Women in the control group were monitored by an electronic version of the WHO partograph, as is standard in Norway, with an alert line (drawn on the partograph) that showed the expected cervical dilatation if labour were progressing by at least 1 cm per h, and an action line drawn 4 h later than the alert line. Labour dystocia was diagnosed in the active phase of the first stage of labour (0–10 cm of cervical dilatation; divided into the latent phase [0–3 cm] and the active phase [4–10 cm]) if the action line was crossed. Labour dystocia in the second stage of labour

(from 10 cm of cervical dilatation until the baby is born; divided into the latent phase [from 10 cm of dilatation until the baby's head reaches the pelvic floor] and the active or expulsion phase [when the mother pushes the baby's head out]) was diagnosed if the latent phase lasted longer than 1 h (or 2 h for women with epidural analgesia [EDA]) or if the expulsion phase lasted longer than 1 h (appendix).

Women in the intervention group were monitored with Zhang's guideline for labour progression,[12] which calculates the expected labour progression during the active phase of the first stage of labour on the basis of time intervals from one integer cm to the next. Labour dystocia during the first stage of labour was diagnosed as time intervals of the 95th percentile or more. Labour dystocia during the second stage of labour was diagnosed as a descending phase that lasted longer than 1 h 45 min (or 2 h 30 min for women with EDA) or an expulsion phase that lasted longer than 1 h (appendix). The obstetric units that were assigned to the intervention group used a paper version of the guideline because an electronic version is not available.

National guidelines for intrapartum care[19] were followed if labour dystocia occurred. If labour dystocia was believed to be caused by insufficient uterine contractions and if the membranes were intact, the membranes were artificially ruptured. After 1 h and if artificial rupture of the membranes alone did not lead to sufficient contractions, oxytocin was administered. If the membranes were broken, oxytocin was given at the time at which labour dystocia was identified. Oxytocin was administered as an intravenous infusion of 10 international units (U) in 1000 mL saline at an infusion rate that started at 300 mU/h and with a dose increment of 150 mU/h every 15 min until a satisfactory number of contractions (3–5 in 10 min) was reached, or until the maximum dose of 1800 mU/h was reached.[19] Necessary interventions based on the women's or the fetus' needs were used, regardless of trial group.

All data were entered into the unit's electronic medical record system by the midwife in charge of the labour, as is routine. A customised web-based case report form was designed by the Unit of Applied Clinical Research at the Norwegian University of Science and Technology (Trondheim, Norway), to ensure that all variables entered by the local coordinators were equally presented. The system was transparent, such that all corrections could be traced with dates and signatures. The local coordinators only had access to their own case report forms, and they were responsible for checking that all data entered were de-identified, complete, and accurate; this check was the first quality-control step. The second quality-control step was to check that all the required boxes in the case report form contained accurate information, and this step was organised by one of the researchers in the LaPS research group. Before closing the database, two of the LaPS group members did a final quality-control check of all variables. When missing data were identified, the local coordinators were contacted, and they were asked to search for the missing data in the patient's medical record. If implausible values were found, local coordinators were asked to correct or verify the values.

Outcomes

The primary outcome was the frequency of ICS use during the trial period, which was assessed in all eligible women giving birth in obstetric units that had been randomly assigned to groups and had consented to be included. The secondary outcomes included the use of versus no use of operative vaginal delivery, artificial rupture of the membranes, augmentation with oxytocin, EDA use, blood transfusion, an Apgar score (indicating vital signs in the fetus) of less than 7 at 5 min, and an arterial umbilical cord pH of less than 7·00. The use of perineal surgical incision and the degree of obstetric anal sphincter injury (OASIS) were also secondary outcomes. Labour duration and labour dystocia, based on the allocated guidelines and as an indication for ICS, were also assessed as prespecified exploratory endpoints. Other secondary outcomes (appendix) will be reported elsewhere. Additional prespecified robustness analyses of the primary and secondary endpoints were also included, to account for missing data and covariates. All analyses were done by intention to treat.

Statistical analysis

The sample size (ie, the number of clusters and individuals) was based on the proportion of ICSs relative to the total number of deliveries in the eligible hospitals (n=24) at the time of sample size calculation in 2012, which was 9·2%. We examined 100 previous WHO

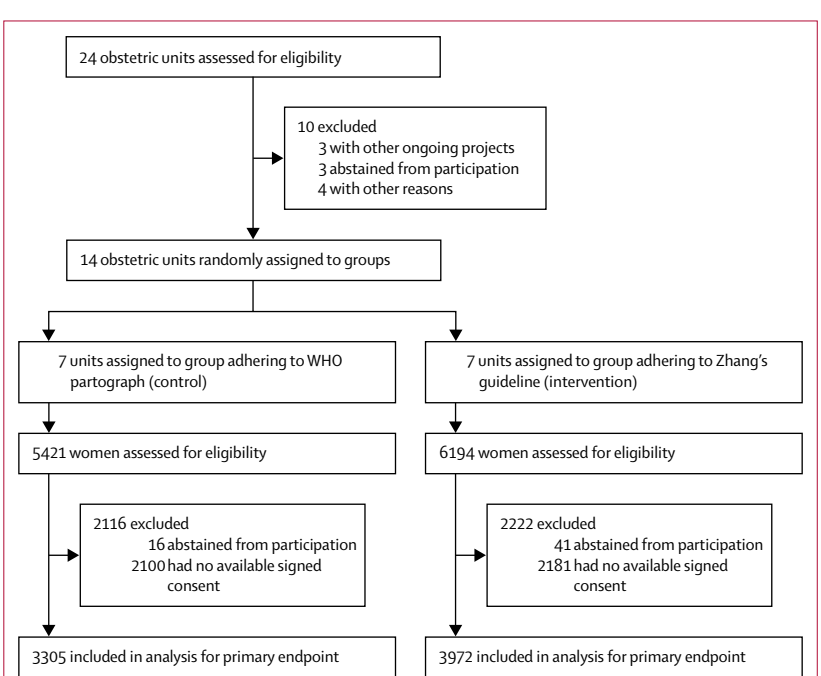

Figure: **Trial profile**

	WHO partograph (control) group (n=3305)	Zhang's guideline (intervention) group (n=3972)
Obstetric unit characteristics		
Number of deliveries per year		
500–999	133 (1·8%)	0
1000–2999	2100 (28·8%)	2688 (36·9%)
≥3000	1072 (14·7%)	1284 (17·6%)
Maternal characteristics		
Age at delivery, years		
≤25	784 (23·7%)	971 (24·4%)
25–35	2275 (68·8%)	2679 (67·4%)
≥35	246 (7·4%)	322 (8·1%)
Marital status is cohabitant or married	3137 (95·9%)*	3741 (94·8%)†
Higher education for ≥12 years	2017 (61·0%)	2412 (60·7%)
Smoked during the first trimester	210 (6·5%)‡	230 (5·8%)§
Body-mass index before pregnancy, kg/m²		
Mean	23·8 (4·3)¶	23·6 (4·3)‖
Range		
≤18·5	142 (4·3%)¶	172 (4·3%)‖
18·5–24·9	2178 (66·3%)¶	2692 (67·9%)‖
25–29·9	688 (20·9%)¶	764 (19·3%)‖
≥30	279 (8·5%)¶	338 (8·5%)‖
Cervical dilatation at first registration, cm		
4	1642 (49·7%)	1954 (49·2%)
5	841 (25·4%)	1006 (25·3%)
6	338 (10·2%)	403 (10·1%)
7	178 (5·4%)	222 (5·6%)
8	118 (3·6%)	167 (4·2%)
9	99 (3·0%)	106 (2·7%)
10	89 (2·7%)	114 (2·9%)
Neonatal characteristics		
Gestational age at onset of active labour, days	281 (8)	281 (7)
Birthweight, g	3518 (414)	3528 (427)
Head circumference, cm	35·0 (1·4)	35·0 (1·4)
Sex		
Female	1661 (50·3%)	1983 (49·9%)
Male	1664 (49·7%)	1989 (50·1%)

Data are n (%) or mean (SD). In the control group, one obstetric unit was responsible for 500–999 deliveries a year, five obstetric units were responsible for 1000–2999 deliveries a year, and one obstetric unit was responsible for 3000 or more deliveries a year. In the intervention group, six obstetric units were responsible for 1000–2999 deliveries a year and one obstetric unit was responsible for 3000 or more deliveries a year. Because of missing values, data are out of: *3271; †3946; ‡3247; §3963; ¶3287; and ‖3966 participants.

Table 1: **Baseline characteristics**

partographs for women with labour dystocia who consequently underwent ICS and we found that 25 (25%) of these women would not have been diagnosed with labour dystocia according to Zhang's guideline at the time of the ICS (unpublished data). To obtain an 80% power to detect a 25% relative reduction in ICS use with the new guideline and a between-cluster variation coefficient of 0·08, at least 14 obstetric units and 6582 participants had to be included, assuming a 0·05 two-sided significance level.[20] Before locking the database, and without knowledge of allocation, a statistical analysis plan was written and approved, prespecifying all analyses to be done (appendix).

The primary outcome was analysed with a mixed logistic regression model, with obstetric units as a random intercept and the treatment strategy as fixed effect. In the model, we adjusted for stratification variables (annual ICS rates and number of deliveries) and for predefined covariates that are considered to be potential risk factors for ICS on an individual level (maternal age, body-mass index, marital status, and educational level of the mother; birthweight and head circumference of the neonate). A two-tailed p value of 0·05 or less was considered significant. Estimates of the adjusted risk ratio and adjusted risk difference with CIs were computed with the delta method.[21] We also estimated the intraclass correlation coefficient (ICC) by the logistic mixed model. The primary outcome was assessed in all eligible women who provided informed consent.

The secondary outcomes were binary, and they were therefore analysed with the same methods as the primary outcome. Since there was only one identified primary analysis, no adjustments for multiple testing were made in the secondary analyses. Analyses of secondary outcomes were based on all included women, except for analyses of perineal surgical incision and OASIS, which were restricted to women with vaginal deliveries. Calculation of labour dystocia as an indication for ICS was restricted to women who received an ICS. Missing data were imputed with the best outcome in the primary analysis, and with the worst outcome in robustness analyses (appendix). Missing covariate data were imputed with stochastic linear regression single imputation.

The robustness of all results was checked with several additional prespecified analyses models, including unadjusted models, hospital-level only adjusted models, cluster-level analysis models, and standard logistic regression (appendix). Details of post-hoc robustness analyses are included in the appendix.

All statistical analyses were done with Stata version 15.1.1 or SAS version 9.4. LaPS was registered at ClinicalTrials.gov, number NCT02221427.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 1, 2014, and Sept 1, 2014, 14 clusters of obstetric units were enrolled in the LaPS trial (figure). Seven obstetric units were randomly assigned to the

control group (adhering to the WHO partograph; Møre and Romsdal Hospital Trust, Molde; Innlandet Hospital Trust, Elverum; Innlandet Hospital Trust, Lillehammer; Møre and Romsdal Hospital Trust, Ålesund; Vestfold Hospital Trust, Tønsberg; Vestre Viken Hospital Trust, Drammen; and St Olav's Hospital Trust, Trondheim) and seven obstetric units were randomly assigned to the intervention group (adhering to Zhang's guideline; Nordland Hospital Trust, Bodø; Sørlandet Hospital Trust, Arendal; University Hospital of North Norway Trust, Tromsø; Vestre Viken Hospital Trust, Bærum; Telemark Hospital Trust, Skien; Østfold Hospital Trust, Grålum; and Stavanger University Hospital Trust, Stavanger). Between Dec 1, 2014, and Jan 31, 2017, 11615 women who were considered eligible were asked to participate in the trial, which comprised 5421 (46·7%) women in the control group units and 6194 (53·3%) women in the intervention group units. In the control group, 2100 (38·7%) of 5421 women did not give signed consent to participate and 16 (0·3%) women abstained from participation. In the intervention group, 2181 (35·2%) of 6194 women did not give signed consent to participate and 41 (0·7%) women abstained from participation. 7277 (62·7%) of 11615 eligible women were therefore included in the analysis of the primary endpoint and the secondary endpoints (except for perineal incisions and OASIS). Of these women, 3305 (45·4%) participants were in an obstetric unit that was randomly assigned to the control group (adhering to the WHO partograph) and 3972 (54·6%) participants were in an obstetric unit that was randomly assigned to the intervention group (adhering to Zhang's guideline). There were no dropouts during the trial.

The two study groups were well balanced regarding baseline characteristics, except for variations in marital status (table 1). Additional baseline characteristics are shown in the appendix. Between 2012 and the start of the trial, ICS was used in 9·5% of deliveries to women in TGCS group 1 in obstetric units assigned to the control (WHO partograph) group and in 9·3% of deliveries to women in TGCS group 1 in units assigned to the intervention (Zhang's guideline) group (appendix). No data were missing for the covariates that were included in the analyses, except for body-mass index (in 0·3% of women) and marital status (in 0·8% of women).

ICS was used in 196 (5·9%) of 3305 women in the control group and 271 (6·8%) of 3972 women in the intervention group (table 2). There was no significant difference in the adjusted relative risk of ICS, which was 1·17 (95% CI 0·98–1·40; p=0·08) in the intervention group versus the control group, with an adjusted risk difference of 1·0% (95% CI –0·1 to 2·1). The estimated ICC was $3·4\times10^{-34}$. ICS was used in response to labour dystocia before 6 cm of cervical dilatation for 28 (21·2%) women in the control group and 25 (14·0%) women in the intervention group. There were no missing data for the primary outcome.

	WHO partograph (control) group		Zhang's guideline (intervention) group	
	n (%)	Number assessed	n (%)	Number assessed
Primary endpoint				
Intrapartum caesarean sections*	196 (5·9%)	3305	271 (6·8%)	3972
Descriptive endpoints				
Intrapartum caesarean sections for labour dystocia	132 (67·3%)	196	178 (65·7%)	271
Intrapartum caesarean sections for labour dystocia at a cervical dilatation of less than 6 cm	28 (21·2%)	132	25 (14·0%)	178
Labour dystocia, according to the allocated guideline	1512 (45·7%)	3305	1882 (47·4%)	3972
Labour dystocia, according to the allocated guideline, diagnosed at a cervical dilatation of less than 6 cm	214 (14·2%)	1512	222 (11·8%)	1882
Initiation of synthetic oxytocin during labour at a cervical dilatation of less than 6 cm	289 (18·5%)	1561	244 (14·7%)	1658
Duration of active phase of labour, hours†	6·05 (3·38–9·50)	NA	6·59 (3·55–10·53)	NA

NA=not applicable. *Adjusted relative risk is 1·17 (95% CI 0·98–1·40; p=0·08), giving an adjusted risk difference of 1·0% (95% CI –0·1 to 2·1), and an intraclass correlation coefficient (estimated within centres) of $3·4\times10^{-34}$; the number needed to treat with the WHO guideline to avoid one intrapartum caesarean section was therefore 100. †Data are median (IQR).

Table 2: **Intrapartum caesarean sections and labour dystocia**

Labour dystocia, as defined by the allocated guidelines, was reported in 1512 (45·7%) of 3305 women in the control group and 1882 (47·4%) of 3972 women in the intervention group. Of these women, labour dystocia before a cervical dilatation of 6 cm was diagnosed in 214 (14·2%) women in the control group and 222 (11·8%) women in the intervention group. Labour dystocia was the indication that prompted 132 (67·3%) of 196 uses of ICS in the control group and 178 (65·7%) of 271 uses of ICS in the intervention group (table 2).

There were no differences between the groups in any of the secondary outcomes (table 3). There were no reported maternal or neonatal deaths, and the results were found to be robust in post-hoc robustness analyses (appendix).

Discussion

LaPS was a cluster-randomised controlled trial that aimed to investigate whether the frequency of ICS use differed when adhering to Zhang's guideline for labour progression compared with that when adhering to the WHO partograph. We hypothesised that there would be a 25% reduction in the frequency of ICS use when adhering to Zhang's guideline versus adhering to the WHO partograph. We found no significant difference in ICS use between these groups. ICS was used for labour dystocia before women reached a cervical dilatation of 6 cm in a greater of proportion of deliveries in the control (WHO partograph) group than in the intervention (Zhang's guideline) group. Our study therefore provides important evidence to guide clinical practice and is an

	WHO partograph (control) group (n=3305)	Zhang's guideline (intervention) group (n=3972)	Adjusted relative risk (95% CI)	Adjusted risk difference (95% CI)	p value	Intraclass correlation coefficient, assessed within centres (95% CI)
Clinical interventions during labour						
Operative vaginal delivery	581 (17·6%)	839 (21·1%)	1·06 (0·84–1·34)	1·1% (–3·3 to 5·5)	0·62	0·02 (0·01–0·06)
Artificial rupture of the membranes	1223 (37·0%)	1396 (35·1%)	0·92 (0·79–1·06)	–3·2% (–8·4 to 2·0)	0·23	0·01 (0·01–0·03)
Augmentation with oxytocin during labour	1561 (47·2%)	1658 (41·7%)	0·98 (0·84–1·15)	–0·8% (–7·8 to 6·1)	0·81	0·02 (0·01–0·05)
Epidural analgesia	1653 (50·0%)	1913 (48·2%)	0·96 (0·81–1·15)	–1·9% (–10·5 to 6·8)	0·67	0·03 (0·01–0·07)
Perineal surgical incision in women delivering vaginally	881 (28·3%)*	1151 (31·1%)†	0·91 (0·68–1·20)	–2·9% (–11·3 to 5·5)	0·50	0·04 (0·02–0·09)
Other secondary outcomes						
Obstetric anal sphincter injuries in women delivering vaginally	79 (2·5%)*	112 (3·0%)†	1·14 (0·86–1·52)	0·4% (–0·4 to 1·2)	0·36	$1·9 \times 10^{-34}$ (NE)
Blood transfusion administered	82 (2·5%)	115 (2·9%)	1·16 (0·79–1·69)	0·4% (–0·6 to 1·4)	0·45	0·02 (0·01–0·11)
Apgar score of less than 7 after 5 min	36 (1·1%)	49 (1·2%)	1·14 (0·74–1·75)	0·2% (–0·3 to 0·7)	0·55	$1·7 \times 10^{-35}$ (NE)
Neonates with an umbilical cord artery pH of less than 7·0‡	19 (0·6%)	22 (0·6%)	0·99 (0·46–2·15)	0 (–0·4 to 0·4)	0·98	0·04 (0·01–0·46)

Data are n (%). NE=not estimable. *Out of 3109 participants assessed. †Out of 3701 participants assessed. ‡Missing values (33%) were imputed with best outcome.

Table 3: **Secondary outcomes**

important contribution to the discussion on whether implementation of the new labour progression guideline is beneficial or not.

We observed that ICS use was reduced in both the control group (by 37·8%) and the intervention group (by 26·5%) relative to the frequency of ICS use in 2012, before our study started; this reduction cannot be explained by the introduction of Zhang's guideline because a reduction was noted in both groups. The intense focus on assessing labour progression in the study period might have led to an optimisation of labour management and an overall decrease in ICS use, which could be explained as the Hawthorn effect.[22] The decrease in the frequency of ICS use in both groups suggests that the global challenge of increases in ICS use can be addressed by focusing on interventions, as previously reported.[23] Even in Norway, where the frequency of ICS use is low, we found a substantial reduction in ICS use; thus, countries with more frequent ICS use might reduce their ICS use to a greater extent by increased focus on labour progression.

Previous research[24] suggests that the universal standardisation of an expected linear labour progression curve is not applicable to today's physiological patterns of labour. We found that a dynamic curve with wider intervals early in the active phase of the first stage appeared to be common in women today.[12] However, we did not find any difference between the groups regarding ICS use in the context of labour dystocia. One could question whether standard guidelines are applicable for all women if they do not account for the normal and individual variations of labour progression.[25]

Previous work has shown diverse effects of different labour progression guidelines on ICS use. In 2014, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine implemented Zhang's guideline in their recommendations for assessment and management of labour on the basis of research from lower on the hierarchy of evidence.[14] Thuilliers and colleagues[26] did a retrospective cohort study and found a significant decrease in ICS after implementation of new recommendations for preventing use of ICS that is not medically indicated.[14] Rosenbloom and colleagues[27] found no change in the frequency of ICS use, but they found an increase in maternal and neonatal morbidity after implementation of the new recommendations for preventing medically unnecessary ICSs.[14]

It has been suggested that new labour management guidelines should be based on the best outcome for the mother and baby through a robust randomised controlled trial.[15] LaPS is such a study[28] with an appropriate sample size calculation. Our study has several strengths. First, the trial was carefully planned, and guidelines were taught rigorously to the birth care units included. Second, because compliance of the study protocol of labour management is known to be a challenge,[29] all units were closely monitored during the trial period, which was intended to improve adherence to the guidelines and to enable thorough implementation of the study. The level of attention and focus on assessing labour progression was probably more intense than expected, and equal in both groups, which implies that, if there was a difference in ICS use between the groups, we would be able to detect it. However, the results might have differed if randomisation was done on an individual level. Third, to address external validity more thoroughly, we considered cluster eligibility, cluster inclusion and retention, cluster generalisability, and the feasibility and acceptability of the intervention to health-care providers in clusters.[30]

Finally, we did several robustness analyses to strengthen internal validity by assessing the effects of different assumptions and choices.[30] Our results were consistent over all analyses that adjusted for cluster effects, suggesting validity of our findings. The cluster design was incorporated into the power calculations to ensure an adequate sample size from the clusters. The choice of a mixed logistic regression model as the main statistical method allowed for inclusion of both individual-level and cluster-level covariates and estimation of the ICC. The adjustments for covariates increased the estimate precisions, adjusting for imbalance in baseline characteristics of the treatment groups. The ICCs for the primary outcome was small—less than 0·001—which indicated that the variation in the outcome that was attributable to clusters was small. Ignoring cluster design in analyses resulted in lower p values and narrower CIs (indicating the importance of not ignoring the cluster effect), as expected (appendix). Several additional analyses were done to check the robustness of the findings. All results were robust to alternative model specifications, which strengthened our findings.

Our study also has possible limitations. First, the intervention group used a paper version of the guideline, whereas the control group who used an electronic version. Second, our study was restricted to women in TGCS group 1. Since the TGCS group 1 accounts for approximately 30% of the annual birth population in Norway, our results cannot be generalised to other sub-groups or to overall caesarean section use. Third, during the trial period, there was an ongoing project in Norway with a focus on limiting caesarean sections to those that are medically indicated. The results of that study show that the project probably had little effect on our study (appendix).

In conclusion, we found no significant difference in the frequency of ICS use in nulliparous women between obstetric units that adhered to the WHO partograph and those that adhered to Zhang's guideline. An increased focus on assessment of labour progression might have a stronger effect on reducing the use of ICSs more than the guidelines themselves.

Contributors

SB, EB, and PØ initiated the trial, designed the study and wrote the first draft of the protocol. SB, RD, and EB coordinated the data collection and acquired the data. SB, RD, KFF and ICO analysed the data. All authors interpreted the data. SB and RD wrote the first draft of the manuscript with input from all authors, and all authors contributed to the manuscript, approved the final version, and agreed to be accountable for all aspect of the work.

Declaration of interests

We declare no competing interests.

Data sharing

Anonymised participant data and a data dictionary will be available on request from Jan 1, 2020, after approval of a proposal and a signed data access agreement. Appropriate institutional data transfer agreements will be required. Requests should be made via email to the corresponding author, along with an analysis proposal. The study protocol is available online. The statistical analysis plan is available with publication, in the appendix.

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References

1 Niino Y. The increasing cesarean rate globally and what we can do about it. *Biosci Trends* 2011; **5:** 139–50.
2 Macfarlane AJ, Blondel B, Mohangoo AD, et al. Wide differences in mode of delivery within Europe: risk-stratified analyses of aggregated routine data from the Euro-Peristat study. *BJOG* 2016; **123:** 559–68.
3 Bernitz S, Aas E, Øian P. Economic evaluation of birth care in low-risk women. A comparison between a midwife-led birth unit and a standard obstetric unit within the same hospital in Norway. A randomised controlled trial. *Midwifery* 2012; **28:** 591–99.
4 Miller S, Abalos E, Chamillard M, et al. Beyond too little, too late and too much, too soon: a pathway towards evidence-based, respectful maternity care worldwide. *Lancet* 2016; **388:** 2176–92.
5 Neal JL, Lowe NK, Patrick TE, Cabbage LA, Corwin EJ. What is the slowest-yet-normal cervical dilation rate among nulliparous women with spontaneous labor onset? *J Obstet Gynecol Neonatal Nurs* 2010; **39:** 361–69.
6 Lavender T, Hart A, Smyth RM. Effect of partogram use on outcomes for women in spontaneous labour at term. *Cochrane Database Syst Rev* 2013; **7:** CD005461.
7 Friedman E. The graphic analysis of labor. *Am J Obstet Gynecol* 1954; **68:** 1568–75.
8 Philpott RH, Castle WM. Cervicographs in the management of labour in primigravidae. I. The alert line for detecting abnormal labour. *J Obstet Gynaecol Br Commonw* 1972; **79:** 592–98.
9 Philpott RH, Castle WM. Cervicographs in the management of labour in primigravidae. II. The action line and treatment of abnormal labour. *J Obstet Gynaecol Br Commonw* 1972; **79:** 599–602.
10 World Health Organization Maternal Health and Safe Motherhood Programme. World Health Organization partograph in management of labour. *Lancet* 1994; **343:** 1399–404.
11 Zhang J, Troendle JF, Yancey MK. Reassessing the labor curve in nulliparous women. *Am J Obstet Gynecol* 2002; **187:** 824–28.
12 Zhang J, Landy HJ, Branch DW, et al. Contemporary patterns of spontaneous labor with normal neonatal outcomes. *Obstet Gynecol* 2010; **116:** 1281–87.
13 Laughon SK, Branch DW, Beaver J, Zhang J. Changes in labor patterns over 50 years. *Am J Obstet Gynecol* 2012; **206:** 419.

For the **study protocol** see https://sykehuset-ostfold.no/Documents/Protocol%20LaPS.pdf

14 Caughey AB, Cahill AG, Guise JM, Rouse DJ. Safe prevention of the primary cesarean delivery. *Am J Obstet Gynecol* 2014; **210:** 179–93.

15 Cohen WR, Friedman EA. Obstetric practice guidelines: labor's love lost? *J Matern Fetal Neonatal Med* 2017; 1–71.

16 Norwegian Ministry of Health and Care Services. En gledelig begivenhet—om en sammenhengende svangerskaps-, fødsels- og barselomsorg. Feb 13, 2009. https://www.regjeringen.no/contentassets/25a45886201046488d9c53abc0c8ad3a/no/pdfs/stm200820090012000dddpdfs.pdf (accessed April 26, 2018; in Norwegian).

17 Robson MS. Can we reduce the caesarean section rate? *Best Pract Res Clin Obstet Gynaecol* 2001; **15:** 179–94.

18 Bernitz S, Dalbye R, Øian P, Zhang J, Eggebø TM, Blix E. Study protocol: the Labor Progression Study, LaPS—does the use of a dynamic progression guideline in labor reduce the rate of intrapartum cesarean sections in nulliparous women? A multicenter, cluster randomized trial in Norway. *BMC Pregnancy Childbirth* 2017; **17:** 370.

19 Norwegian Medical Association. Augmentation of labor. 2014. http://www.nfog.org/files/guidelines/34%20NGF%20Obst%20Augmentation%20of%20labour%20Eggeb%C3%B8.pdf (accessed March 7, 2014).

20 Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. *Int J Epidemiol* 1999; **28:** 319–26.

21 Reeve R. Confidence interval of difference of proportions in logistic regression in presence of covariates. *Stat Methods Med Res* 2018; **27:** 451–65.

22 Mayo E. The human problems of an industrial civilization, 1st edn. London: Macmillian Publishers, 2010.

23 Chaillet N, Dumont A, Abrahamowicz M, et al. A cluster-randomized trial to reduce cesarean delivery rates in Quebec. *N Engl J Med* 2015; **372:** 1710–21.

24 Oladapo OT, Diaz V, Bonet M, et al. Cervical dilatation patterns of "low-risk" women with spontaneous labour and normal perinatal outcomes: a systematic review. *BJOG* 2018; **125:** 944–54.

25 Oladapo OT, Souza JP, Fawole B, et al. Progression of the first stage of spontaneous labour: a prospective cohort study in two sub-Saharan African countries. *PLoS Med* 2018; **15:** e1002492.

26 Thuillier C, Roy S, Peyronnet V, Quibel T, Nlandu A, Rozenberg P. Impact of recommended changes in labor management for prevention of the primary cesarean delivery. *Am J Obstet Gynecol* 2018; **218:** 341.

27 Rosenbloom JI, Stout MJ, Tuuli MG, et al. New labor management guidelines and changes in cesarean delivery patterns. *Am J Obstet Gynecol* 2017; **217:** 689.

28 Donner A, Klar, N. Design and analysis of cluster randomization trials in health research, 1st edn. Hoboken, NJ, USA: John Wiley & Sons, 2010.

29 Lee NJ, Neal J, Lowe NK, Kildea SV. Comparing different partograph designs for use in standard labor care: a pilot randomized trial. *Matern Child Health J* 2018; **22:** 355–63.

30 Eldridge S, Ashby D, Bennett C, Wakelin M, Feder G. Internal and external validity of cluster randomised trials: systematic review of recent trials. *BMJ* 2008; **336:** 876–80.

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Sponsor address	PO Box 300, 1714 Grålum, Norway
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The Labor Progression Study - LaPS

SIGNATURE PAGE

PRINCIPAL/COORDINATING INVESTIGATOR:

Stine Bernitz, Midwife, PhD

Department of Obstetric and Gynecology

Østfold Hospital Trust, po box 300, 1714 Grålum, Norway

Signature

16/2. 2018

Date

TRIAL STATISTICIAN:

Inge Christoffer Olsen Statistician PhD

Oslo Centre for Biostatistics & Epidemiology

Sogn Arena 3.etg Pb 4950 Nydalen 0424 Oslo

Norway

Signature

16/2-2018

Date

Study Coinvestigator

Rebecka Dalbye, Midwife MSc

Department of Obstetric and Gynecology

Østfold Hospital Trust, po box 300, 1714 Grålum, Norway

Signature

16/2-2018

Date

ABBREVIATIONS

AE	Adverse Event
BD	Base Deficit
BMI	Body Mass Index
BPM	Beats Per Minute
CEQ	Childbirth Experiences Questionnaire
CI	Confidence Interval
CRF	Case Report Form
CTG	Cardiotocography
ECD	Emergency Cesarean Delivery
EDC	Electronic Data Capture
EDA	Epidural analgesia
MedDRA	Medical Dictionary for Regulatory Activities
NICU	Neonatal Intensive Care Unit
P0	Nulliparous women
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
STAN	ST ANalyzes
TGCS	Ten Group Classification System
TNS	Transcutaneous Nervous Stimulation
WHO	World Health Organization

TABLE OF CONENTS

AMENDMENTS TO THE SAP

This is the first version

1 STUDY OBJECTIVES

1.1 Primary Objective

To assess the impact of adhering to the guideline for labor progression presented by Zhang (Zhang et al., 2010) on the rate of emergency cesarean delivery (ECD) in nulliparous women compared to adhering to the WHO-partograph based on Friedman's curve (Friedman, 1954).

1.2 Secondary Objectives

To assess the impact of adhering to the guideline for labor progression presented by Zhang (Zhang et al., 2010) on other efficacy and safety outcomes in nulliparous women and their neonates compared to adhering to the WHO-partograph. (Friedman, 1954)

2 OVERALL STUDY DESIGN

This is a cluster randomized, multi center, strategy trial.

3 GENERAL STATISTICAL CONSIDERATIONS

All analyzes described in this plan are considered *a priori* analyzes in that they have been defined in the protocol and/or this SAP. All *post hoc* analyzes will be identified as such. Although this is an open study, all analyzes decisions in this document are based on blinded assessments of the data, i.e. without knowing hospital allocation to labor progression guideline (not even group A and B).

All categorical (binary and ordinal) data will be summarized using frequency counts and percentages of patient characteristics. Percentages will be calculated using the study population (defined as "full analysis set" in section 8); any exceptions to this will be highlighted in the table footnote. The continuous variables will be summarized using number of patients (N), and range (minimum/maximum) in combination with mean and, standard deviation (SD), if data are normally distributed, and median, lower and upper quartiles if data are skewedly distributed. In general, minimum and maximum will be presented to the same degree of precision as data is recorded, with mean, median and quartiles having 1 additional place after the decimal, and standard deviation having 1 or 2 additional places after the decimal, depending on the size of the mean. Percentages less than 100 will be displayed to 1 place after the decimal, where space permits.

Baseline characteristics are given without *p*-values.

p-values larger than 0.01 will be reported to two decimal places, those between 0.01 and 0.001 to three decimal places. *p*-values below 0.001 will be displayed as "<0.001".

Data will be presented, unless otherwise indicated, according to the two guideline strategy groups.

In general, analyses presented in the tables, listings, and figures will be confined to those subjects included in the full analysis set (defined in section 8).

4 HYPOTHESES AND DECISION RULES

4.1 Statistical Hypotheses

This protocol is designed to establish the superiority of adhering to the guideline for labor progression presented by Zhang compared to adhering to the WHO-partograph in nulliparous women with regard to the rate of ECD.

The null hypothesis is that there is no difference in the probability of ECD between the two guideline strategies.

The alternative hypothesis is that there is a difference in the probability of ECD between the two guideline strategies.

4.2 Statistical Decision Rule

This protocol is designed to address a single primary endpoint.

Superiority of adhering to the guideline for labor progression presented by Zhang over the WHO-partograph is claimed if the primary null hypothesis is rejected, and the group difference is in favor of the Zhang guideline.

Statistical significance is claimed if the null hypothesis is rejected on the significance level (alpha) of 0.05 (two-sided).

That is, if the p-value of the null hypothesis test is less than or equal to 0.05.

5 DEFINITIONS AND DERIVED VARIABLES

5.1 Change from baseline

Not applicable

5.2 Other calculations

Age (years) = [(date of baseline – date of birth)/365.25].

BMI = weight in kilograms / (height in metres) x (height in metres)

BMI will be categorized according to the WHO definitions for underweight, normal, overweight and obese.

Different delivery phase/stage is defined as follows (see figure 3)

- Latent phase of first stage is defined as the time of the onset of labor (patient reported) until the cervix is dilated to 4 cm.
- Active phase of first stage of labor is defined as regular painful uterine contractions and cervical dilatation from 4 centimeters until the cervix is fully dilated, 10 cm, or until ECD.

- Descending phase of second stage is defined as the period from full dilatation of cervix until the expulsion phase starts, or until ECD.
- The expulsion phase of the second stage is defined as the period from expulsion starts until the baby is completely out of the birth canal, or until ECD.
- Total length of active labor is described as the period from the partograph registration (minimum 4 cm) until the baby is born (vaginally or by ECD).
- Length of active phase of first stage of labor, length of second stage, descending phase and expulsion phase will also be described.

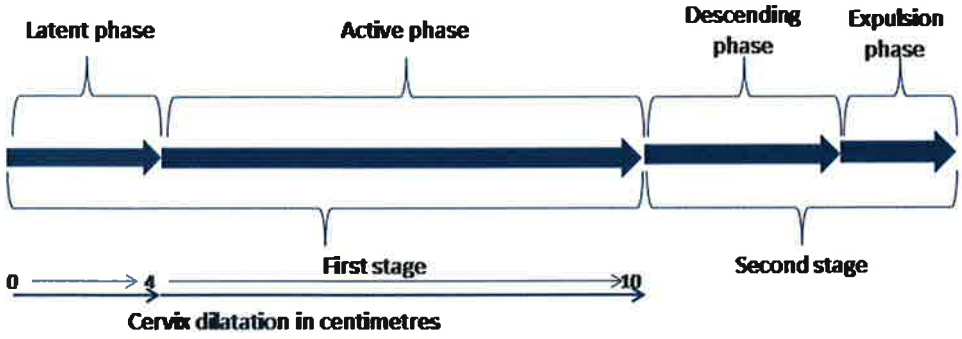

Fig 1

Computing of time variables for the different delivery phase/stage

The length of active phase of first stage of labor was recoded based on the cervix dilatation data in the CRF. In the CRF, dilatation data could be entered for every half hour from the start of the partograph registration. If no examination of the cervix dilatation was done, the corresponding data point in the CRF was not entered. The active phase of first stage was computed as time from 4cm cervix dilatation or first partograph registration to last partograph registration.

Descending and expulsion phase of second stage are directly registered in the CRF. The total length of second stage is computed as the sum of these. Total length of active labor is computed as the sum of the length of active phase of first stage, and the total length of second stage.

Labor dystocia is defined as follows:

Labor dystocia according to Zhang's guideline is diagnosed if the cervix dilatation rate according to the 95 % percentile, does not meet the expected progression from centimeter to the next centimeter. During second stage of labor, dystocia is diagnosed, if the time from full dilatation to active expulsion phase (passive second stage) exceeds 1 hour and 45 minutes (2 hours and 30 minutes for women with epidurals), or if the expulsion phase (active second stage) exceeds 60 minutes (see figure 2).

Dilation of the cervix	95 percentile * (dystocia)
From 4 to 5 cm	6 h / 30 min
From 5 to 6 cm	3 h / 15 min
From 6 to 7 cm	2 h / 15 min
From 7 to 8 cm	1 h / 30 min
From 8 to 9 cm	1 h / 30 min
From 9 to 10 cm	1 h / 45 min
2. stage without EDA Expulsion phase max 60 min	2 h / 45 min
2. stage with EDA Expulsion phase max 60 min	3 h / 30 min
Total time without EDA	19 h / 30 min
Total time with EDA	20 h / 15 min

Fig 2

Labor dystocia according to the WHO partograph/standard care guideline is diagnosed if cervix dilatation rate is slower than one centimeter per hour, assessed after four hours i.e. if the four-hours action line is crossed. During second stage of labor, dystocia is diagnosed if the time from full dilatation to active expulsion phase exceeds 1 hour (2 hours for women with epidurals), or if the expulsion phase (active second stage) exceeds 60 minutes (see figure 3).

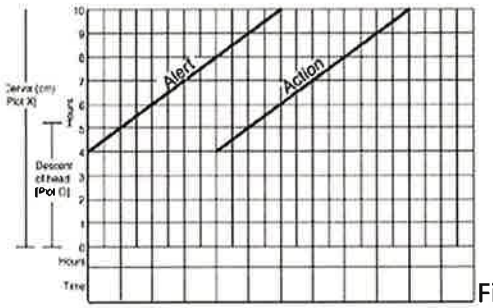

Fig 3

Apgar score is defined as follows

The Apgar score is a method to quickly summarize the health of newborn children. The Apgar scale is determined by evaluating the newborn baby on five simple criteria on a scale from zero to two, then summing up the five values thus obtained. The resulting Apgar score ranges from zero to 10. The five criteria are summarized using words chosen to form an acronym (Appearance, Pulse, Grimace, Activity, Respiration). We recorded Apgar score 1, 5 and 10 minutes after delivery.

Metabolic acidosis is defined as follows:

Umbilical cord (artery) pH <7.0 + base excess (BE) ≤ -12 mmol/l in the umbilical artery (dichotomous)

Episiotomy is defined as follows.

A surgical incision made in the area between the vagina and anus (perineum) to expand the opening of the vagina.

A perinatal tear is defined as follows.

All classifications clinically are done by midwives or doctors.

- 1st degree tear: Injury to skin only.

- 2nd degree tear: Injury to the perineum involving perineal muscles, not the anal sphincters
- 3rd degree tear: Injury to the perineum involving the anal sphincter complex
  - 3a: Less than 50% of external anal sphincter thickness torn
  - 3b: More than 50% of external anal sphincter thickness torn
  - 3c: Both the external and internal anal sphincters torn
- 4th degree tear: Injury to the perineum involving the anal sphincter complex and the anal/rectal epithelium
- Labia tear defined as tears to the labia either as a superficial abrasions or actual tearing of the labia.
- Cervical tears defined as cervical laceration.
- Vaginal tears defined as tears of minor lacerations of the vaginal mucosa or deeper tears to expose the inner muscles.

Obstetrical Anal Sphincter Injuries (OASIS) is defined as follows
Any 3rd or 4th degree tears.

6 EFFICACY AND SAFETY ENDPOINTS / VARIABLES

6.1 Primary Endpoint

The primary endpoint of this study is the need for emergency cesarean delivery. This is a dichotomous endpoint.

6.2 Secondary Endpoints

6.2.1 Efficacy

The secondary endpoints as defined in the protocol are as follows:

- Spontaneous vaginal delivery rate (dichotomous)
- Operative vaginal delivery rate (dichotomous) defined as vacuum and/or forceps delivery
- The proportion of amniotomy (dichotomous)
- The proportion of oxytocin augmentation in active labor (dichotomous)
- The proportion of epidural analgesia (dichotomous)
- The proportion of episiotomies (dichotomous)
- The proportion of OASIS (dichotomous)
- The proportion of blood transfusions (dichotomous)
- The proportion of post partum haemorrhage ≥ 1000 ml (dichotomous)
- Time related aspects of labor progress including

- active phase of first stage
- descending phase of second stage
- expulsion phase of second stage
- total length of second stage
- total length of active labor

- The proportion of neonates with Apgar score < 7 after 5 minutes (dichotomous)
- The proportion of neonates with umbilical cord artery pH < 7.0 (dichotomous)
- The proportion of neonates with umbilical cord artery pH < 7.05 (dichotomous)
- The proportion of neonates with metabolic acidosis (dichotomous)
- The proportion of transfer to the Neonatal Intensive Care Unit after birth (dichotomous)
- Information on Oxytocin augmentation throughout labor
  - Startdose presented in ml/hour or mU/hour (continuous)
  - Maximum dose presented in ml/hour or mU/hour (continuous)
  - Total duration of Oxytocin augmentation presented in hours and/or minutes (continuous)

6.2.2 Patient Reported Outcomes (PRO)

The women's experience with birth care will be investigated using "The Childbirth Experience Questionnaire, CEQ" (Dencker, Taft, Bergqvist, Lilja, & Berg, 2010) which will be sent to each participant approximately 4 weeks after discharge.

The CEQ consists of 22 questions related to childbirth experience. Three of the questions are answered as markings on a visual analogue scale (VAS), while 19 of the questions are answered on a four-point numerical rating scale (NRS). Each question is rated 0-3, with the VAS responses scored 0-100 and categorized as 0 – 40 = 0, 41 – 60 = 1, 61 – 80 = 2 and 81 – 100 = 3. Following the rating, four dimension sub-scores are calculated as the mean of questions related to Own capacity, Professional support, Perceived safety and Participation. A total CEQ score is also calculated as the mean of all 22 questions. If more than half of the questions in each sub-score or total are missing, the corresponding score is set to missing.

6.2.3 Exploratory endpoints

- **Detailed information on emergency cesarean delivery**

- Indications for emergency cesarean delivery are categorized into three different indications in the webCRF and are as follow: fetal distress, slow progress of labor/labor dystocia and other reasons. Only one option is possible
- Cervical dilatation when performed emergency cesarean delivery

- **Indications for operative delivery**
  - Three different indications described as fetal distress, dystocia, or other reason (several options are possible).

- **Detailed information on labor dystocia**
  - If labor dystocia is diagnosed according to current guidelines).
  - Cervical dilatation when dystocia is diagnosed.
  - If labor dystocia is diagnosed in the expulsion phase
  - Stage of descending head when dystocia is diagnosed as follow: over spinae, stage spinae, below spinae or at pelvic flor. One possible option.

- **Detailed information on oxytocin augmentation**
  - Was the indication for initiating oxytocin infusion labor dystocia
  - Cervical dilatation at onset of augmentation
  - If shutdown of augmentation was done due to mothers own contractions

- **The use of medical and nonmedical analgesia**
  - Six different medical methods (Pudendum analgesic, N2O, Opioids, Spinae analgesic or other). Several options are possible.
  - Cervical dilatation at onset of EDA is recorded.
  - Seven different nonmedical methods (acupuncture, sterile water injections, shower, bath, massage, TNS and other). Several options are possible.

- **Detailed information on fetal monitoring during active labor**
  - Four different fetal monitoring methods during active labor, categorized as intermittent auscultation, intermittent cardiotocography (CTG), continuous CTG and ST-analyzes (STAN). Several options of monitoring methods are possible.
  - Cervical dilatation at onset of fetal monitoring is recorded .

- **Detailed information on pH and BE in the umbilical cord**
  - The proportion of neonates with metabolic acidosis after birth

- **Detailed information on transfer neonates to Neonatal Intensive Care Unit after birth**
  - The proportion of transfer to the Neonatal Intensive Care Unit after birth(dichotomous)
  - Indications for transfer (four different indications: asphyxia, suspect infections, respiratory problems or other reasons). One possible option.
  - Length of stay, defined as more or less than 24 h.

- **Detailed information on episiotomy**

- Including four different indications (fetal distress, threatening perineal rupture, vaginal operative delivery or other reason). Several options are possible.

- **Detailed information on amniotomy**
  - including indications (dystocia, fetal distress and other reason), only one possible option
  - cervical dilatation at amniotomy

- **Detailed information on perinatal tear as defined above.**

- **Detailed information on non invasive actions for stimulating of contractions describes as:**
  - none
  - change positions
  - emptied bladder
  - given food
  - given liquid to drink

- **Detailed information on admission to the labor ward, including**
  - indication of admission
  - time from rupture of the membranes until admission
  - cervical dilatation when rupture of the membranes
  - characteristics of the amniotic fluid
  - rate of contractions before and upon admission
  - time of contractions until admission
  - cervical dilatation upon admission
  - fetal heart rate
  - if CTG was used
  - classification of the CTG

- **Detailed information regarding total length of birth in the different phases**

6.3 Safety Parameters

Not applicable

7 DETERMINATION OF SAMPLE SIZE

The determination of the sample size (number of clusters and individuals) is based on a power calculation with the least occurring outcome; intrapartum cesarean delivery, which was 9.2% (at time of sample size calculation) in the study population (p1). Further, we expect that the intrapartum cesarean delivery rate will be 6.7% (p2) which is a 25% reduction, when using the new guideline. Formula (4) on page 320 in the article by Hayes et al. is used to calculate the needed number of clusters and participants.(Hayes & Bennett, 1999) According to this formula, with a chosen significance level of 0.05, a power of 80% and p1 = 9.2% and p2 = 6.9%, we should include at least 14 clusters and 6582 individuals. The design allows flexibility, so that larger birth care units may contribute with more study subjects than smaller units.

8 DATA SETS TO BE ANALYZED

There will be four analyzes sets in this study.

- The **Eligible Analysis Set (EAS)** will include all eligible women within the inclusion period at each site
- The **Full Analysis Set (FAS)** will include all eligible women with signed informed consent.
- The **Vaginal Delivery Set (VDS)** will include all eligible women with signed informed consent delivering vaginally.
- The **Cesarean Delivery Set (CDS)** will include all eligible women with signed informed consent with emergency cesarean delivery.

9 BLIND REVIEW

Prior to finalization of this statistical analysis plan, a blinded review will be performed. The blinded review will be performed without any knowledge of the randomized allocation. Thus, decisions made during the blind review will be regarded as blinded decisions and not introduce bias. Decisions in the blind review include data validation, population assignment, final choice of statistical models, assessment of model convergence and output formats.

10 STATISTICAL METHODOLOGY

The primary and secondary efficacy analyzes will be based on the Full Analysis Set (FAS) only. As there is only one identified primary analysis, there will be no adjustments for multiple testing in the secondary analyzes.

When random numbers are warranted for inference (such as for bootstrapping and multiple imputation), the seed will be set to the date the statistical analysis plan is signed-off (in the format yyyymmdd).

All efficacy analyzes will be presented by the size (point estimate) of the difference between the treatments and the associated 95% confidence interval, in addition to p-values of the corresponding statistical hypothesis test

All statistical analyzes will be done in Stata v15 (StataCorp. 2015. Stata Statistical Software: Release 15.1. College Station, TX, USA).

10.1 Adjustment for covariates

We will use the following covariates in all primary and secondary statistical models analyzes:

10.1.1 Maternal and neonatal characteristics

Maternal age
Maternal BMI
Civil status (single vs cohabitant/married)
Level of education (university/college education)

Cervical dilatation at first registration (time to event endpoints only)
Birth weight
Baby's head circumference

10.1.2 Hospital levels

Stratification variables

Annual emergency Cesarean delivery rate in Ten Group Classification System (TGCS) group 1 women in 2012
Annual number of deliveries in TGCS group 1 women in 2012

10.2 Center effect

As this is a cluster-randomized study with center as cluster, center will be included in the statistical models to adjust for within-cluster dependencies.

10.3 Multiplicity adjustments

As there is only one identified primary analysis, there will be no adjustments for multiple testing in the secondary analyzes. Secondary analyzes on secondary endpoints will be regarded as supportive.

10.4 Demographic and other baseline characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group for women in the FAS and in the EAS.

In addition, demographic and baseline data will be displayed separately for each of the study centres.

10.5 Primary efficacy analysis

The primary endpoint (the need for ECD) will be analysed using a mixed logistic regression model with center as random intercept and treatment strategy as fixed effect, adjusted for the covariates given in 10.1. Estimates of adjusted incidence-rate ratio (relative risk) and adjusted risk difference with confidence intervals will be computed using the delta method. (Reeve, 2018) Adjusted number needed to treat (NNT) will be presented if the 95% confidence limits of the adjusted risk difference excludes zero. The NNT with 95% confidence limits will be calculated as the reciprocal of the adjusted risk difference. Estimates of the intraclass correlation coefficient (ICC) within centers will be presented.

Robustness of the results will be checked using a standard logistic regression without adjusting for center as a random intercept, but adjusted for the covariates given in section 10.1. Treatment strategy will be included as fixed effect. Also a cluster-level analysis will be performed where the aggregated center proportion of ECD used to compare the treatment effect. We will use an Analysis of Covariance (ANCOVA) model with proportion of ECD as dependent variable, and treatment and previous year ECD rate as independent variables. The analysis will be weighted according to the reciprocal of the variance of the ECD rate by cluster (site) i given by

$$W_i = m_i/[1 + (m_i - 1)\rho]$$

where W_i is the weight, m_i is the cluster size and ρ is the intraclass correlation coefficient. (Donner & Klar, 2010)

The primary analysis will be performed on the primary analysis set, (the full analysis set).

10.5.1 Discussion regarding primary efficacy analysis

There are multiple different methods for analyzing cluster randomized trials.(Donner & Klar, 2010; Murray, Varnell, & Blitstein, 2004) Generally they can be divided into cluster-level and individual-level methods. Cluster-level methods are based on analyzes on aggregated data by cluster, and analyzed using a standard method, e.g. t-test or ANCOVA. The analyzes might be weighted by cluster size if there are enough clusters to estimate the ICC. An objection to this solution is that the method might be under-powered when the number of clusters is small, and that it is not possible to adjust for covariates on the individual level. Individual-level methods are based on individual observations, with the analyzes adjusted for clustering effects. Simple methods which adjusts the chi-square estimates exists (Donner & Klar, 2010), in addition to more model based approaches such as marginal generalized estimating equations (GEE) and conditional logistic mixed models. Between these two models, the logistic mixed model seems more robust when the number of clusters is less than 40. (Murray et al., 2004) Compared to the simple methods, model based methods allow for both cluster and individual specific covariates. Note that there is an interpretation difference of the treatment effect estimates between the marginal and conditional models. The marginal model effect measures have a population average interpretation, while the conditional model estimates the average effect for individual hospitals. In this study, the low number of clusters suggests that the conditional mixed model approach is the most robust method for analysis.

For survival endpoints, there are also several described methods adjusting for cluster effects. In line with the analysis of binary data, we aim at using a parametric mixed model (Weibull), as this has good performance (Stedman et al., 2012).

10.6 Secondary efficacy analyzes

Secondary efficacy measures in this study consist of dichotomous as well as time to event variables. Secondary dichotomous variables will be analysed as the primary variable.

Time to event variables will be analyzed using Weibull regression with cluster as random intercept and treatment strategy as fixed effect, adjusted with covariates as given in section 10.1 in addition to first registration of cervical dilatation in cm. Unadjusted Kaplan-Meier plots will be presented. Time to event variables will be analyzed in the FAS and VDS.

10.7 Missing data imputation and sensitivity analyzes

Missing data assessments are based on a blinded review of the data.

All included women have been assessed for birth delivery method, and thus there are no missing data for the primary endpoint.

There are no missing data in any of the covariates as described in section 10.1, except for BMI where 0.3% of the observations are missing and cohabitant with 0.8% missing values. Given the low missing data rate, we have decided to use a stochastic linear regression single imputation (Buuren, 2012) for

BMI and to use cohabitant status not known as one of the categories in addition to cohabitant/married and single.

Robustness analyzes will be performed with the hospital level covariates from 2013 due to the time gap between the assessment of the stratification variables (2012) and the study onset.

Additional robustness analyzes will include non-adjusted models and models adjusted only for hospital level covariates.

There are also no missing data in any of the secondary endpoints, except for the umbilical cord artery pH-variables and metabolic acidosis, which have 33% missing values. For these endpoints the main analyzes will be imputed with best outcome. Robustness analyses will be performed with worst outcome imputation.

Best outcome for the dichotomous umbilical cord artery pH < 7.0 variable is a pH-value above or equal to 7.0.

Best outcome for the dichotomous umbilical cord artery pH < 7.05 variable is a pH-value above or equal to 7.05.

Best outcome of the dichotomous metabolic acidosis variable is "no metabolic acidosis".

10.8 Patient Characteristics

10.8.1 Patient Disposition

The disposition of all patients will be listed and summarised by treatment arm.

10.8.2 Background and Demographic Characteristics

Patient demographics and baseline characteristics will be summarized for all patients in the FAS.

Patient demographics and baseline characteristics will be summarized by randomized treatment arm and overall using descriptive statistics as described in detail in section 3.

The maternal demographics and baseline characteristics include age at date of delivery, co-habitual status, education, smoking habits, body mass index (BMI) and cervical dilatation at first registration.

The neonatal characteristics include gestational age, birth weigth, head circumference and gender.

10.8.3 Site characteristics

Site characteristics will be summarised for all sites by treatment strategy. Characteristics to be summarized include yearly emergency Cesarean delivery rate and number of deliveries in TGCS group 1 women in 2012 and in 2013.

10.8.4 Treatment Compliance

To secure a thorough implementation of the trial, the management at all participating birth care units read and approved the trial protocol and signed a cooperation agreement committing to

adhere to the protocol. All birth care units underwent a strict teaching program including information and allocated guideline instructions, securing that all birth attendants had profound knowledge about the guidelines. Throughout the whole trial period and on a regular basis, researchers from the LaPS group revisited the units to ensure that all units adhered to the allocated guideline. Written information about the trial and the guidelines was printed on posters and made visible and available for midwives and obstetricians at all times. No exceptional measurements of treatment compliance were performed.

10.8.5 Concomitant Medications and Other Therapies

Not applicable

10.8.6 Patient reported outcome measure data

The total and sub-scores of the CEQ will be analysed using a linear mixed model with site as random intercept and treatment strategy as fixed effect, adjusted with covariates as given in section 10.1.

10.8.7 Concomitant treatment

The only concomitant treatment registered in this trial is the use of oxytocin, which will be analyzed as a secondary endpoint.

10.9 Exploratory Analysis

Hypothesis generating exploratory analyzes will be performed on exploratory endpoints. These analyzes will not be detailed in this analysis plan and will be regarded as post-hoc analyzes.

Dichotomous and time to event exploratory endpoints will initially be analyzed as for the primary and secondary endpoints. Continuous exploratory endpoints will initially be analyzed with a linear mixed model with site as random intercept and treatment strategy as fixed effect, adjusted with covariates as given in section 10.1. However, these initial analyzes might be altered based on analysis results in the pursuit of interesting clinical hypotheses.

There are no pre-specified subgroup analyzes defined in this SAP.

11 Safety Analysis

11.1 Adverse events

There will be no additional analyzes of adverse events than those described as efficacy endpoints (episiotomies, OASIS, blood transfusions).

12 Interim analysis

No interim analysis was planned during the trial.

13 Data monitoring

There was no formal Data Monitoring Committee for this trial.

14 Table of Contents of Tables, Listings and Figures

14.1 List of Tables

14.2 List of Listings

14.3 List of Figures

15 References

Buuren, S. (2012). Flexible Imputation of Missing Data (Vol. 20125245). Chapman and Hall/CRC. http://doi.org/10.1201/b11826

Dencker, A., Taft, C., Bergqvist, L., Lilja, H., & Berg, M. (2010). Childbirth experience questionnaire (CEQ): development and evaluation of a multidimensional instrument. Bmc Pregnancy and Childbirth, 10(1). http://doi.org/10.1186/1471-2393-10-81

Donner, A., & Klar, N. (2010). Design and Analysis of Cluster Randomization Trials in Health Research. Wiley.

Friedman, E. A. (1954). The graphic analysis of labor. American Journal of Obstetrics and Gynecology, 68(6), 1568–1575. http://doi.org/10.1016/0002-9378(54)90311-7

Hayes, R. J., & Bennett, S. (1999). Simple sample size calculation for cluster-randomized trials. International Journal of Epidemiology, 28(2), 319–326. http://doi.org/10.1093/ije/28.2.319

Murray, D. M., Varnell, S. P., & Blitstein, J. L. (2004). Design and analysis of group-randomized trials: A review of recent methodological developments. American Journal of Public Health, 94(3), 423–432.

Reeve, R. (2018). Confidence interval of difference of proportions in logistic regression in presence of covariates. Statistical Methods in Medical Research, 27(2), 451–465. http://doi.org/10.1177/0962280216631583

Stedman, M. R., Lew, R. A., Losina, E., Gagnon, D. R., Solomon, D. H., & Brookhart, M. A. (2012). A comparison of statistical approaches for physician-randomized trials with survival outcomes. Contemporary Clinical Trials, 33(1), 104–115. http://doi.org/10.1016/j.cct.2011.08.008

Zhang, J., Landy, H. J., Branch, D. W., Burkman, R., Haberman, S., Gregory, K. D., et al. (2010). Contemporary Patterns of Spontaneous Labor With Normal Neonatal Outcomes. Obstetrics and Gynecology, 116(6), 1281–1287. http://doi.org/10.1097/AOG.0b013e3181fdef6e

Correction to the statistical analysis plan

Concerning CEQ questionnaire, section 6.2.2, second paragraph, line 3:

“Each question is rated 0-3”

The questions should be rated 1-4 according to the developer of the questionnaire, Anna Dencker. https://bmcpregnancychildbirth.biomedcentral.com/

Corrections will be made when presenting the CEQ data to provide the correct numbers and values.

Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Bernitz S, Dalbye R, Zhang J, et al. The Labour Progression Study (LaPS): Intrapartum caesarean section rates following Zhang's guideline and the WHO partograph. A cluster randomised trial

Table of contents

Section 1. Organization of the LaPS study

The following investigators, institutions and colloborators, all in Norway, contributed to the LaPS study:

Steering Group

Stine Bernitz, RM., PhD., Rebecka Dalbye, RM., MSc., Jun Zhang, MD., PhD., Torbjørn M. Eggebø, MD., PhD., Ellen Blix, RM., DrPH., Pål Øian, MD., PhD.

Authors

Stine Bernitz, RM., PhD., Rebecka Dalbye, RM., MSc., Jun Zhang, MD., PhD., Torbjørn M. Eggebø, MD., PhD., Kathrine F. Frøslie, Statistician., PhD., Inge Christoffer Olsen, Statistician, PhD., Ellen Blix, RM., DrPH., Pål Øian, MD., PhD.

Data Monitoring

Berit Marianne Bjelkåsen MSc., Stine Bernitz, RM., PhD., Inge Christoffer Olsen, Statistician, PhD.

Statistical Analysis Plan

Stine Bernitz, RM., PhD., Rebecka Dalbye, RM., MSc., Torbjørn M. Eggebø, MD., PhD., Kathrine F. Frøslie, Statistician., PhD., Inge Christoffer Olsen, Statistician, PhD., Ellen Blix, RM., DrPH., Pål Øian, MD., PhD.

Statistical Analyses - Inge Christoffer Olsen, Statistician, PhD., Kathrine F. Frøslie, Statistician., PhD., Stine Bernitz, RM., PhD., Rebecka Dalbye, RM., MSc.

The LaPS study group

Grete Teigland, Berit Fiksdal, Helen-Marit Torvik, Anne-Birthe Lømo, Anne-Gro Klokkehaug, Heidi Frostad Sivertsen, Marit Mathisen, Ole-Georg Torjusen, Marit Innervik, Stian Westad, Tove-Ragnhild Johnsen, Bente Mietinen, Gunnbjørg Andreassen, Janita Skogeng, Sissel Hjelle, Elin Ytterbø Hansen, Ingerid Herstad Nygaard, Birgitte Janson, Åse-Kari Kringlåk, Kjersti Skoe, Linn Nistov, Irene Jensen, Marieke Claessen, Margit Rosenberg, Eirin Paulsen, Stine Bernitz, Marit Martinussen, Gunnel Dyb, Philip von Brandis, Daniella Rozsa.

Section 2. Statistical analysis

Mixed logistic regression model for caesarean section rate

We used a mixed logistic regression model with the center as random intercept and treatment strategy as the fixed effect, adjusted for the covariates maternal age, BMI, civil status, and level of education. The hospital-level covariates used for stratification were the annual numbers of delivery and Intrapartum Caesarean Section (ICS) rates in the TGCS group 1 woman at the time of sample size calculation in 2012. Estimates of the adjusted relative risk and adjusted risk difference with confidence intervals were computed with the delta method. Estimates of the Intraclass Correlation Coefficient (ICC) within centres are presented in Table A4.

There are many different methods for analysing cluster randomised trials.[1,2] Generally they can be divided into cluster-level and individual-level methods. Cluster-level methods are based on analyses of aggregated data by cluster, and analysed using a standard method, e.g. t-test or Analysis of Covariance (ANCOVA). The analyses might be weighted by cluster size if there are enough clusters to estimate the ICC. An objection to this solution is that the method might be under-powered when the number of clusters is small, and that it is not possible to adjust for covariates on the individual level. Individual-level methods are based on individual observations, with the analyses adjusted for clustering effects. There are simple methods to adjust the chi-square estimates,[2] in addition to more model-based approaches such as marginal Generalized Estimating Equations (GEE) and conditional logistic mixed models. Between these two models, the logistic mixed model seems more robust when the number of clusters is less than 40.[1]

Compared with simple methods, model-based methods allow for covariates specific for both clusters and individuals. There is an interpretation difference for the treatment effect estimates between the marginal and conditional models. The marginal model estimates the mean effect in the population, while the conditional model estimates the mean effect for individual hospitals. In this study, the low number of clusters suggested that the conditional mixed model approach was the most robust method for analysis.

Section 3. Supplementary Figures

Figure A1. Zhang's guideline[3] for calculating the expected progression during the active phase of the first stage of labour according to time intervals from cm to cm.

Cervical Dilation (cm)	Parity 0 (n=25,624)	Parity 1 (n=16,755)	Parity 2+ (n=16,219)
3–4	1.8 (8.1)	—	—
4–5	1.3 (6.4)	1.4 (7.3)	1.4 (7.0)
5–6	0.8 (3.2)	0.8 (3.4)	0.8 (3.4)
6–7	0.6 (2.2)	0.5 (1.9)	0.5 (1.8)
7–8	0.5 (1.6)	0.4 (1.3)	0.4 (1.2)
8–9	0.5 (1.4)	0.3 (1.0)	0.3 (0.9)
9–10	0.5 (1.8)	0.3 (0.9)	0.3 (0.8)
Second stage with epidural analgesia	1.1 (3.6)	0.4 (2.0)	0.3 (1.6)
Second stage without epidural analgesia	0.6 (2.8)	0.2 (1.3)	0.1 (1.1)

Data are median (95th percentile).

Reprinted with permission of Wolters Kluwer Health, Inc. from Zhang J, Landy HJ, Branch DW, et al. (2010) Contemporary patterns of spontaneous labor with normal neonatal outcomes. Obstetrics and gynecology, 116:1281-7.

Figure A2. Zhang's guideline (paper version) used for the birth care units randomised to the Zhang group

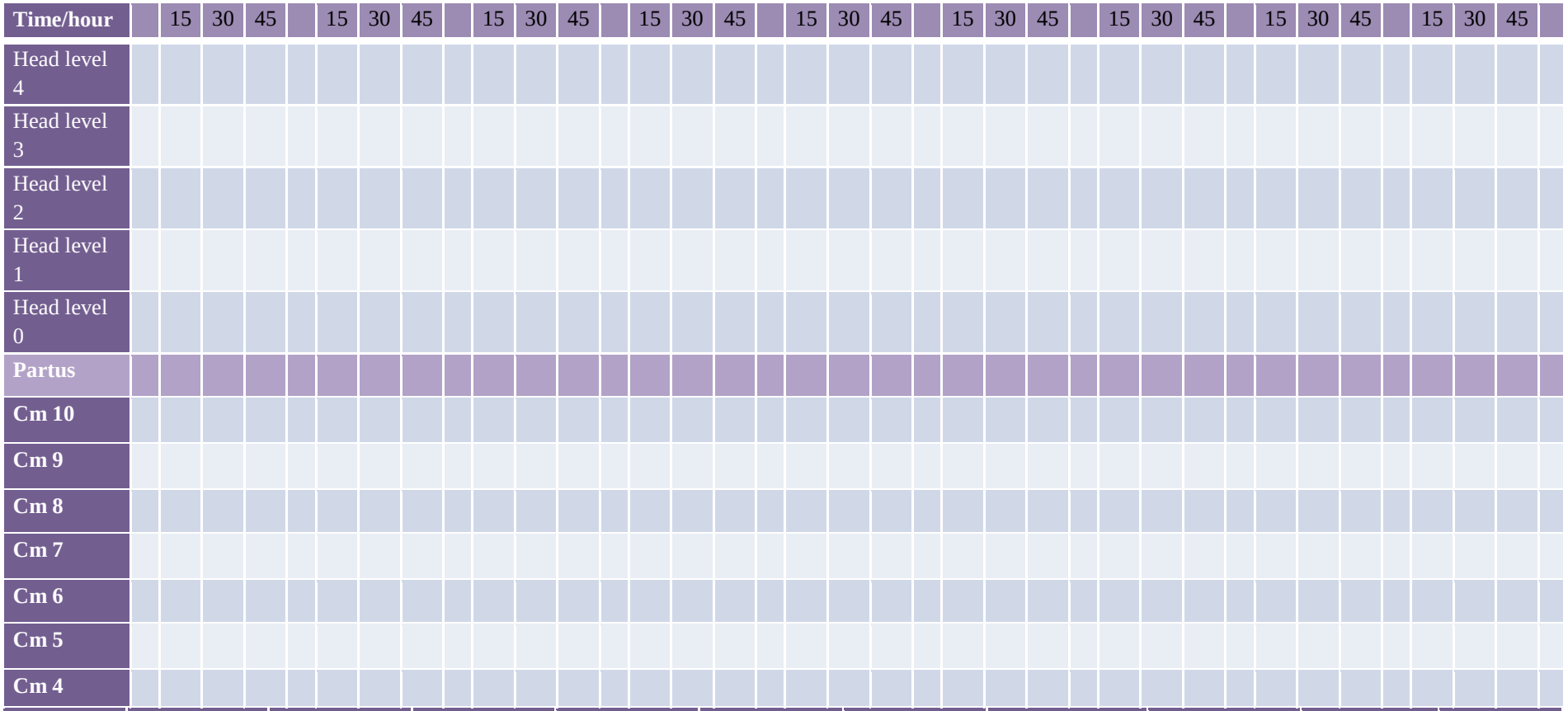

Figure A3. The WHO partograph[4,5] for labour progression during the active phase of labour with cervical dilatation of at least 1 cm (alert line) per hour assessed after 4 hours (action line).

Reprinted with permission of the World Health Organization from Managing complications in pregnancy and childbirth: a guide for midwives and doctors. World Health Organization, 2003.

Section 4. Supplementary Tables

Table A1. The robustness to handling of missing data showed negligible differences compared with the results presented in the article.*

	Intervention group **n=3972**	**Control group** **n= 3305**	**Adjusted relative risk** **(95%CI)**	**Adjusted risk difference (95% CI)**	**P-value**
	no. of neonates (%)				
Neonates with umbilical cord artery pH < 7.0	22 (0·6)	19 (0·6)	1·10 (0·82 to 1·48)	3·2% (-6·5 to 12·.9)	0·51

* Robustness analyses was performed with worst outcome imputation

Table A2. Summary of robustness analyses

			Mixed effects logistic regression adjusted for centres as random intercept				**Cluster level analyses¶**		**Standard logistic regression ¶¶**	
			Unadjusted ∫		Adjusted for hospital level covariates as fixed effects∫∫					
	Zhang	**WHO**	**RR (95%CI)**	**p-value**	**RR (95%CI)**	**p-value**	**Risk diff (95%CI)**	**p-value**	**RR (95%CI)**	**p-value**
Types of clinical intervention during labour	*no. of patients/total no.* (%)*									
Intrapartum caesarean section	271 (6·8)	196 (5·9)	1·18 (0·90 to 1·54)	0·22	1·19 (0·98 to 1·43)	0·07	1·1% (-0·2 to 2·4)	0·096	1·17 (0·98 to 1·40)	0·08
Operative vaginal delivery	839 (21·1)	581 (17·6)	1·11 (0·86 to 1·43)	0·42	1·07 (0·85 to 1·35)	0·55	1·4% (-3·8 to 6·6)	0·57	1·16 (1·06 to 1·28)	0·002
Artificial rupture of the membranes	1396 (35·1)	1223 (37·0)	0·94 (0·80 to 1·09)	0·40	0·93 (0·80 to 1·07)	0·30	-2·8% (-9·7 to 4·1)	0·39	0·94 (0·88 to 1·00)	0·03
Oxytocin augmentation	1658 (41·7)	1561 (47·2)	0·97 (0·80 to 1·18)	0·76	0·99 (0·84 to 1·17)	0·91	-0·8% (-11·6 to 9·9)	0·87	0·91 (0·87 to 0·96)	<0·001
Epidural analgesia	1913 (48·2)	1653 (50·0)	0·98 (0·83 to 1·17)	0·86	0·97 (0·82 to 1·15)	0·76	-1·4% (-11·9 to 9·1)	0·78	0·95 (0·90 to 0·99)	0·02
Perineal surgical incision**	1151/3701 (31·1)	881/3109 (28·3)	0·90 (0·68 to 1·20)	0·48	0·92 (0·69 to 1·22)	0·55	-3·1% (-14·0 to 7·8)	0·55	1·09 (1·02 to 1·18)	0·02
Obstetric anal sphincter injury**	112/3701 (3·0)	79/3109 (2·5)	1·19 (0·90 to 1·58)	0·23	1·15 (0·86 to 1·53)	0·34	0·4% (-0·2 to 1·1)	0·14	1·14 (0·86 to 1·52)	0·36
Blood transfusion	115 (2·9)	82 (2·5)	1·20 (0·80 to 1·80)	0·37	1·19 (0·81 to 1·75)	0·38	0·4% (-1·1 to 1·9)	0·54	1·16 (0·87 to 1·53)	0·31
Apgar score <7 after 5 minutes	49 (1·2)	36 (1·1)	1·14 (0·71 to 1·83)	0·59	1·15 (0·75 to 1·77)	0.52	0·2% (-0·4 to 0·8)	0·46	1·14 (0·74 to 1·75)	0·55
Neonates with umbilical cord artery pH < 7.0¥	22 (0·6)	19 (0·6)	1·02 (0·49 to 2·14)	0·96	0·99 (0·45 to 2·15)	0.98	-0·01% (-0·5 to 0·6)	0·80	0·93 (0·50 to 1·73)	0·82

Abbreviations: RR: Risk ratio; estimated RR for clinical interventions (primary and secondary outcomes) in the Zhang group compared with the WHO group; CI: Confidence interval; ICC: Intraclass correlation coefficient

*Total numbers are included when they differ from those in the overall study group. ** The analyses were based to all women who underwent a vaginal delivery. ¥Missing values (33%) are imputed with best outcome. ∫ An unadjusted mixed-effects logistic regression model only adjusted for centers as random intercept. ∫∫ A mixed-effects logistic regression model adjusting for centers as random intercept and hospital level covariates (annual ICS rates and number of deliveries in 2012) as fixed effects. ¶ A cluster-level analysis where the aggregated centre proportions of ICS were compared. Analysis of Covariance (ANCOVA) model with proportion of ICS at each hospital as the dependent variable, and treatment and annual ICS rates in 2012 as independent variables. The analyses were weighted according to the reciprocal of the variance of the ICS rate by cluster (site) given by: $W_i=m_i/[1+(m_i-1)\rho]$ where W_i is the weight, m_i is the cluster size and ρ is the ICC. ¶¶ A standard logistic regression not adjusted for centres as random intercept, but adjusted for hospital level and individual level covariates as specified in the primary analysis. The treatment strategy was included as a fixed effect. The reason for including the standard logistic regression as a pre-defined robustness analysis was to have available analyses in case the mixed-effects logistic regression models did not converge. Having pre-specified these analyses, we include them in the reporting. However, as all mixed-effects logistic regression models converged these analyses should not be taken into consideration as they do not take the cluster design into consideration.

Table A3. Robustness analyses with the pre-trial log-odds of ICS substituting the pre-trial proportion of ICS as covariate following request from reviewer

	Zhang group	WHO group	RR (95%CI)	Risk diff (95%CI)	p-value
Types of clinical intervention during labour	*no. of patients/total no.* (%)*				
Intrapartum caesarean section	271 (6·8)	196 (5·9)	1·18 (0·99 to 1·41)	1·0% (-0·1 to 2·2)	0·07
Operative vaginal delivery	839 (21·1)	581 (17·6)	1·06 (0·84 to 1·33)	1·0% (-3·4 to 5·4)	0·64
Artificial rupture of the membranes	1396 (35·1)	1223 (37·0)	0·91 (0·79 to 1·05)	-3·3% (-8·4 to 1·8)	0·20
Oxytocin augmentation	1658 (41·7)	1561 (47·2)	0·98 (0·84 to 1·15)	-0·9% (-7·8 to 6·1)	0·80
Epidural analgesia	1913 (48·2)	1653 (50·0)	0·96 (0·81 to 1·14)	-2·1% (-10·6 to 6·4)	0·63
Perineal surgical incision**	1151/3701 (31·1)	881/3109 (28·3)	0·89 (0·67 to 1·19)	-3·1% (-11·1 to 4·9)	0·44
Obstetric anal sphincter injury**	112/3701 (3·0)	79/3109 (2·5)	1·14 (0·86 to 1·52)	0·3% (-0·4 to 1·1)	0·36
Blood transfusion	115 (2·9)	82 (2·5)	1·15 (0·79 to 1·69)	0·4% (-0·6 to 1·4)	0·46
Apgar score <7 after 5 minutes	49 (1·2)	36 (1·1)	1·15 (0·75 to 1·77)	0·2% (-0·3 to 0·7)	0·52
Neonates with umbilical cord artery pH < 7.0¥	22 (0·6)	19 (0·6)	0·98 (0·45 to 2·13)	0% (-0·4 to 0·4)	0·96

Abbreviations: RR: Risk ratio; estimated RR for clinical interventions (primary and secondary outcomes) in the Zhang group compared with the WHO group; CI: Confidence interval; *Total numbers are included when they differ from those in the overall study group. ** The analyses were based to all women who underwent a vaginal delivery; ¥Missing values (33%) are imputed with best outcome.

Table A4. Post-hoc robustness analyses with small sample correction

Following the request from reviewer, post-hoc robustness analyses were performed to assess the impact of small sample corrections to the main analyses. The analyses follow the recommendation in (McNeish, 2016) to use the residual penalized quasi-likelihood (RPQL) estimation method with the Kenward-Roger (KR) correction supplementary to the adaptive Gauss-Hermite quadrature (AGQ) estimation method used in the main analyses.[6] As Stata v15 does not provide RPQL estimation, these analyses were done in SAS v9.4. The results are presented as parameter estimates from the mixed logistic regression models (logarithm of the odds ratio) with standard error and p-value.

Endpoint	Main analyses (AGQ estimation)			Small sample correction analyses (RPQL-KR) estimation		
	Estimate	Standard Error	p-value	Estimate	Standard Error	p-value
Intrapartum caesarean sections	0·173	0·099	0·08	0·181	0·111	0·14
Operative vaginal delivery	0·075	0·152	0·62	0·068	0·179	0·71
Artificial rupture of the membranes	-0·140	0·116	0·23	-0·143	0·139	0·33
Augmentation with oxytocin during labour	-0·037	0·155	0·81	-0·034	0·181	0·85
Epidural analgesia	-0·078	0·184	0·67	-0·078	0·219	0·73
Perineal surgical incision	-0·149	0·209	0·48	-0·155	0·247	0·55
Obstetric anal sphincter injury	0·140	0·151	0·35	0·140	0·151	0·52
Blood transfusion	0·152	0·200	0·45	NA	NA	NA
Apgar score <7 after 5 minutes	0·135	0·223	0·55	NA	NA	NA
Neonates with umbilical cord artery pH < 7.0	-0·009	0·397	0·98	NA	NA	NA

NA: Estimates not available because the model did not converge. Generally, the results from the analyses with small sample corrections were consistent with the main analyses with estimates slightly higher but with larger standard errors. The p-values were also slightly higher, but none to a degree where the interpretation of the results was changed compared to the main analyses. There were also a problem that the RPQL method did not converge for some of the endpoints.

Table A5. Baseline characteristics of the included and non-included women

Due to unavailable consent and women abstaining participation, 4338 were not included in the trial. The number of unavailable signed consents might be caused by occasionally high activity levels in the birth care units which does not allow time to obtain consents. It might also be partly explained by ethical aspects in that women in labour, experience labour pain, might not be in a situation where information about research projects are prioritized. Due to the risk of selection bias, no consents were obtained after delivery. To assess if there were differences between the included and non-included women, we performed an additional analysis of the basic characteristics of the non-included women for the following variables: Maternal age, civil status, level of education, smoking in first trimester, pregnant body mass index (BMI), and gestational age at onset of active labour. Baseline characteristics showed differences in the proportions aged ≥ 35 years, who were cohabitants/married, who attended higher education, and those with low BMI between the included and non-included women during the trial period (Table A5).

	Included women n=7277	Missing	**Non-included women** n= 4338	Missing	P-value
Maternal characteristics					
Age at delivery (years)*	28 ± 4		28 ± 5	1	1·0
< 25	1755 (24·1)		1026 (23·7)		0·57
25-35	4954 (68·1)		2923 (67·4)		0·44
≥ 35	568 (7·8)		388 (8·9)		0·03
Cohabitant or married	6878 (94·5)	60	3976 (91·7)	24	<0·001
Higher education ≥ 12 years	4429 (60·9)		2387 (55·0)	70	<0·001
Smoking first trimester	440 (6·0)	67	224 (5·2)	10	0·05
Pre-pregnant body mass index *†	24 ± 4	24	24 ± 4	197	1·0
≤ 18·5	314 (4·3)		220 (5·1)		0·06
18·5-24·9	4870 (66·9)		2725 (62·8)		<0·001
25·0-29·9	1452 (20·0)		824 (19·0)		0·2
≥ 30·0	617 (8·5)		372 (8·6)		0·86
Gestational age at onset of active labour (days)*	281 ± 7		281 ± 8	7	1·0

Numbers are no. (%) unless otherwise stated. *Values are means ± SD. †The body-mass index is the weight in kilograms divided by the square of the height in meters. The body-mass index was missing for 4·5% of the non-included women, thus the percentages do not add up to 100%.

Table A6. Birth care unit-specific intrapartum caesarean section (ICS) rates in 2012 vs. LaPS trial period

	Pre- intervention period (1.1.2012 - 31.12.2012)				**LaPS trial period**	
Unit	No. of births	No. of births	ICS TGCS1 No. (%)	Randomised*	No. of births	ICS TGCS1 No. (%)
	Total	TGCS 1			TGCS1	
3	1002	277	20 (7·2)	1	280	19 (6·8)
4	1046	296	32 (10·8)	1	304	24 (7·9)
6	1380	416	50 (12·0)	1	419	40 (9·5)
8	1547	438	35 (8·0)	1	428	24 (5·6)
9	1804	480	36 (8·1)	1	469	27 (5·8)
12	2874	769	89 (11·6)	1	788	74 (9·4)
14	4855	1244	102 (8·2)	1	1284	63 (4·9)
Sum	14 508	3920	364 (9·3)		3972	271 (6·8)
1	528	134	21 (15·7)	0	133	10 (7·5)
2	996	282	30 (10·6)	0	261	22 (8·4)
5	1126	319	32 (10·0)	0	327	15 (4·6)
7	1397	370	31 (8·4)	0	368	21 (5·7)
10	2009	618	55 (8·9)	0	649	32 (4·9)
11	2065	481	39 (8·1)	0	495	24 (4·8)
13	3796	1112	108 (9·7)	0	1072	72 (6·7)
Sum	11 917	3316	316 (9·5)		3305	196 (5·9)
Total	26 425	7236	680 (9·4)		7277	467 (6·4)

*Randomised to either 1= Zhang group or 0=WHO group

Table A7. Project in Norway during the LaPS trial period, focusing on reducing Caesarean section rate.

Numbers of births and intrapartum caesarean section (ICS) in TGCS 1 women in 2012 vs. LaPS trial period, in birth care unit > 500 deliveries/year, not participating in the LaPS- project.

	Pre- intervention period (1.1.2012 - 31.12.2012)		LaPS trial period (1.1.2015 - 31.12.2016)	
Unit	No. of births TGCS 1	ICS TGCS1 N (%)	No. of births TGCS1	ICS TGCS1 N (%)
Akershus University Hospital	1530	99 (6·5)	2767	245 (8·9)
Oslo University Hospital, Ullevål	2275	180 (7·9)	4868	423 (8·7)
Oslo University Hospital, Rikshospitalet	675	53 (7·9)	1337	93 (7·0)
Innlandet Hospital Trust, Gjøvik	220	22 (10·0)	420	55 (13·1)
Vestre Viken Hospital Trust, Ringerike	216	22 (10·2)	423	47 (11·1)
Sørlandet Hospital Trust, Kristiansand	545	40 (5·3)	990	71 (7·2)
Fonna Health Trust, Haugesund	393	24 (6·1)	738	33 (4·5)
Haukeland University Hospital, Bergen	1511	104 (6·9)	2981	187 (6·3)
North Trøndelag Health Trust, Levanger	244	35 (14·3)	424	42 (9·9)
Total	7609	579 (7·6)	14948	1196 (8·0)

References

1. Murray DM, Varnell SP, Blitstein JL. Design and analysis of group-randomized trials: a review of recent methodological developments. *Am J Public Health* 2004; **94**(3): 423-32.
2. Donner A, Klar, N. Design and Analysis of Cluster Randomization Trials in Health Research. 1.st ed ed. New York, USA: John Wiley & sons; ; 2010.
3. Zhang J, Landy HJ, Branch DW, et al. Contemporary patterns of spontaneous labor with normal neonatal outcomes. *Obstetrics and gynecology* 2010; **116**(6): 1281-7.
4. World Health Organization partograph in management of labour. World Health Organization Maternal Health and Safe Motherhood Programme. *Lancet* 1994; **343**(8910): 1399-404.
5. World Health Organization. Managing complications in pregnancy and childbirth: a guide for midwives and doctors. 2003. http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf.

Paper II

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ORIGINAL RESEARCH ARTICLE

The Labor Progression Study: The use of oxytocin augmentation during labor following Zhang's guideline and the WHO partograph in a cluster randomized trial

Rebecka Dalbye[1,2] | Stine Bernitz[1,2] | Inge Christoffer Olsen[3] | Jun Zhang[4] | Torbjørn Moe Eggebø[5,6] | Daniella Rozsa[6] | Kathrine Frey Frøslie[7] | Pål Øian[8] | Ellen Blix[2]

[1]Department of Obstetrics and Gynecology, Østfold Hospital Trust, Grålum, Norway

[2]Department of Nursing and Health Promotion, Faculty of Health Sciences, Oslo Met—Oslo Metropolitan University, Oslo, Norway

[3]Research Support Services, Clinical Trial Unit, Oslo University Hospital, Oslo, Norway

[4]MOE-Shanghai Key Lab of Children's Environmental Health, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

[5]National Center for Fetal Medicine, Trondheim University Hospital (St Olav's Hospital), Trondheim, Norway

[6]Department of Obstetrics and Gynecology, Stavanger University Hospital, Stavanger, Norway

[7]Norwegian National Advisory Unit on Women's Health, Oslo University Hospital, Oslo, Norway

[8]Department of Obstetrics and Gynecology, University Hospital of North Norway, Tromsø, Norway

Correspondence
Rebecka Dalbye, Department of Obstetrics and Gynecology, Østfold Hospital Trust, Postbox 300, 1714 Grålum, Norway.
Email: rebecka.dalbye@so-hf.no

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Abstract

Introduction: This study aims to investigate the use of oxytocin augmentation during labor in nulliparous women following Zhang's guideline or the WHO partograph.

Material and methods: This is a secondary analysis of a cluster randomized controlled trial in 14 birth-care units in Norway, randomly assigned to either the intervention group, which followed Zhang's guideline, or to the control group, which followed the WHO partograph, for labor progression. The participants were nulliparous women who had a singleton full-term fetus in a cephalic presentation and spontaneous onset of labor, denoted as group 1 in the Ten Group Classification System.

Results: Between December 2014 and January 2017, 7277 participants were included. A total of 3219 women (44%) received augmentation with oxytocin during labor. Oxytocin was used in 1658 (42%) women in the Zhang group compared with 1561 (47%) women in the WHO group. The adjusted relative risk for augmentation with oxytocin was 0.98 (95% CI 0.84-1.15; P = .8) in the Zhang vs WHO group, with an adjusted risk difference of −0.8% (95% CI −7.8 to 6.1). The participants in the Zhang group were less likely to be augmented with oxytocin before reaching 6 cm of cervical dilatation (24%) compared with participants in the WHO group (28%), with an adjusted relative risk of 0.84 (95% CI 0.75-0.94; P = .003). Oxytocin was administered for almost 20 min longer in the Zhang group than in the WHO group, with an adjusted mean difference of 17.9 min (95% CI 2.7-33.1; P = .021). In addition, 19% of the women in the Zhang group and 23% in the WHO group received augmentation with oxytocin without being diagnosed with labor dystocia.

Conclusions: Although no significant difference in the proportion of oxytocin augmentation was observed between the 2 study groups, there were differences in how oxytocin was used. Women in the Zhang group were less likely to receive oxytocin augmentation before 6 cm of cervical dilatation. The duration of augmentation with oxytocin was longer in the Zhang group than in the WHO group.

Abbreviations: AMD, adjusted mean difference; ARD, adjusted risk difference; ARR, adjusted relative risk; CI, confidence interval; LaPS, The Labor Progression Study; TGCS, Ten-Group Classification System; WHO, World Health Organization.

KEYWORDS
labor dystocia, labor progression guidelines, nulliparous, oxytocin augmentation, Ten Group Classification System 1

1 | INTRODUCTION

Augmentation with oxytocin is a widely used method to treat labor dystocia during the active phase of labor,[1-4] aiming to produce sufficient uterine contractions for cervical dilatation and fetal descent. At the same time, it is also important to avoid uterine hyperstimulation and fetal compromise. The use of augmentation with oxytocin is recommended by the World Health Organization (WHO)[2] and the National Institute for Health and Care Excellence,[5] even if the recommendations are based on low-quality evidence.[2]

A systematic review including randomized studies only, reported an association between oxytocin administration and a reduction in the mean duration of labor of approximately 2 hours. However, there was no decrease in the rates of cesarean sections and nor were there improved birth outcomes for mothers and babies.[6] In addition, observational studies reported that oxytocin augmentation was associated with an increased risk of instrumental vaginal delivery, episiotomy, emergency cesarean section, sphincter ruptures, a low Apgar score, a low cord pH in neonates, and newborn transfer to the neonatal intensive care unit.[7-9] Synthetic oxytocin has been classified as a potentially harmful medication and is included in the list of high-alert medications by the Institute for Safe Medication Practices in the USA.[10] Despite this fact, the rate of oxytocin administration in western countries has been reported to be between 44% and 75% over the last decade.[11-13]

Labor dystocia has no universal definition. Consensus concerning its management is lacking, and diagnostic criteria and guidelines for labor progression depend on local definitions.[4,14,15]

For more than 6 decades, labor progression has been assessed on the basis of Friedman's research.[16] In the early 1970s, Philpott & Castle[17] developed guidelines for assessing labor progression according to Friedman's findings. These guidelines consist of an action line to detect abnormal labor progress. In 1994, the WHO partograph[18] was presented based on the work of Philpott & Castle[17] and is currently used worldwide.[5] Because of a substantial change in labor management over the past half century, questions have been raised on the appropriateness of the recommendations of expected cervical dilatation in labor.[19-22]

In 2010, Zhang et al[21] presented a hyperbolic labor curve based on a large contemporary cohort that included 27 170 nulliparous women. His findings present a substantially slower labor progression than previously thought, and research suggests that some interventions, such as oxytocin augmentation, might be performed too soon according to the prevailing definitions of labor dystocia.[4] The WHO has identified a knowledge gap regarding which design, if any, is preferable for a partograph.[23] The overall aim of this study is to provide detailed knowledge on the use of oxytocin augmentation during labor and will be an important contribution when evaluating different labor progression guidelines. The specific aim is to investigate if there were differences in oxytocin for augmentation during labor in nulliparous women randomized to adhere to Zhang's guideline compared with the WHO partograph.

Key message
We did not observe any significant differences in the proportion of oxytocin for augmentation between the two study groups, but women in the Zhang group were less likely to be augmented with oxytocin before 6 cm of cervical dilatation.

2 | MATERIAL AND METHODS

We used data from the Labor Progression Study (LaPS), a cluster randomized controlled trial undertaken in Norway, with the aim of evaluating the effect of the 2 different guidelines for labor progression. The study protocol was published in 2017,[24] and detailed methodological considerations, information regarding the intervention and procedures, and the results for the primary outcome are recently published.[25]

Approximately 60 000 babies are born annually in 46 birthing institutions in Norway. Birth-care units were eligible to participate if their annual delivery rate exceeded 500 infants. The inclusion criteria for participating individuals were nulliparous women with a singleton fetus in a cephalic presentation and spontaneous onset of active labor, defined as at least 4 cm of cervical dilatation with regular contractions, in gestational week 37 or greater. This group is denoted as group 1 in the Ten Group Classification System (TGCS) by Robson et al.[26] Women who understood the Norwegian language were included.

The randomization procedure was computer generated, and it was stratified for annual birth number and previous rates of cesarean sections for TGCS group 1. Neither the staff at the birth-care units nor the participants were masked to group affiliation because of the nature of the design. In this trial, hospitals were the units of randomization, and women were the units of analysis. The estimated day of delivery was determined in a second-trimester ultrasound scan. At this examination or upon admission to the labor ward, eligible women received written information about the trial. Data for eligible women who provided informed consent were included in the analyses.

Before randomization and trial onset, staff at all sites received information about the LaPS protocol and were trained on how to use the allocated guidelines. Seven birth-care units were randomized to the intervention group adhering to Zhang's guideline, and seven birth-care units were randomized to the control group adhering to the WHO partograph. The active phase of first stage is defined as being from at least 4 cm to 10 cm of cervical dilatation. For women adhering to Zhang's guideline, labor dystocia was diagnosed if the cervical dilatation did not meet the expected progression from one integer cm to the next according to the 95th centile. Labor dystocia in the second stage was diagnosed if the descending phase lasted longer than 1 hour and 45 minutes, 2 hours and 30 minutes for women with epidural analgesia, or if the expulsion phase lasted longer than 60 minutes (see Supplementary material, Figure S1). For women adhering to the WHO partograph for labor progression, labor dystocia was diagnosed if the cervical dilatation was slower than one integer centimeter per hour, assessed after 4 hours, i.e if the 4-hour action line was crossed. Labor dystocia in the second stage was diagnosed if the descending phase lasted longer than 1 hour, 2 hours for women with epidural analgesia, or if the expulsion phase lasted longer than 60 minutes (see Supplementary material, Figure S2). If labor dystocia was diagnosed, the guideline on treatment because of insufficient contractions was followed as a common routine at all birth-care units in Norway.[27]

The primary outcome in the present paper was the proportion of oxytocin augmentation in active labor. The secondary outcome measurements included duration of oxytocin augmentation in minutes, maximum dose of oxytocin in mL/h, dose when initiating augmentation, cervical dilatation when initiating augmentation with oxytocin, proportion of discontinuation of oxytocin, proportion of labor dystocia according to the allocated guideline, and cervical dilatation when labor dystocia was diagnosed. In addition, a comparison between oxytocin augmentation during active labor and labor dystocia was presented. The clinical outcomes were registered in a web-based case report form, designed by the Unit of Applied Clinical Research at the Norwegian University of Science and Technology, to ensure consistent data recording.

2.1 | Statistical analyses

The LaPS sample size was calculated to show a 25% decrease in the proportion of intrapartum cesarean sections when adhering to

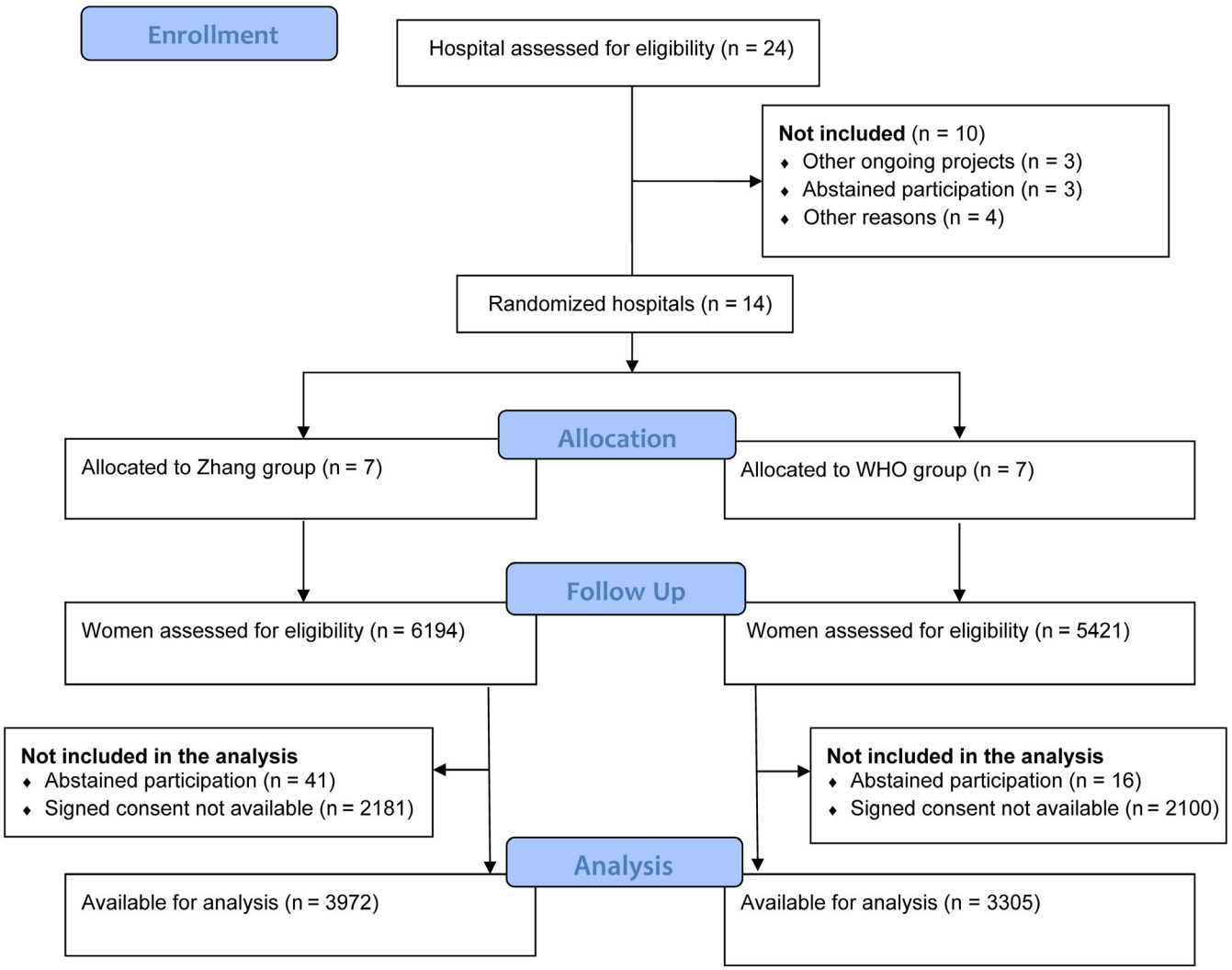

FIGURE 1 Flow chart of the inclusion of hospitals and participant [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of included hospitals (n = 14) and participants (n = 7277)

	Zhang group		WHO group	
	Hospitals (n = 7)	Participants (n = 3972)	**Hospitals (n = 7)**	Participants (n = 3305)
Hospital characteristics				
Deliveries per year				
<3000	6	2688 (36.9)	6	2233 (30.7)
≥3000	1	1284 (17.6)	1	1072 (14.7)
Characteristics related to the mother				
Maternal age at delivery (years)		28.4 (4.6)		28.5 (4.5)
Civil status (cohabitant or married)[a]		3741/3946 (94.8)		3137/3271 (95.9)
Higher education ≥ 12 years		2412 (60.7)		2017 (61.0)
Smoking during first trimester[a]		230/3963 (5.8)		210/3247 (6.5)
Prepregnant body mass index[a,b]		23.6/3966 (4.3)		23.8/3287 (4.3)
Gestational age at onset of active labor (days)		281 (7.0)		281 (8.0)
Characteristics related to labor				
Amniotomy		1396 (35.1)		1223 (37.0)
Epidural analgesia		1913 (48.2)		1653 (50.0)
Labor dystocia		1882 (47.4)		1512 (45.7)
Operative vaginal delivery		839 (21.1)		581 (17.6)
Cesarean section		271 (6.8)		196 (5.9)
Duration of active phase of labor (hours), median (IQR)		6.6 (3.6-10.5)		6.1 (3.4-9.5)
Duration of second stage (minutes), median (IQR)		76 (40-142)[c] n = 3746		75 (40-126)[c] n = 3134
Characteristics related to the newborn				
Birthweight (g)		3528 (427)		3518 (414)
Head circumference (cm)		35.0 (1.4)		35.0 (1.4)

Note: No. (%) or mean (SD) unless otherwise stated.
Abbreviation: IQR, interquartile range.
[a]Total numbers are presented due to missing values.
[b]The body mass index is the weight in kilograms divided by the square of the height in meters.
[c]Numbers are restricted to women who reached 10 cm of cervical dilatation.

Zhang's guideline.[25] The present paper describes secondary and exploratory analyses related to the use of oxytocin augmentation in active labor in the LaPS study (see Supplementary material, Appendix S1 regarding organization of the LaPS study). A separate statistical analysis plan was prepared for the analyses described in the Supplementary material (Appendix S2). The analyses were conducted according to the principle of intention-to-treat to estimate the effect of the two guidelines. Data with dichotomous outcomes were analyzed with a mixed logistic regression model. For continuous outcomes, a generalized linear mixed γ model with a logarithmic link function was used. For both models, birth-care units were included as random intercepts and the treatment strategy as a fixed effect. Furthermore, we adjusted for stratification variables (annual intrapartum cesarean section rates and number of deliveries) and for predefined covariates considered to be potential risk factors for oxytocin administration on an individual level (maternal age, body mass index, civil status, and educational level, as well as birthweight and neonatal head circumference). A 2-tailed *P* value ≤ .05 was considered significant. Estimates of the adjusted risk ratio, risk difference, and mean difference with confidence intervals (CI) were computed

with the delta method.[28] The analyses of the primary and secondary end points in this paper were based on all included women, except for the analyses of the duration of oxytocin administration, the maximum dose of oxytocin administration, and cervical dilatation when initiating oxytocin, which were restricted to women with oxytocin administration only. The calculation of cervical dilatation when labor dystocia was diagnosed was restricted to those diagnosed with labor dystocia.

No data were missing for the covariates included in the analyses, except for the body mass index (0.3%) and civil status (0.8%). Missing covariate data were imputed using stochastic linear regression single imputation. Some of the eligible women were not included in the study (Figure 1), and the characteristics of these women are presented in the Supplementary material (Table S1). All statistical analyses were performed in STATA v15 (Stata Corp. 2015; STATA statistical software: release 15.1.1 College Station, TX, USA).

2.2 | Ethical approval

This study, including patient information, informed consent and the baseline characteristics of the non-included women, was approved by the Regional Committee for Medical and Health Research Ethics (2013/1862/REK) South East and the Norwegian Social Science Data Services. It was registered at www.clinicaltrials.gov before the enrolment of the participants (NCT02221427), and the study protocol was published in *BMC Pregnancy and Childbirth*.[24] The protocol was approved and signed by the management at each birth-care unit before trial commencement.

3 | RESULTS

During the 26 months of inclusion, between 1 December 2014 and 31 January 2017, 14 birth-care units throughout Norway took part in the study. In all, 11 615 mothers in TGCS group 1 were assessed for eligibility to participate. Of these, 7277 were included in the analyses, 3972 and 3305 in the Zhang and WHO groups, respectively (Figure 1). The baseline characteristics of the 2 study groups are presented in Table 1. No data were missing for the primary outcome of oxytocin use for augmentation, and a total of 3219 women (44%) were augmented with oxytocin during active labor. Oxytocin augmentation was used in 1658 (42%) nulliparous women adhering to Zhang's guideline compared with 1561 (47%) nulliparous women

TABLE 2 The use of oxytocin augmentation

	Intervention group (n = 3972)	Control group (n = 3305)	Estimated difference (95% CI)	*P*-value
Oxytocin augmentation during labor, n (%)	1658 (41.7)	1561 (47.2)	ARR: 0.98 (0.84 to 1.15) ARD: −0.8% (−7.8 to 6.1)	0.8
Duration of oxytocin augmentation (minutes),[a] median (IQR)	134 (57-270)	115 (50-250)	AMD: 17.9 (2.7 to 33.1)	0.021
Maximum dose of oxytocin augmentation (mL/h),[a] median (IQR)	75 (45-120)	90 (60-120)	AMD: −0.1 (−13.5 to 13.3)	0.99
Dose of oxytocin when initiating augmentation (mL/h)[a] median (IQR)	30 (30-30)	30 (15-30)	AMD: −0.4 (−3.6 to 2.9)	0.82
Discontinuation of oxytocin,[a] n (%)[b]	74 (4.5%)	54/1554 (3.5%)		
Cervical dilatation when initiating oxytocin (cm),[a] n (%)[c]				
4 cm	101 (6.1)	128 (8.2)	ARR: 0.73 (0.55 to 0.98) ARD: −2.2 (−4.2 to −0.1)	0.04
5 cm	244 (14.7)	289 (18.5)	ARR: 0.79 (0.66 to 0.95) ARD: −3.9 (−6.9 to −0.9)	0.01
6 cm	399 (24.1)	443 (28.4)	ARR: 0.84 (0.75 to 0.94) ARD: −4.6 (−7.6 to −1.6)	0.003
7 cm	552 (33.3)	565 (36.2)	ARR: 0.92 (0.83 to 1.01) ARD: −3.0 (−6.3 to 0.2)	0.07
8 cm	712 (42.9)	692 (44.3)	ARR: 0.96 (0.88 to 1.05) ARD: −1.7 (−5.7 to 2.3)	0.40
9 cm	914 (55.1)	835 (53.5)	ARR: 1.01 (0.93 to 1.11) ARD: 0.8 (−4.1 to 5.7)	0.8
10 cm	1658 (100)	1561 (100)	ARR: 0.98 (0.88 to 1.09) ARD: −0.8 (−5.7 to 4.1)	0.8

Abbreviations: AMD, adjusted mean difference; ARD, adjusted risk difference; ARR, adjusted relative risk; IQR, interquartile range.

[a]Include women with oxytocin augmentation during labor.

[b]Total numbers are presented due to missing values.

[c]Numbers in % are cumulative.

TABLE 3 Labor dystocia and cervical dilatation when labor dystocia is diagnosed

	Intervention group (n = 3972)	Control group (n = 3305)	Adjusted relative risk (95% CI)	Adjusted risk difference (95% CI)	*P*-value
Labor dystocia, n (%)	1882 (47.4%)	1512 (45.7%)	1.1 (0.96 to 1.28)	4.8 (−1.8 to 11.3)	0.16
Cervical dilatation when labor dystocia was diagnosed (cm),[a] n (%)					
4 cm	49 (2.6)	74 (4.9)	0.54 (0.36-0.80)	−2.2 (−3.7 to 0.8)	0.002
5 cm	173 (9.2)	140 (9.3)	0.97 (0.79-1.20)	−2.7 (−2.2 to 1.7)	0.79
6 cm	217 (11.5)	162 (10.7)	1.06 (0.86 to 1.30)	0.6 (−1.7 to 3.0)	0.59
7 cm	232 (12.3)	106 (7.0)	1.76 (1.37 to 2.25)	5.3 (3.1 to 7.5)	<0.001
8 cm	236 (12.5)	99 (6.5)	1.90 (1.52 to 2.38)	5.9 (4.0 to 7.9)	<0.001
9 cm	247 (13.1)	120 (7.9)	1.68 (1.36 to 2.07)	5.3 (3.3 to 7.4)	<0.001
10 cm	728 (38.7)	811 (53.6)	0.72 (0.65 to 0.79)	−15.2 (−19.4 to −11.1)	<0.001

[a]Include women with labor dystocia only.

adhering to the WHO partograph. No significant difference in the risk of oxytocin augmentation was found; the adjusted relative risk in the intervention group vs the control group was 0.98 (95% CI 0.84-1.15; *P* = .8), and the corresponding adjusted risk difference was −0.8% (95% CI −7.8 to 6.1).

The median duration of oxytocin augmentation was 134 minutes in the Zhang group compared with 115 minutes in the WHO group, with an adjusted mean difference of 17.9 minutes (95% CI 2.7-33.1, *P* = .021), whereas the median of the maximum dose of oxytocin augmentation was 75 mL/h in the Zhang group compared with 90 mL/h in the WHO group, with an adjusted difference of −0.11 mL/h (95% CI −13.5 to 13.3, *P* = .99) (Table 2).

Table 2 also shows a detailed description of cervical dilatation in centimeters when initiating oxytocin, presented with a 95% CI among TGCS group 1 women in the 2 study groups. Women allocated to Zhang's guideline were less likely to receive augmentation with oxytocin before 6 cm of cervical dilatation compared with those allocated to the WHO partograph (adjusted relative risk of 0.84; 95% CI 0.75-0.94), with an adjusted risk difference of −4.6% (95% CI −7.6 to −1.6). In addition, discontinuation of oxytocin was used for 74 (4.5%) women in the intervention group and 54 (3.5%) women in the control group.

There was no significant difference in the adjusted relative risk for labor dystocia, which was 1.1 (95% CI 0.96-1.28; *P* = .2) in the intervention group vs the control group, with an adjusted risk difference of 4.8% (95% CI −1.8-11.3). In Table 3, detailed descriptions of the differences between the 2 study groups in cervical dilatation when labor dystocia was diagnosed are presented. A comparison between the 2 study groups for oxytocin augmentation and labor dystocia is presented in Table 4. For the women in the Zhang group, approximately 42% received oxytocin, of whom 81% were diagnosed with labor dystocia. In the WHO group, 47% women received oxytocin, of whom 77% were diagnosed with labor dystocia. No other differences in maternal and neonatal outcomes have been presented elsewhere.[25]

4 | DISCUSSION

Although no significant difference in the proportion of augmentation with oxytocin was observed between the two study groups, there were differences in the use of oxytocin during labor between the two study groups. The women allocated to follow Zhang's guideline were less likely to be augmented with oxytocin before 6 cm of cervical dilatation compared with the women in the control group, but the median duration of oxytocin augmentation was longer in the Zhang group.

The strength of our study is its rigorous design that helps achieve the research purpose[15,29] and its appropriate sample size calculation strengthens the internal validity. The external validity is strengthened by the data covering all areas in Norway, which allows the results to be generalized to a larger population. Furthermore, these data have been triple-checked, with few errors and missing values found. To assess the risk and effect of selection bias, we recorded the age, civil status, level of education, smoking habits, body mass index, and gestational age of the women not included in the trial; these baseline characteristics are presented in the Supplementary material (Table S1).

TABLE 4 A comparison between oxytocin augmentation and labor dystocia

	Zhang's group (n = 3972)		WHO group (n = 3305)	
	Oxytocin (n = 1658)	No oxytocin (n = 2314)	Oxytocin (n = 1561)	No oxytocin (n = 1744)
Labor dystocia, n (%)	1351 (81.5)	531 (22.9)	1199 (76.8)	313 (17.9)
No labor dystocia, n (%)	307 (18.5)	1783 (77.1)	362 (23.2)	1431 (82.1)

A limitation of this study is that the included women were not admitted to the maternity ward with the same cervical dilatation and, therefore, did not contribute equally to the measurements of the active phase of labor. The women who were admitted early in labor might be different from those who were admitted later in labor. The intervention during labor could have therefore been influenced by the different cervical dilatations on admission.

Furthermore, the definitions of labor dystocia according to current guidelines were based merely on the time of cervical dilatation; not on descent of the fetal head or contractions. This limitation is a known research challenge in the definition of normal labor progression.[30]

Furthermore, the WHO has identified a knowledge gap regarding which design, if any, is preferable for a partograph.[23] Our cluster randomized trial is an important contribution to clinicians and decision-makers when deciding which guidelines are preferable to guide clinical practice with regard to oxytocin augmentation and to reduce unnecessary interventions. The results are also an important step toward possibly forming a new guideline. Evidence from trials comparing different guidelines and partographs for labor progression show a small difference in cesarean section rates,[15,25] but different labor progression guidelines have been suggested to also have an impact on other interventions during labor.[15] Compared with numbers from the participating hospitals from the year before the LaPS study, we observed an overall reduction in oxytocin augmentation in both the Zhang and WHO groups by 14% and 8%, respectively (see Supplementary material, Table S2). However, we did not observe a significant difference in the overall proportion of oxytocin augmentation between the two study groups. The reduction can therefore not be explained by one of the guidelines alone.

However, total duration of oxytocin augmentation was longer for the women adhering to Zhang's guideline than for those adhering to the WHO partograph. Oxytocin augmentation lasted almost 20 minutes longer in the Zhang group, still without the need for higher doses if adhering to Zhang's guideline. The WHO group reported higher maximum doses of oxytocin during augmentation compared with the Zhang group, but no statistically significant difference. The clinical impact is unknown, but our findings are in accordance with previous research that has identified a high rate of oxytocin augmentation without an improvement in birth outcome for the mother or the baby.[6-8] In a few cases, the oxytocin augmentations were discontinued due to the establishment of the woman's own uterine contractions. This is not in accordance with a meta-analysis that suggests discontinuation of oxytocin augmentation when the woman is in the active phase of labor.[31] No difference in the proportion of labor dystocia according to the guidelines was observed in the two study groups. It should be mentioned that the definitions of labor dystocia were different, and that direct comparisons are therefore inappropriate. At the same time, it is remarkable that 21% of the women in TGSC group 1 received augmentation with oxytocin without having labor dystocia diagnosed, and there were more women in the WHO group (23%) who were augmented than those in the Zhang group (19%) without being diagnosed with labor dystocia. The trial has a pragmatic approach and our results represent real-world practice. It is well known that oxytocin for augmentation is not only given on indication when labor dystocia is diagnosed, but unfortunately also in cases without labor dystocia. The duration of the active phase was longer for women adhering to Zhang's guideline, and this might be explained by the fact that Zhang's guideline allows a longer time before dystocia is diagnosed, especially before 6-cm dilatation. This result is in accordance with a previous study.[32] The investigators assumed that women allocated to Zhang's guideline may labor longer because the introduction of an intervention would be delayed compared with the case for the women adhering to the WHO partograph.

5 | CONCLUSION

We observed no significant difference in the proportion of oxytocin augmentation between the two study groups. However, there were differences in the use of oxytocin during labor between the two study groups. Women in the Zhang group were less likely to be augmented with oxytocin before 6 cm of cervical dilatation compared with the WHO group. The length of oxytocin augmentation was longer for women in the Zhang group. In addition, more women in the WHO group were augmented with oxytocin without an indication of labor dystocia. The results of this multicenter cluster randomized controlled trial make an important contribution to guiding clinical practice.

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CONFLICT OF INTERESTS

None.

ORCID

Rebecka Dalbye https://orcid.org/0000-0002-0522-0526
Torbjørn Moe Eggebø https://orcid.org/0000-0002-3162-9595
Pål Øian https://orcid.org/0000-0002-7391-5311

REFERENCES

1. American College of O, Gynecology Committee on Practice B-O. ACOG Practice Bulletin Number 49, December 2003: Dystocia and augmentation of labor. *Obstet Gynecol*. 2003;102(6):1445-1454.
2. World Health Organization. *WHO Recommendations for Augmentation of Labour*. Geneva, Switzerland: World Health Organization; 2014.
3. Caughey AB, Cahill AG, Guise JM, Rouse DJ. Safe prevention of the primary cesarean delivery. *Am J Obstet Gynecol*. 2014;210(3):179-193.

4. Rhoades JS, Cahill AG. Defining and managing normal and abnormal first stage of labor. *Obstet Gynecol Clin North Am*. 2017;44(4):535-545.
5. NICE guidelines. Intrapartum care: NICE National Institute for Health and Clinical Excellence 2014 www.nice.org.uk/guidance/cg190. Accessed January 15, 2018.
6. Bugg GJ, Siddiqui F, Thornton JG. Oxytocin versus no treatment or delayed treatment for slow progress in the first stage of spontaneous labour. *Cochrane Database Syst Rev*. 2013;6:Cd007123.
7. Bernitz S, Oian P, Rolland R, Sandvik L, Blix E. Oxytocin and dystocia as risk factors for adverse birth outcomes: a cohort of low-risk nulliparous women. *Midwifery*. 2014;30(3):364-370.
8. Oscarsson ME, Amer-Wahlin I, Rydhstroem H, Kallen K. Outcome in obstetric care related to oxytocin use. A population-based study. *Acta Obstet Gynecol Scand*. 2006;85(9):1094-1098.
9. Simpson KR, James DC. Effects of oxytocin-induced uterine hyperstimulation during labor on fetal oxygen status and fetal heart rate patterns. *Am J Obstet Gynecol*. 2008;199(1):34 e1-5.
10. Clark SL, Simpson KR, Knox GE, Garite TJ. Oxytocin: new perspectives on an old drug. *Am J Obstet Gynecol*. 2009;200(1):35 e1-6.
11. Osterman MMJ. *Changes in cesarean delivery rates by gestational age: United States, 1996–2011*. Hyattsville, MD: National Center for Health Statistics; 2013.
12. NHS. Hospital Episode Statistics NHS Maternity Statistics England, 2013-14. NHS.
13. Norwegian Birth Registry of Norway: Norwegian Institute of Public Health; 2018 https://www.fhi.no/en/hn/health-registries/medical-birth-registry-of-norway/. Accessed August 15, 2018.
14. Rossen J, Ostborg TB, Lindtjorn E, Schulz J, Eggebo TM. Judicious use of oxytocin augmentation for the management of prolonged labor. *Acta Obstet Gynecol Scand*. 2016;95(3):355-361.
15. Lavender T, Cuthbert A, Smyth RM. Effect of partograph use on outcomes for women in spontaneous labour at term and their babies. *Cochrane Database Syst Rev*. 2018;8:CD005461.
16. Friedman E. The graphic analysis of labor. *Am J Obstet Gynecol*. 1954;68(6):1568-1575.
17. Philpott RH, Castle WM. Cervicographs in the management of labour in primigravidae. II. The action line and treatment of abnormal labour. *J Obstet Gynaecol Br Commonw*. 1972;79(7):599-602.
18. World Health Organization. World Health Organization partograph in management of labour. World Health Organization Maternal Health and Safe Motherhood Programme. *Lancet*. 1994;343(8910):1399-1404.
19. Neal JL, Lowe NK, Patrick TE, Cabbage LA, Corwin EJ. What is the slowest-yet-normal cervical dilation rate among nulliparous women with spontaneous labor onset? *J Obstet Gynecol Neonatal Nurs*. 2010;39(4):361-369.
20. Zhang J, Troendle JF, Yancey MK. Reassessing the labor curve in nulliparous women. *Am J Obstet Gynecol*. 2002;187(4):824-828.
21. Zhang J, Landy HJ, Branch DW, et al. Contemporary patterns of spontaneous labor with normal neonatal outcomes. *Obstet Gynecol*. 2010;116(6):1281-1287.
22. Laughon SK, Branch DW, Beaver J, Zhang J. Changes in labor patterns over 50 years. *Am J Obstet Gynecol*. 2012;206(5):419 e1-9.
23. World Health Organization. WHO recommendations: Intrapartum care for a positive childbirth experience 2018 http://apps.who.int/iris/bitstream/handle/10665/260178/9789241550215-eng.pdf;jsessionxml:id=F1F5397399F448885328491174AC61C6?sequence=1. Accessed December 15, 2018.
24. Bernitz S, Dalbye R, Oian P, Zhang J, Eggebo TM, Blix E. Study protocol: the Labor Progression Study, LAPS—does the use of a dynamic progression guideline in labor reduce the rate of intrapartum cesarean sections in nulliparous women? A multicenter, cluster randomized trial in Norway. *BMC Pregnancy Childbirth*. 2017;17(1):370.
25. Bernitz S, Dalbye R, Zhang J, et al. The frequency of intrapartum caesarean section use with the WHO partograph versus Zhang's guideline in the Labour Progression Study (LaPS): a multicentre, cluster-randomised controlled trial. *Lancet*. 2019;393(10169):340-348.
26. Robson M, Murphy M, Byrne F. Quality assurance: The 10-Group Classification System (Robson classification), induction of labor, and cesarean delivery. *Int J Gynaecol Obstet*. 2015;131(Suppl 1):S23-S27.
27. Norwegian Medical Association. Augmentation of labor: Norwegian Society in Obstetrics and Gynecology; 2014 [Chapter 34]. http://www.nfog.org/files/guidelines/34%20NGF%20Obst%20Augmentation%20of%20labour%20Eggeb%C3%B8.pdf. Accessed March 15, 2014.
28. Reeve R. Confidence interval of difference of proportions in logistic regression in presence of covariates. *Stat Methods Med Res*. 2018;27(2):451-465.
29. Cohen WR, Friedman EA. Perils of the new labor management guidelines. *Am J Obstet Gynecol*. 2015;212(4):420-427.
30. Vahratian A, Troendle JF, Siega-Riz AM, Zhang J. Methodological challenges in studying labour progression in contemporary practice. *Paediatr Perinat Epidemiol*. 2006;20(1):72-78.
31. Vlachos DE, Pergialiotis V, Papantoniou N, Trompoukis S, Vlachos GD. Oxytocin discontinuation after the active phase of labor is established. *J Matern Fetal Neonatal Med*. 2015;28(12):1421-1427.
32. Lee NJ, Neal J, Lowe NK, Kildea SV. Comparing different partograph designs for use in standard labor care: a pilot randomized trial. *Matern Child Health J*. 2018;22(3):355-363.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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The Labor Progression Study - LaPS

SIGNATURE PAGE

PRINCIPAL/COORDINATING INVESTIGATOR:

Stine Bernitz, Midwife, PhD

Department of Obstetric and Gynecology

Østfold Hospital Trust, po box 300, 1714 Grålum,
Norway

Signature

24th October 2018

Date

TRIAL STATISTICIAN FOR LaPS:

Inge Christoffer Olsen Statistician PhD

Oslo Centre for Biostatistics & Epidemiology

Sogn Arena 3.etg Pb 4950 Nydalen 0424 Oslo

Norway

Signature

24 oct 2018

Date

Study Coinvestigator

Rebecka Dalbye, Midwife MSc

Department of Obstetric and Gynecology

Østfold Hospital Trust, po box 300, 1714 Grålum,
Norway

Signature

24th October 2018

Date

ABBREVIATIONS

AE	Adverse Event
BD	Base Deficit
BMI	Body Mass Index
BPM	Beats Per Minute
CEQ	Childbirth Experiences Questionnaire
CI	Confidence Interval
CRF	Case Report Form
CTG	Cardiotocography
ECD	Emergency Cesarean Delivery
EDC	Electronic Data Capture
EDA	Epidural analgesia
MedDRA	Medical Dictionary for Regulatory Activities
NICU	Neonatal Intensive Care Unit
P0	Nulliparous women
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
STAN	ST Analyses
TGCS	Ten Group Classification System
TNS	Transcutaneous Nervous Stimulation
WHO	World Health Organization

TABLE OF CONENTS

AMENDMENTS TO THE SAP

This is the first version of the SAP for the use of oxytocin in the LaPS.

1 STUDY OBJECTIVES of the analysis of endpoints related to the use of oxytocin in LaPS.

The present statistical analysis plan (SAP) describes the analyses of secondary endpoints and exploratory analyses related to the use of oxytocin in active labour in the LaPS study.

1.1 Primary Objective of the analysis

To assess the impact of adhering to the guideline for labour progression presented by Zhang(1)on the rate of oxytocin augmentation during active labour among nulliparous women compared to adhering to the WHO-partograph(2) based on Friedman's curve(3).

1.2 Secondary Objectives of the analysis

To assess the impact of adhering to the guideline for labour progression presented by Zhang (1) 2010) on other aspects related to the use of synthetic oxytocin in nulliparous women and their neonates, compared to adhering to the WHO-partograph(2).

2 OVERALL STUDY DESIGN

This is a cluster randomized, multi center, strategy trial.

3 GENERAL STATISTICAL CONSIDERATIONS

All analyses described in the protocol and the original SAP, published as supplementary material to the article accepted for publication in The Lancet (accept 16.08.2018) were considered *a priori* analyses. The present SAP describes and elaborates the analyses of the use of synthetic oxytocin, defined as secondary endpoints in the LaPS study, and exploratory analyses related to these. All analyses that are described in the present document, but that were not described in the main trial analysis plan will be regarded as post-hoc analyses.

All categorical (binary and ordinal) data will be summarized using frequency counts and percentages of patient characteristics. Percentages will be calculated using the study population (defined as "full analysis set" in section 8); any exceptions to this will be highlighted in the table footnote. The continuous variables will be summarized using number of patients (N), and range (minimum and maximum) in combination with mean and, standard deviation (SD), if data are normally distributed, and median, lower and upper quartiles if data are skewedly distributed. In general, minimum and maximum will be presented to the same degree of precision as data is recorded, with mean, median and quartiles having 1 additional place after the decimal, and standard deviation having 1 or 2 additional places after the decimal, depending on the size of the mean. Percentages less than 100 will be displayed to 1 place after the decimal, where space permits.

Baseline characteristics are given without *p*-values.

p-values larger than 0.01 will be reported to two decimal places, those between 0.01 and 0.001 to three decimal places. *p*-values below 0.001 will be displayed as "<0.001".

Data will be presented, unless otherwise indicated, according to the two guideline strategy groups.

In general, analyses presented in the tables, listings, and figures will be confined to participants included in the full analysis set (defined in section 8).

4 HYPOTHESES AND DECISION RULES

4.1 Statistical Hypotheses

This analysis plan describes the analyses of aspects related to the use of oxytocin in the LaPS trial, defined as secondary outcome in the LaPS.

Among these, the primary question of interest in the present SAP is if the rate of oxytocin augmentation during active labour in nulliparous women adhering to the guideline for labour progression presented by Zhang(1) differ from the rate of oxytocin augmentation in nulliparous women adhering to the WHO-partograph(2) based on Friedman's curve(3). The main focus of the analyses will be on the differences between the two groups, i.e. the effect sizes with corresponding 95% confidence intervals.

This SAP also describes the analyses of other secondary endpoints. There will be no confirmatory statistical hypotheses testing as part of these analyses. All group comparisons including p-values from hypotheses tests of null hypotheses for other secondary or exploratory outcomes (that the outcomes among nulliparous women adhering to the guideline for labour progression presented by Zhang will not differ from outcomes among those adhering to the WHO-partograph based on Friedman's curve will therefore be interpreted as hypothesis supporting and not confirmatory. The main focus of these analyses will also be on the differences between the two groups, i.e. the effect sizes with corresponding 95% confidence intervals.

4.2 Statistical Decision Rule

Group comparisons resulting in a p-value below 0.05 will be denoted as a statistical significant difference, but no claim of superiority either way will be made based on such findings.

5 DEFINITIONS AND DERIVED VARIABLES

5.1 Change from baseline

Not applicable

5.2 Other calculations

Age (years) = [(date of baseline – date of birth)/365.25].

BMI = weight in kilograms / (height in metres) x (height in metres)

BMI will be categorized according to the WHO definitions for underweight, normal, overweight and obese.

Different delivery phase/stage is defined as follows (see figure 1)

- Latent phase of first stage is defined as the time of the onset of labor (patient reported) until the cervix is dilated to 4 cm.
- Active phase of first stage of labor is defined as regular painful uterine contractions and cervical dilatation from 4 centimeters until the cervix is fully dilated, 10 cm, or until ECD.
- Descending phase of second stage is defined as the period from full dilatation of cervix until the expulsion phase starts, or until ECD.
- The expulsion phase of the second stage is defined as the period from expulsion starts until the baby is completely out of the birth canal, or until ECD.
- Total length of active labor is described as the period from the partograph registration (minimum 4 cm) until the baby is born (vaginally or by ECD).
- Length of active phase of first stage of labor, length of second stage, descending phase and expulsion phase will also be described.

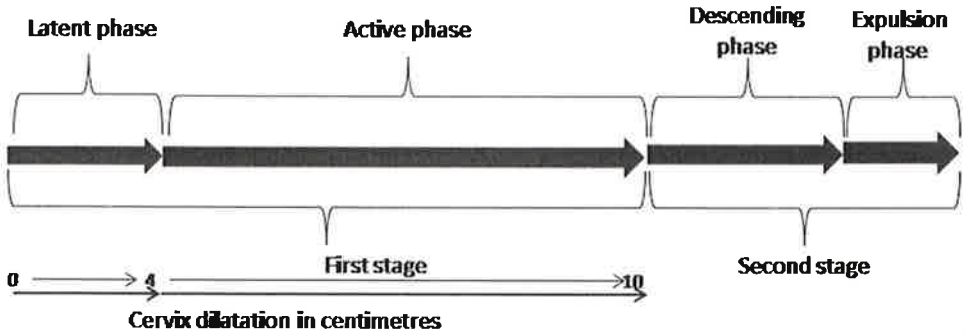

Fig 1

Computing of time variables for the different delivery phase/stage

The length of active phase of first stage of labor was recoded based on the cervix dilatation data in the CRF. In the CRF, dilatation data could be entered for every half hour from the start of the partograph registration. If no examination of the cervix dilatation was done, the corresponding data point in the CRF was not entered. The active phase of first stage was computed as time from 4cm cervix dilatation or first partograph registration to last partograph registration.

Descending and expulsion phase of second stage are directly registered in the CRF. The total length of second stage is computed as the sum of these. Total length of active labor is computed as the sum of the length of active phase of first stage, and the total length of second stage.

Labor dystocia is defined as follows:

Labor dystocia according to Zhang's guideline is diagnosed if the cervix dilatation rate according to the 95 % percentile, does not meet the expected progression from centimeter to the next centimeter. During second stage of labor, dystocia is diagnosed, if the time from full dilatation to active expulsion phase (passive second stage) exceeds 1 hour and 45 minutes (2 hours and 30

minutes for women with epidurals), or if the expulsion phase (active second stage) exceeds 60 minutes (see figure 2).

Dilation of the cervix	95 percentile * (dystocia)
From 4 to 5 cm	6 h / 30 min
From 5 to 6 cm	3 h / 15 min
From 6 to 7 cm	2 h / 15 min
From 7 to 8 cm	1 h / 30 min
From 8 to 9 cm	1 h / 30 min
From 9 to 10 cm	1 h / 45 min
2. stage without EDA Expulsion phase max 60 min.	2 h / 45 min
2. stage with EDA Expulsion phase max 60 min.	3 h / 30 min
Total time without EDA	19 h / 30 min
Total time with EDA	20 h / 15 min

Fig 2

Labor dystocia according to the WHO partograph/standard care guideline is diagnosed if cervix dilatation rate is slower than one centimeter per hour, assessed after four hours i.e. if the four-hours action line is crossed. During second stage of labor, dystocia is diagnosed if the time from full dilatation to active expulsion phase exceeds 1 hour (2 hours for women with epidurals), or if the expulsion phase (active second stage) exceeds 60 minutes (see figure 3).

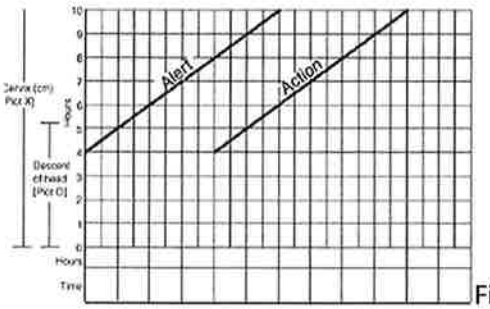

Fig 3

Apgar score is defined as follows

The Apgar score is a method to quickly summarize the health of newborn children. The Apgar scale is determined by evaluating the newborn baby on five simple criteria on a scale from zero to two, then summing up the five values thus obtained. The resulting Apgar score ranges from zero to 10. The five criteria are summarized using words chosen to form an acronym (Appearance, Pulse, Grimace, Activity, Respiration). We recorded Apgar score 1, 5 and 10 minutes after delivery.

Metabolic acidosis is defined as follows:

Umbilical cord (artery) pH <7.0 + base excess (BE) ≤ -12 mmol/l in the umbilical artery (dichotomous)

6 EFFICACY AND SAFETY ENDPOINTS / VARIABLES

6.1 Endpoints

The secondary endpoints as defined in the original LaPS protocol and presented in the SAP for the main publication, accepted 16.8 2018 in The Lancet are as follows:

- **Detailed information on Oxytocin augmentation throughout labour**
    - The proportion of synthetic oxytocin augmentation in active labour.
    - Cervical dilatation at onset of augmentation
    - Maximum dose presented in ml/hour or mU/hour (continuous)
    - Total duration of Oxytocin augmentation presented in hours and/or minutes (continuous)
    - Startdose presented in ml/hour or mU/hour (continuous)

The primary endpoint of the present analysis is the proportion of synthetic oxytocin augmentation in active labour. This is a dichotomous endpoint.

6.1.1 Secondary and exploratory endpoints

The other secondary endpoints in the LaPS trial, as described in the original SAP, will be considered as exploratory analyses.

- **Detailed information on labor dystocia**
    - Rate of labor dystocia according to the allocated guideline
    - Cervical dilatation when dystocia is diagnosed.

Other endpoints from the original SAP

In the LaPS article published in Lancet, the primary and several secondary endpoints were presented in Table 2 and Table 3, respectively. In the present analysis, these data, and some of the secondary endpoints not presented in the Lancet publication, are treated as descriptive, e.g. as "Delivery characteristics". This applies to:

- **Spontaneous vaginal delivery rate**
- **Operative vaginal delivery rate defined as vacuum and/or forceps delivery**
- **Intra partum caesarean section rate**
- **Time related aspects of labor progress including:**
    - active phase of first stage
    - descending phase of second stage
    - expulsion phase of second stage
    - total length of second stage
    - total length of active labor
- **Detailed information on amniotomy**

- The proportion of amniotomy
- Indications (dystocia, fetal distress and other reason), only one possible option
- Cervical dilatation at amniotomy

- **The proportion of epidural analgesia**
- **Cervical dilatation at onset of EDA**
- **The proportion of episiotomies**
- **The proportion of OASIS**
- **The proportion of blood transfusions**
- **The proportion of post partum haemorrhage ≥ 1000 ml**
- **Detailed information on pH and BE in the umbilical cord**
  - The proportion of neonates with metabolic acidosis after birth
- **Detailed information on transfer neonates to Neonatal Intensive Care Unit after birth**
  - The proportion of transfer to the Neonatal Intensive Care Unit after birth
  - Indications for transfer (four different indications: asphyxia, suspect infections, respiratory problems or other reasons). One possible option.
  - Length of stay, defined as more or less than 24 h.
- **Detailed information on perinatal tear as defined above.**
- **Detailed information on non invasive actions for stimulating of contractions describes as:**
  - none
  - change positions
  - emptied bladder
  - given food
  - given liquid to drink
- **Detailed information on admission to the labor ward, including**
  - indication of admission
  - time from rupture of the membranes until admission
  - cervical dilatation when rupture of the membranes
  - characteristics of the amniotic fluid
  - rate of contractions before and upon admission
  - time of contractions until admission
  - cervical dilatation upon admission
  - fetal heart rate
  - if CTG was used
  - classification of the CTG

6.2 Safety Parameters

Not applicable

7 DETERMINATION OF SAMPLE SIZE

Sample size calculation is based to calculate the power for the overall primary endpoint for the LaPS described and presented in the protocol, the original SAP and in the main publication (ref). The determination of the sample size (number of clusters and individuals) is based on a power calculation with the least occurring outcome; intrapartum cesarean delivery, which was 9.2% (at time of sample size calculation) in the study population (p1). Further, we expect that the intrapartum cesarean delivery rate will be 6.7% (p2) which is a 25% reduction, when using the new guideline. Formula (4) on page 320 in the article by Hayes et al. is used to calculate the needed number of clusters and participants (4). According to this formula, with a chosen significance level of 0.05, a power of 80% and p1 = 9.2% and p2 = 6.9%, we should include at least 14 clusters and 6582 individuals. The design allows flexibility, so that larger birth care units may contribute with more study subjects than smaller units.

8 DATA SETS TO BE ANALYSED

There will be six analysis sets in this study.

- The **Eligible Analysis Set (EAS)** will include all eligible women within the inclusion period at each site
- The **Full Analysis Set (FAS)** will include all eligible women with signed informed consent.
- The **Vaginal Delivery Set (VDS)** will include all eligible women with signed informed consent delivering vaginally.
- The **Cesarean Delivery Set (CDS)** will include all eligible women with signed informed consent with emergency cesarean delivery.
- The **Oxytocin Analysis Set (OAS)** will include all eligible women with signed informed consent with oxytocin augmentation during the active phase of labour.
- The **Labour Dystocia Analysis Set (LaDAS)** will include all eligible women with LD according to allocated guideline.

9 PRESPECIFICATION OF ANALYSES

Although the allocation to each strategy has been revealed during the main article analyses, an effort will be made to keep decisions made in this document as unbiased as possible. This will be done by not performing any group comparison analyses prior to the finalization of this document, thus avoiding result-driven analyses.

10 STATISTICAL METHODOLOGY

The primary efficacy analyses will be based on the Full Analysis Set (FAS) only. Secondary efficacy analyses will be based on the Full Analysis Set (FAS), Oxytocin Analysis Set (OAS), The Labour Dystocia Analysis Set (LaDAS), Descending Analysis Set (DAS) and the Expulsion Analysis Set (ExAS).

When random numbers are warranted for inference (such as for bootstrapping and multiple imputation), the seed will be set to the date the statistical analysis plan is signed-off (in the format yyyymmdd).

All efficacy analyses will be presented by the size (point estimate) of the difference between the treatments and the associated 95% confidence interval, and p-values of the corresponding statistical hypothesis test as supporting information.

All statistical analyses will be done in Stata v15 (StataCorp. 2015. Stata Statistical Software: Release 15.1. College Station, TX, USA).

10.1 Adjustment for covariates

We will use the following covariates in all primary and secondary statistical models analyses:

10.1.1 Maternal and neonatal characteristics

Maternal age
Maternal BMI
Civil status (single vs cohabitant/married)
Level of education (university/college education)
Cervical dilatation at first registration (time to event endpoints only)
Birth weight
Baby's head circumference

10.1.2 Hospital levels

Stratification variables

Annual emergency Cesarean delivery rate in Ten Group Classification System (TGCS) group 1 women in 2012
Annual number of deliveries in TGCS group 1 women in 2012

10.2 Center effect

As this is a cluster-randomized study with center as cluster, center will be included in the statistical models to adjust for within-cluster dependencies.

10.3 Multiplicity adjustments

There will be no adjustments for multiplicity in these sub-analyses. There will be no confirmatoty hypothesis testing, and therefore there will be no need for formal adjustments for multiplicity.

10.4 Demographic and other baseline characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group for women in the FAS and in the EAS.

In addition, demographic and baseline data will be displayed separately for each of the study centres.

10.5 Efficacy analysis

The primary endpoint (the proportion of synthetic oxytocin augmentation in active labor) will be analysed as described in the primary statistical analysis plan.

Secondary efficacy measures in this study consist of dichotomous as well as time to event and continuous outcome variables. Dichotomous variables will be analysed as the primary variable, presented in the original SAP.

Time to event variables will be analysed using Weibull regression with cluster as random intercept and treatment strategy as fixed effect, adjusted with covariates as given in section 10.1 in addition to first registration of cervical dilatation in cm. Unadjusted Kaplan-Meier plots will be presented.

Continuous outcome variables will be analysed using mixed effects generalized linear gamma models with logarithmic link.

10.6 Missing data imputation and sensitivity analyses

Missing data assessments are based on a blinded review of the data prior to the primary publication.

All included women have been assessed for oxytocin use, and there are no missing data for the dichotomous Oxytocin endpoint.

There are no missing data in any of the covariates as described in section 10.1, except for BMI where 0.3% of the observations are missing and cohabitant with 0.8% missing values. Given the low missing data rate, we have decided to use a stochastic linear regression single imputation(5) for BMI and to use cohabitant status not known as one of the categories in addition to cohabitant/married and single.

There will be no sensitivity analyses in this supportive report.

10.7 Patient Characteristics

10.7.1 Patient Disposition

The disposition of all patients will be listed and summarised by treatment arm.

10.7.2 Background and Demographic Characteristics

Patient demographics and baseline characteristics for the FAS is summarized in the primary publication. Demographics and baseline characteristics for women with oxytocin augmentation will be summarised.

Patient demographics and baseline characteristics will be summarized by randomized treatment arm and overall using descriptive statistics as described in detail in section 3.

The maternal demographics and baseline characteristics include age at date of delivery, co-habitual status, education, smoking habits, body mass index (BMI) and cervical dilatation at first registration.

The neonatal characteristics include gestational age, birth weight, head circumference and gender.

10.7.3 Site characteristics

Site characteristics are summarized in the primary publication for all sites by treatment strategy. Characteristics to be summarized include yearly emergency Cesarean delivery rate and number of deliveries in TGCS group 1 women in 2012 and in 2013.

10.7.4 Treatment Compliance

To secure a thorough implementation of the trial, the management at all participating birth care units read and approved the trial protocol and signed a cooperation agreement committing to adhere to the protocol. All birth care units underwent a strict teaching program including information and allocated guideline instructions, securing that all birth attendants had profound knowledge about the guidelines. Throughout the whole trial period and on a regular basis, researchers from the LaPS group revisited the units to ensure that all units adhered to the allocated guideline. Written information about the trial and the guidelines was printed on posters and made visible and available for midwives and obstetricians at all times. No exceptional measurements of treatment compliance were performed.

10.7.5 Concomitant Medications and Other Therapies

Not applicable

10.7.6 Concomitant treatment

The only concomitant treatment registered in this trial is the use of oxytocin.

11 Safety Analysis

11.1 Adverse events

There will be no additional analyses of adverse events than those described as efficacy endpoints in the primary publication (episiotomies, OASIS, blood transfusions).

12 Interim analysis

No interim analysis was planned during the trial.

13 Data monitoring

There was no formal Data Monitoring Committee for this trial.

14 Table of Contents of Tables, Listings and Figures

14.1 List of Tables

14.2 List of Listings

14.3 List of Figures

15 References

1. Zhang J, Landy HJ, Branch DW, Burkman R, Haberman S, Gregory KD, et al. Contemporary patterns of spontaneous labor with normal neonatal outcomes. Obstetrics and gynecology. 2010;116(6):1281-7.
2. World Health Organization partograph in management of labour. World Health Organization Maternal Health and Safe Motherhood Programme. Lancet. 1994;343(8910):1399-404.
3. Friedman E. The graphic analysis of labor. American journal of obstetrics and gynecology. 1954;68(6):1568-75.
4. Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. International journal of epidemiology. 1999;28(2):319-26.
5. Buuren S. Flexible Imputation of Missing Data: Chapman and Hall/CRC. ; 2012 [Available from: http://doi.org/10.1201/b11826.

Paper III

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The Labour Progression Study (LaPS): Duration of labour following Zhang's guideline and the WHO partograph – A cluster randomised trial

Rebecka Dalbye[a,b,*], Ellen Blix[b], Kathrine Frey Frøslie[c], Jun Zhang[d], Torbjørn Moe Eggebø[e,f], Inge Christoffer Olsen[g], Daniella Rozsa[f], Pål Øian[h,i], Stine Bernitz[a,b]

[a] Department of Obstetrics and Gynaecology, Østfold Hospital Trust, Grålum, Norway
[b] Department of Nursing and Health Promotion, Faculty of Health Sciences, OsloMet – Oslo Metropolitan University, Oslo, Norway
[c] Norwegian National Advisory Unit on Women's Health, Oslo University Hospital, Oslo, Norway
[d] Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
[e] National Centre for Fetal Medicine, Trondheim University Hospital (St Olavs Hospital), Trondheim, Norway
[f] Department of Obstetrics and Gynaecology, Stavanger University Hospital, Stavanger, Norway
[g] Research Support Services, Clinical Trial Unit, Oslo University Hospital, Oslo, Norway
[h] Department of Obstetrics and Gynaecology, University Hospital of North Norway, Norway
[i] Department of Clinical Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

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ABSTRACT

Objective: To investigate labour duration in different phases of labour when adhering to Zhang's guideline for labour progression compared with the WHO partograph.

Design: A secondary analysis of a cluster randomised controlled trial.

Setting: Fourteen Norwegian birth care units, each with more than 500 deliveries per year constituted the clusters.

Participants: A total of 7277 nulliparous women with singleton foetus in a cephalic presentation and spontaneous onset of labour at term were included.

Intervention: Seven clusters were randomised to the intervention group that adhered to Zhang's guideline (n = 3972) and seven to the control group that adhered to the WHO partograph (n = 3305) for labour progression.

Measurements: The duration of labour from the first registration of cervical dilatation (≥ 4 cm) to the delivery of the baby and the duration of the first and second stages of labour; the time-to-event analysis was used to compare the duration of labour between the two groups after adjusting for baseline covariates.

Findings: The adjusted median duration of labour was 7.0 h in the Zhang group, compared with 6.2 h in the WHO group; the median difference was 0.84 h with 95% confidence interval [CI] (0.2–1.5). The adjusted median duration of the first stage was 5.6 h in the Zhang group compared with 4.9 h in the WHO group; the median difference was 0.66 h with 95% CI (0.1–1.2). The corresponding adjusted median duration of the second stage was 88 and 77 min; the median difference was 0.18 h with 95% CI (0.1–0.3).

Key Conclusions: : The women who adhered to Zhang's guideline had longer overall duration and duration of the first and second stages of labour than women who adhered to the WHO partograph.

Implications for practice: : Understanding the variations in the duration of labour is of great importance, and the results offer useful insights into the different labour progression guidelines, which can inform clinical practice.

* Corresponding author at: Department of Obstetrics and Gynaecology, Østfold Hospital Trust, PO box 300, 1714 Grålum, Norway.
E-mail address: rebecka.dalbye@so-hf.no (R. Dalbye).

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Introduction

Traditionally, the progress of labour is measured by cervical dilatation; however, the expected progression varies between countries and according to guidelines. There is no standardised definition of labour duration and the onset of labour, nor is there a consensus as to which guideline is best suited for clinical use (Abalos et al., 2018; Caughey, 2015; Hanley et al., 2016; Souza et al., 2018; Vahratian et al., 2006).

The first stage of labour is often divided into two phases; latent and active. The active phase is conventionally defined as the interval when the cervix is effaced and dilated from four centimetres to full dilatation. Similarly, the second stage is divided into the latent and active phases. In the latent (descending) phase, the baby's head is descending towards the pelvic floor and, in the active (expulsion) phase, the mother is actively pushing the baby out (NICE guidelines, 2014; World Health Organization, 2000).

The clinical expectations of cervical dilatation amongst nulliparous women have been influenced by the work of Friedman from the mid-1950s (Friedman, 1954). Accordingly, Philpott and Castle (1972a, 1972b) developed guidelines for assessing labour progression, which became part of the partograph prompted by the World Health Organization (WHO) since 1994 (World Health Organization, 1994). However, with an increased use of obstetric interventions during labour, increasing maternal body mass index (BMI) and childbearing age, questions were raised whether the progress of active labour, according to the WHO partograph, was still relevant to women today (Souza et al., 2018; Zhang et al., 2010b, 2002). In the early 2000, (Zhang et al., 2002) presented a labour curve with a hyperbolic shape based on data from 1329 low-risk women. The findings were confirmed in a large cohort with 27 170 nulliparous women in 2010 (Zhang et al., 2010a). They found that labour progresses more slowly than previously thought and that cervical dilatation accelerate as labour advances.

However, the applicability of stages, phases and time limits in labour is challenging, mainly because of variations in defining the onset of labour and transition of phases and stages (Abalos et al., 2018; Hanley et al., 2016). Thus, understanding the normal variations of duration of labour is of great importance and should be the basis for identifying the actual slow progress of labour, which requires interventions (Neal et al., 2010, 2015; Souza et al., 2018; Zhang et al., 2010b, 2002), mainly because the slow progress of labour (labour dystocia) is a common indication of interventions in labour. The purpose of this paper is to investigate labour duration from a cervical dilatation of 4 cm to delivery when adhering to Zhang's guideline for labour progression compared with the WHO partograph.

Methods

Design, participants and procedure

This is a secondary analysis of the Labour Progression Study (LaPS), a cluster randomised controlled trial undertaken in Norway, with the aim to evaluate the effects of two different guidelines for labour progression. The study protocol was published in 2017 (Bernitz et al., 2017), and detailed methodological considerations and results for the primary outcome have been published elsewhere (Bernitz et al., 2019). The trial was registered at www.clinicaltrial.org (NCT02221427) prior to the inclusion of clusters and participants.

Participating clusters and individuals

Intrapartum care in Norway takes place in governmental institutions and is free of charge. Midwives are present at all births and responsible for women with low-risk labours and assist with all spontaneous deliveries. Obstetricians are involved in care for high-risk women and called upon if medical assistance is needed during labour. Approximately 60 000 babies are born annually in 46 birth institutions, 24 of which have more than 500 deliveries per year. The birth care is organised at three different levels: Level 1 consists of obstetric units as well as neonatal intensive care unit in large hospitals, which have obstetricians, paediatricians and anaesthesiologists available 24 h a day. Level 2 consists of obstetric units within hospitals with obstetricians and anaesthesiologists on call, and Level 3 consists of midwife-led units, both alongside and free-standing. In case of complications or change in risk status at Level 3, the woman is transferred to a reference hospital of Level 1 or 2. This study was conducted at Levels 1 and 2 with more than 500 births annually. To create a representative selection of obstetric units in Norway, all geographic health regions were included. The management at the obstetric units were contacted by a LaPS study group member. Units with the ability to adhere to the protocol were considered eligible. To secure a thorough implementation of the trial, the management at all participating obstetric units signed a cooperation agreement committing to adhere to the protocol. Fourteen birth care units participated in the trial, of which seven were randomised to the intervention group and seven to the control group. The sites were randomly allocated to the two treatments using the randomization.com webpage (Dallal, 2008). The randomization was stratified by annual number of deliveries and proportion of intrapartum caesarean sections (ICS), provided from the national birth registry. Nulliparous women with a singleton term foetus with cephalic presentation and spontaneous onset of labour in gestational age of 37 weeks or more, denoted as Group 1 in the Ten Group Classification System (TGCS) (Robson et al., 2015), and who understood Norwegian were eligible for participation. The birth care units adhered to the allocated guideline for all TGCS Group 1 women. The eligible women who provided their informed consent were included in the analyses. The estimation of gestational age was based on a second trimester ultrasound scan.

Procedures

Prior to the onset of the trial, the staff at all sites received identical information about the LaPS study. This information was also printed on flyers and distributed at the information meetings. After randomisation, information according to the trial arms and how to use the allocated guidelines was distributed to the staff at new meetings. Written information about the trial and the guidelines was also printed on posters and made visible and available for midwives and obstetricians at all times. The women received written information regarding the study on flyers at the second trimester ultrasound scan or upon admission in the labour ward. During this time, the women were also asked by a midwife to sign an informed consent. No women consent after delivery and only eligible women who provided an informed consent were included in the analysis.

Each birth care unit provided a local coordinator who was responsible for the recruitment and inclusion of the participants and recording the required data. For the intervention group who adhered to Zhang's guideline for labour progression (Supplementary Material, SAP), labour dystocia was diagnosed if the cervical dilatation did not meet the expected progression from one centimetre to the next according to the 95th percentile. Labour dystocia in the second stage was diagnosed if the descending phase lasted longer than one hour and 45 min or two and a half hours for women with epidural analgesia (EDA), or if the expulsion phase lasted longer than 60 min. For the control group who adhered to WHO partograph for labour progression (Supplementary Material, SAP), labour dystocia was diagnosed if cervical dilatation was slower than 1 cm

per hour, assessed after four hours. Labour dystocia in the second stage was diagnosed if the descending phase lasted longer than one hour or two hours for women with EDA, or if the expulsion phase lasted longer than 60 min. If labour dystocia was diagnosed, the guideline according to augmentation with amniotomy and synthetic oxytocin infusion was followed as a common routine at all birth care units in Norway (Norwegian Medical Association, 2014). The women in the LaPS study were monitored from a cervical dilatation of 4 cm or more and regular contractions. During the whole study period, all the birth care units were closely followed up by a member of the LaPS research group to assist and motivate them. The clinical outcomes were registered in a web-based Case Report Form (web-CRF), designed by the Unit of Applied Clinical Research at the Norwegian University of Science and Technology to ensure consistent recording of information. The system is transparent, so that all corrections can be traced with dates and signatures. The local coordinators had access only to their own part of the CRF and were responsible for assuring that all data entered were de-identified, complete, and accurate.

Outcomes of the current study

The main outcome of this paper was the duration of labour, defined as the time from the first registration of a cervical dilatation of 4 cm or more to the delivery of the baby. Other outcomes included the duration of the first stage (from 4 to 10 cm of cervical dilatation) and the duration of the second stage (from 10 cm of cervical dilatation to delivery). In addition, the descriptive statistics on cervical dilatation from one integer centimetre to the next for the two study groups are presented.

Statistical analysis

The sample size calculation was based on ICS endpoint, described and presented elsewhere (Bernitz et al., 2019). A Statistical Analysis Plan (SAP) for this study was written and approved, pre-specifying all the analyses prior to group comparison analysis, with the purpose of avoiding result-driven analyses (Supplementary Material, SAP). Simple frequencies and proportions were used to describe the characteristics of the birth care units and the participating women.

The outcome duration of labour, duration of the first stage and the duration of the second stage were time-to-event variables and were analysed using a mixed Weibull regression model with cluster as a random intercept and treatment as fixed effect (Stedman et al., 2012). The analyses are presented in adjusted estimated group-specific marginal median times and adjusted study group differences. In addition, the accelerated delivery time factor is presented, used to quantify how slow or fast the birth time progress was for women in the Zhang group compared with the women in the WHO group. In the model, we adjusted for stratification variables (the annual ICS rates and number of deliveries) and for predefined covariates, considered to be potential risk factors for ICS on an individual level (maternal age, BMI, civil status and educational level as well as birth weight and neonatal head circumference), in addition we adjusted for the first registration of cervical dilatation. Kaplan-Meier curves were included for descriptive purposes (Supplementary Material, Figure S1-3). Both EDA and augmentation with synthetic oxytocin are difficult to investigate, because slow progress is a potential indication of these interventions. Neither augmentation with synthetic oxytocin nor EDA were included in the analyses, because they were started after the onset of labour and, therefore, were considered mediators rather than confounders (Hernan et al., 2002).

For the outcome duration of labour, delivery was defined as the event of interest. The duration of labour, from the first partograph registration ($\geq$ 4 cm) to delivery, either vaginally or by ICS, was registered for all the participating women; there were no unobserved event in this analysis, hence no censoring. The event of interest for the outcome duration of the first stage was cervical dilatation of 10 cm; thus, women with ICS in the first stage were right censored at the time of ICS. Delivery was the event for the outcome duration of the second stage, and women with ICS in the first stage of labour were left censored at the time of ICS. The missing covariate data were imputed using stochastic linear regression single imputation. The time intervals for cervical dilatation by centimetre are presented descriptively. The missing intermediate dilatation values were imputed using linear interpolation. The missing values due to ICS were not imputed. The women with less than two recordings of cervical dilatation were excluded (see further clarifications in the appended SAP). The time-to-event analyses were analysed in Stata v15 (StataCorp. 2015. Stata Statistical Software: Release 15.1. College Station, TX, USA). The duration of progression from one integer centimetre to the next was analysed in R, version 3.5.0.

Results

Fourteen birth care units throughout Norway took part in this study. Between December 1, 2014 and January 31, 2017, 7277 of 11 615 eligible women were included—3972 and 3305 women in the Zhang and WHO groups, respectively (Fig. 1). The baseline characteristics of the two study groups are described in Table 1. No data were missing for the covariates included in the analyses except for BMI (0.3%) and civil status (0.8%). The characteristics of the women who were not included are presented in the Supplementary Material (Table S1).

Duration of labour from 4 cm to delivery

The unadjusted median duration of labour was 6.6 h (Percentile [P] 5th, 95th: 1.4, 16.0) in the Zhang group and 6.1 h (P5th, 95th: 1.3, 13.8) in the WHO group (Table 2). After 3.6 and 10.5 h in active labour, respectively 75% and 25% of the women in the Zhang group had not delivered as compared with 3.4 and 9.5 h for the women in the WHO group. Figure S1 shows the unadjusted Kaplan-Meier plots for women adhering to Zhang's guideline and WHO partograph. The adjusted median duration was 7.0 h in the Zhang group and 6.2 h in the WHO group, with a corresponding adjusted median difference of 0.84 h (95% CI 0.2–1.5). The adjusted accelerated delivery time factor for duration of labour was 1.14 (95% CI 1.0–1.2) (Table 2). There were no missing data for this outcome.

Duration of first stage from 4 to 10 cm

The unadjusted median duration of the first stage was 5.0 h (P5th, 95th: 0.5, 15.0) in the Zhang group and 4.5 h (P5th, 95th: 0.5, 12.5) in the WHO group (Table 2). After 2.5 and 8.5 h in the first stage of labour, respectively 75% and 25% of the women in the Zhang group had not reached 10 cm of cervical dilatation as compared with 2.0 and 8.0 h for the women in the WHO group. Figure S2 shows the unadjusted Kaplan-Meier plots for women adhering to Zhang's guideline and WHO partograph. The adjusted median duration was 5.6 h in the Zhang group and 4.9 h in the WHO group, with a corresponding adjusted median difference of 0.66 h (95% CI 0.1–1.2). The adjusted accelerated delivery time factor for duration of the first stage was 1.13 (95% CI 1.0–1.3) (Table 2).

Duration of the second stage from 10 cm to delivery

The unadjusted median duration of the second stage was 76 min (P5th, 95th: 17, 242) in the Zhang group and 75 min

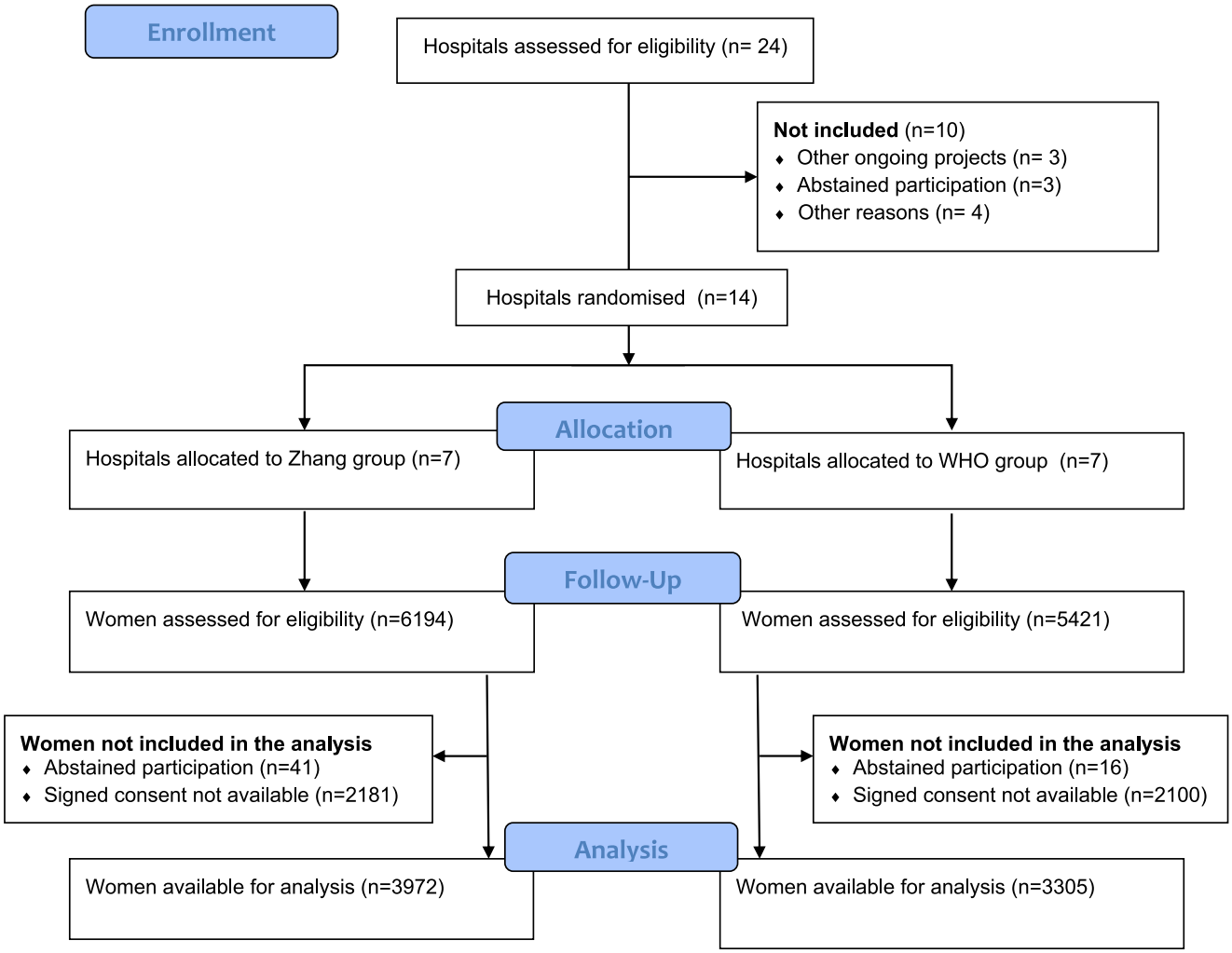

Fig. 1. Flowchart of hospitals and participants.

(P5th, 95th: 16, 204) in the WHO group (Table 2). After 40 and 142 min in the second stage, respectively 75% and 25% of the women in the Zhang group had not delivered as compared with 40 and 127 min for the women in the WHO group. Figure S3 shows the unadjusted Kaplan-Meier plots for women adhering to Zhang's guideline and WHO partograph. The adjusted median duration was 88 min in the Zhang group and 77 min in the WHO group, with a corresponding adjusted median difference of 0.18 h (95% CI, 0.1–0.3). The adjusted accelerated delivery time factor for the duration of the second stage was 1.14 (95% CI, 1.1–1.2) (Table 2).

Duration from one integer centimetre to the next

Table 3 shows the duration required to advance from one integer centimetre of cervical dilatation to the next among the TGCS Group 1 women in the two study groups. The observed median duration from one integer centimetre to the next differed between the two study groups; however, the differences were reduced as labour advanced and from 8 cm of cervical dilatation, the time intervals were equal for women who delivered vaginally.

Discussion

Main findings

Our study found that women who adhered to Zhang's guideline for labour progression had longer overall duration of labour, duration of first and second stages compared with women adhering to the WHO partograph. The differences were statistically significant, although no significant differences were found in maternal or neonatal clinical outcomes, published elsewhere (Bernitz et al., 2019). The results contribute to clarify the duration of different phases of labour when adhering to different guidelines both first and second stages, based on data from a contemporary clinical setting. In 2018, WHO announced a knowledge gap in labour progression (World Health Organization, 2018), and our randomised trial makes an important contribution to the challenge by presenting the duration of different phases of labour.

Strengths and limitations

This study was well planned and offered a thoroughly implemented trial with a sufficiently power. The included variables had few missing values and were tripled checked for errors. Despite the robust design, there are some possible limitations. Due to unavailable consent, 4338 women were not included in the study, which may be explained by periods of high workload in the birth care

Table 1
Characteristics of included hospitals (n = 14) and participants (n = 7277).

	Zhang group Participants (n = 3972)	WHO group Participants (n = 3305)
Hospital characteristics		
Deliveries per year		
<3000, 6 hospitals in each group, n (%)	2688 (36.9)	2233 (30.7)
≥3000, 1 hospital in each group, n (%)	1284 (17.6)	1072 (14.7)
Characteristics related to the mother		
Maternal age in year at delivery, mean (SD)	28.4 (4.6)	28.5 (4.5)
Civil status (cohabitant or married), n (%)	3741/3946** (94.8)	3137/3271** (95.9)
Higher education >12 years, n (%)	2412 (60.7)	2017 (61.0)
Smoking during first trimester, n (%)	230/3963** (5.8)	210/3247** (6.5)
Pre-pregnant body mass index†, mean (SD)	23.6/3966** (4.3)	23.8/3287** (4.3)
Gestational age at onset of active labour (days), mean (SD)	281 (7.0)	281 (8.0)
Characteristics related to labour		
Cervical dilatation at first registration, n (%)		
4 cm	1954 (49.2)	1642 (49.7)
5 cm	1006 (25.3)	841 (25.4)
6 cm	403 (10.1)	338 (10.2)
7 cm	222 (5.6)	178 (5.4)
8 cm	167 (4.2)	118 (3.6)
9 cm	106 (2.7)	99 (3.0)
10 cm	114 (2.9)	89 (2.7)
Amniotomy, n (%)	1396 (35.1)	1223 (37.0)
Oxytocin augmentation, n (%)	1658 (41.7)	1561 (47.2)
Epidural analgesia, n (%)	1913 (48.2)	1653 (50.0)
Labour dyctocia, n (%)	1882 (47.4)	1512 (45.7)
Mode of delivery		
Operative vaginal, n (%)	839 (21.1)	581 (17.6)
Caesarean section, n (%)	271 (6.8)	196 (5.9)
Characteristics related to the newborn		
Birth weight (gram), mean (SD)	3528 (427)	3518 (414)
Head circumference (cm), mean (SD)	35.0 (1.4)	35.0 (1.4)

** Total numbers are presented due to missing values.
† The body-mass index is the weight in kilograms divided by the square of the height in metres.

Table 2
Duration of stages and phases and in active labour.

	Zhang group n = 3972 Unadjusted median (5th, 95th percentile)	Adjusted estimated median (95% CI)	WHO group n = 3305 Unadjusted median (5th, 95th percentile)	Adjusted estimated median (95% CI)	Accelerated delivery time factor (95% CI)	Adjusted median difference (95% CI)	p-value
Duration of labour (≥4 cm to delivery)† (hours)	6.6 (1.4, 16.0)	7.0 (6.5–7.5)	6.1 (1.3, 13.8)	6.2 (5.7–6.6)	1.14 (1.0–1.2)	0.84 (0.2–1.5)	0.008
Duration of 1st stage (4 cm to 10 cm) †,* (hours)	5.0 (0.5, 15.0)	5.6 (5.2–6.0)	4.5 (0.5, 12.5)	4.9 (4.5–5.4)	1.13 (1.0- 1.3)	0.66 (0.1–1.2)	0.023
Duration of 2nd stage (10 cm to delivery)‡ (min)	76 (17, 242)	88 (83.2–92.7)	75 (16, 204)	77 (72.4–81.4)	1.14 (1.1–1.2)	0.18 (0.1–0.3)	0.000

CI: Confidence interval.
Analysed with Weibull regression, adjusted for annual ICS rates and number of deliveries, maternal age, body-mass index, civil status, educational level, cervical dilatation at first registration and birthweight and head circumference of the neonate.
† Full Analysis Set (FAS)
* Censoring; ICS.
‡ Women with ICS in the first stage of labour were left censored at the time of ICS and not included in the analysis.

Table 3
Comparison of duration of labour in hours for Robson group 1*.

Cervical dilatation (cm)	Zhang's guideline N = 3588	WHO partograph N = 3021	Zhang's guideline N = 269	WHO partograph N = 194
	Delivered vaginally		Delivered by ICS	
4 cm to 5 cm	1.5 (6.0)	1.0 (4.5)	2.2 (8.4)	1.9 (8.4)
5 cm to 6 cm	1.0 (3.9)	0.9 (3.5)	1.9 (7.9)	1.4 (6.6)
6 cm to 7 cm	0.8 (3.0)	0.7 (3.5)	1.4 (6.5)	1.1 (6.5)
7 cm to 8 cm	0.6 (2.9)	0.5 (3.0)	0.9 (5.4)	0.9 (5.4)
8 cm to 9 cm	0.5 (2.5)	0.5 (2.5)	1.2 (7.0)	0.9 (5.2)
9 cm to 10 cm	0.5 (3.0)	0.5 (3.0)	1.4 (6.0)	1.5 (5.0)

Data are hours, median (95th percentile).
*Numbers are restricted to women with at least two cervical dilatation measurements during labour.

units. To assess the risk of selection bias, the baseline characteristics of the non-participating women were registered. We found differences between the participating and non-participating women in the proportions of those aged ≥ 35, those who were cohabiting/married, those who had attended higher education and those with low BMI.

The LaPS cover large geographic areas in Norway, which allows the results to be generalised to a larger population in Norway. Owing to the fact that LaPS included all the participating women and did not exclude women in labours with adverse neonatal and maternal outcomes, the results can be generalised to a population of TGCS Group 1 (Robson et al., 2015). However, it is important to note that this is a single country trial (i.e. in Norway), where the ICS rate is considered low. It is a known challenge in labour progression studies that participants are admitted to the labour ward with different cervical dilatation status and, therefore, contribute unequally to the duration of labour (Vahratian et al., 2006), hence our adjustments for this in the analyses. Another challenge is that vaginal examinations were performed upon indication and no continuous observations were recorded; consequently, the exact time when the cervix reached a full centimetre of dilation was impossible to record.

Interpretation

The ways to assess labour progression and define labour dystocia remain unclear, mainly because of a lack of consensus on the expected progression in labour. We found that the adjusted median difference of duration of labour from 4 cm to delivery was 48 min longer in the Zhang group compared with the WHO group, and that the corresponding adjusted median differences were 40 min and 11 min in the first and second stages, respectively. The differences were statistically significant between the two study groups, although the clinical relevance can be questioned.

The length of labour may have been affected in different ways, and the use of synthetic oxytocin may partly explain the differences. More women in the WHO group received augmentation with synthetic oxytocin compared with the Zhang group (47.2% vs 41.7%), and it is known that synthetic oxytocin shortens the duration of labour (Bugg et al., 2013). EDA may also affect the duration of labour and is known to extend the second stage (Anim-Somuah et al., 2011; Grant et al., 2015). The rate of EDA was similar in the Zhang and WHO groups (48.2% vs 50.0%) and, therefore, probably has limited impact on the differences in labour duration.

In general, labour duration in the two study groups were in accordance with the previously reported contemporary results (Oladapo et al., 2018; Zhang et al., 2010a); however, some differences are worth noting. The unadjusted time duration according to the 95th percentile of the second stage reported in both study groups was considerably longer than the previously reported results (Abalos et al., 2018; Oladapo et al., 2018; Zhang et al., 2002). The women who delivered by ICS may have a different labour progression pattern and duration of labour compared with the women who had vaginal births. In contrast to the analyses in the previously reported studies (Oladapo et al., 2018; Zhang et al., 2010a), our analyses included all the participating women regardless of interventions and mode of delivery, representing a real-life clinical situation. Presenting labour duration by including all women in the survival analyses and censoring for ICS allow each woman to contribute to the duration of labour with their unique time-to-event. The women who adhered to Zhang's guideline were diagnosed with labour dystocia to a larger extent than the women who adhered to the WHO partograph (47.4% vs 45.7%), which might have affected the duration of labour. Furthermore, we do not know whether shorter or longer labours affected the women's labour experience. Since a shorter duration of labour was associated with increased use of synthetic oxytocin, and using intravenous infusion line and monitoring of the foetus limit women's mobility, it would be important to make an informed decision on a shorter labour as opposed to more medical interventions.

As shown in Table 3, most median and 95th percentile time in hours to advance from one integer centimetre to the next were longer for women who followed Zhang's guideline than for the women who adhered to the WHO partograph. For those who delivered vaginally, the unadjusted median time difference was 30 min from 4 to 5 cm of cervical dilatation between the two study groups, whereas the 95th percentile differed by 90 min. This indicates the complexity of time limits in labour duration. Even for those 5% of women in the Zhang group who took six hours or more to reach from 4 to 5 cm, the labour resulted in a vaginal delivery. This illustrates the importance of assessing labour progression on an individual level rather than using a universal progression guideline. The differences in the unadjusted median hours decreased as labour advanced, and from 8 cm of cervical dilatation onwards the intervals were equal. The findings are in accordance with the previously reported duration in contemporary research (Oladapo et al., 2017, 2018; Shi et al., 2016; Zhang et al., 2010a) except for one Japanese study (Suzuki et al., 2010) that reported an even longer duration of labour progression from one integer centimetre to the next.

When comparing the 95th percentile for the women who delivered by ICS in the two study groups, the differences were most obvious in the intervals from 5 to 6 cm and from 8 to 9 cm. The 95th percentile to reach from 8 to 9 cm was almost two hours longer for the Zhang group compared with the WHO group, despite the fact that the duration in this interval is shorter according to Zhang's guideline. Overall, the women who delivered by ICS had longer intervals from one centimetre to the next centimetre throughout labour compared with those who delivered vaginally in both study groups.

Conclusion

We found a longer overall duration of labour and duration of first and second stages when adhering to Zhang's guideline compared with the WHO partograph. The results confirm there are wide individual variations in labour patterns, illustrating the importance of assessing labour progression on an individual basis. Our randomised trial makes an important contribution by presenting the duration and transition of the different phases and stages of labour according to two different guidelines. This highlight the complexity of assessing labour progression using a universal progression guideline, and this in sum can inform clinical practice.

Ethical approval

The study, patient information and informed consent details were approved on December 11, 2013 by the Regional Committee for Medical and Health Research Ethics: (2013/1862/REK) South-East and the Norwegian Social Science Data services (NSD). The ethical approval for the baseline characteristics of the dropt-out women was also obtained from the Regional Committee for Medical and Health Research Ethics. The study protocol was published in BMC Pregnancy and Childbirth, and it was also approved and signed by the management of each birth care unit before the commencement of the trial.

Funding sources

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Department of Nursing and Health Promotion, OsloMet – Oslo Metropolitan University, Oslo, Norway.

Clinical trial registry and registration number

The trial was registered at www.clinicaltrials.gov (NCT02221427) before the enrolment of the participants.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgment

We acknowledge the contribution of the midwives, doctors and maternity unit staff in the birth care units of all the hospitals that participated in this project. We are grateful to all the women who participated and made the trial possible. SB, PØ and EB developed the research protocol. RD, KFF and ICO performed the analysis. RD wrote the first draft of the manuscript. All the authors contributed to the interpretation of the data and also commented on and approved the final version.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.midw.2019.102578.

References

Abalos, E., Oladapo, O.T., Chamillard, M., Diaz, V., Pasquale, J., Bonet, M., …, Gulmezoglu, A.M., 2018. Duration of spontaneous labour in 'low-risk' women with 'normal' perinatal outcomes: a systematic review. Eur. J. Obstet. Gynecol. Reprod. Biol. 223, 123–132. doi:10.1016/j.ejogrb.2018.02.026.

Anim-Somuah, M., Smyth, R.M., Jones, L., 2011. Epidural versus non-epidural or no analgesia in labour. Cochrane Database Syst. Rev. (12), CD000331 doi:10.1002/14651858.CD000331.pub3.

Bernitz, S., Dalbye, R., Oian, P., Zhang, J., Eggebo, T.M., Blix, E., 2017. Study protocol: the Labor Progression Study, Laps - does the use of a dynamic progression guideline in labor reduce the rate of intrapartum cesarean sections in nulliparous women? a multicenter, cluster randomized trial in Norway. BMC Pregnancy Childbirth 17 (1), 370. doi:10.1186/s12884-017-1553-8.

Bernitz, S., Dalbye, R., Zhang, J., Eggebø, T.M., Frøslie, K.F., Olsen, I.C., …, Øian, P., 2019. The frequency of intrapartum caesarean section use with the WHO partograph versus Zhang's guideline in the Labour Progression Study (LaPS): a multicentre, cluster-randomised controlled trial. The Lancet 393 (10169), 340–348. doi:10.1016/s0140-6736(18)31991-3.

Bugg, G.J., Siddiqui, F., Thornton, J.G., 2013. Oxytocin versus no treatment or delayed treatment for slow progress in the first stage of spontaneous labour. Cochrane Database Syst. Rev. 6, Cd007123. doi:10.1002/14651858.CD007123.pub3.

Caughey, A.B., 2015. The safe prevention of the primary cesarean. Clin. Obstet. Gynecol. 58 (2), 207–210. doi:10.1097/GRF.0000000000000111.

Dallal, G. (2008). Randomization.com. Retrieved from http://www.randomization.com

Friedman, E., 1954. The graphic analysis of labor. Am. J. Obstet. Gynecol. 68 (6), 1568–1575.

Grant, E.N., Tao, W., Craig, M., McIntire, D., Leveno, K., 2015. Neuraxial analgesia effects on labour progression: facts, fallacies, uncertainties and the future. BJOG 122 (3), 288–293. doi:10.1111/1471-0528.12966.

Hanley, G.E., Munro, S., Greyson, D., Gross, M.M., Hundley, V., Spiby, H., Janssen, P.A., 2016. Diagnosing onset of labor: a systematic review of definitions in the research literature. BMC Pregnancy Childbirth 16, 71. doi:10.1186/s12884-016-0857-4.

Hernan, M.A., Hernandez-Diaz, S., Werler, M.M., Mitchell, A.A., 2002. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am. J. Epidemiol. 155 (2), 176–184.

Neal, J.L., Lowe, N.K., Patrick, T.E., Cabbage, L.A., Corwin, E.J., 2010. What is the slowest-yet-normal cervical dilation rate among nulliparous women with spontaneous labor onset? J Obstet Gynecol Neonatal Nurs 39 (4), 361–369. doi:10.1111/j.1552-6909.2010.01154.x.

Neal, J.L., Lowe, N.K., Schorn, M.N., Holley, S.L., Ryan, S.L., Buxton, M., Wilson-Liverman, A.M., 2015. Labor dystocia: a common approach to diagnosis. J. Midwifery Womens Health 60 (5), 499–509. doi:10.1111/jmwh.12360.

NICE guidelines. (2014, 2017). Intrapartum care. Clinical Guidelines, Intrapartum Care Retrieved from https://www.nice.org.uk/guidance/cg190.

Norwegian Medical Association. (2014). Augmentation of labor. Retrieved from http://www.nfog.org/files/guidelines/34%20NGF%20Obst%20Augmentation%20of%20labour%20Eggeb%C3%B8.pdf

Oladapo, O.T., Diaz, V., Bonet, M., Abalos, E., Thwin, S.S., Souza, H., …, Gulmezoglu, A.M., 2017. Cervical dilatation patterns of 'low-risk' women with spontaneous labour and normal perinatal outcomes: a systematic review. BJOG 125 (8), 944–954. doi:10.1111/1471-0528.14930.

Oladapo, O.T., Souza, J.P., Fawole, B., Mugerwa, K., Perdona, G., Alves, D., …, Gulmezoglu, A.M., 2018. Progression of the first stage of spontaneous labour: a prospective cohort study in two sub-Saharan African countries. PLoS Med. 15 (1), e1002492. doi:10.1371/journal.pmed.1002492.

Philpott, R.H., Castle, W.M., 1972a. Cervicographs in the management of labour in primigravidae. I. The alert line for detecting abnormal labour. J. Obstet. Gynaecol. Br Commonw. 79 (7), 592–598.

Philpott, R.H., Castle, W.M., 1972b. Cervicographs in the management of labour in primigravidae. II. The action line and treatment of abnormal labour. J. Obstet. Gynaecol. Br. Commonw. 79 (7), 599–602.

Robson, M., Murphy, M., Byrne, F., 2015. Quality assurance: the 10-Group classification system (Robson classification), induction of labor, and cesarean delivery. Int. J. Gynaecol. Obstet. 131 (Suppl 1), S23–S27. doi:10.1016/j.ijgo.2015.04.026.

Shi, Q., Tan, X.Q., Liu, X.R., Tian, X.B., Qi, H.B., 2016. Labour patterns in Chinese women in Chongqing. BJOG 123 (Suppl 3), 57–63. doi:10.1111/1471-0528.14019.

Souza, J.P., Oladapo, O.T., Fawole, B., Mugerwa, K., Reis, R., Barbosa-Junior, F., … Gulmezoglu, A.M., 2018. Cervical dilatation over time is a poor predictor of severe adverse birth outcomes: a diagnostic accuracy study. BJOG 125 (8), 991–1000. doi:10.1111/1471-0528.15205.

Stedman, M.R., Lew, R.A., Losina, E., Gagnon, D.R., Solomon, D.H., Brookhart, M.A., 2012. A comparison of statistical approaches for physician-randomized trials with survival outcomes. Contemp. Clin. Trials 33 (1), 104–115. doi:10.1016/j.cct.2011.08.008.

Suzuki, R., Horiuchi, S., Ohtsu, H., 2010. Evaluation of the labor curve in nulliparous Japanese women. Am. J. Obstet. Gynecol. 203 (3). doi:10.1016/j.ajog.2010.04.014, 226 e221-226.

Vahratian, A., Troendle, J.F., Siega-Riz, A.M., Zhang, J., 2006. Methodological challenges in studying labour progression in contemporary practice. Paediatr Perinat Epidemiol 20 (1), 72–78. doi:10.1111/j.1365-3016.2006.00696.x.

World Health Organization, 1994. World health organization partograph in management of labour. world health organization maternal health and safe motherhood programme. Lancet 343 (8910), 1399–1404.

World Health Organization. (2000, 2007). Managing complications in pregnancy and childbirth: a guide for midwives and doctors. Retrieved from http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf

World Health Organization. (2018). WHO recommendations: intrapartum care for a positive childbirth experience. Retrieved from http://apps.who.int/iris/bitstream/handle/10665/260178/9789241550215-eng.pdf;jsessionid=F1F5397399F4488853284911 74AC61C6?sequence=1

Zhang, J., Landy, H.J., Branch, D.W., Burkman, R., Haberman, S., Gregory, K.D., …Consortium on Safe, L., 2010a. Contemporary patterns of spontaneous labor with normal neonatal outcomes. Obstet. Gynecol. 116 (6), 1281–1287. doi:10.1097/AOG.0b013e3181fdef6e.

Zhang, J., Troendle, J., Mikolajczyk, R., Sundaram, R., Beaver, J., Fraser, W., 2010b. The natural history of the normal first stage of labor. Obstet. Gynecol. 115 (4), 705–710. doi:10.1097/AOG.0b013e3181d55925.

Zhang, J., Troendle, J.F., Yancey, M.K., 2002. Reassessing the labor curve in nulliparous women. Am. J. Obstet. Gynecol. 187 (4), 824–828.

Figure S1. Unadjusted Kaplan-Meier plots for women adhering to Zhang's guideline and women adhering to the WHO partograph for duration of labour from 4 cm until delivery

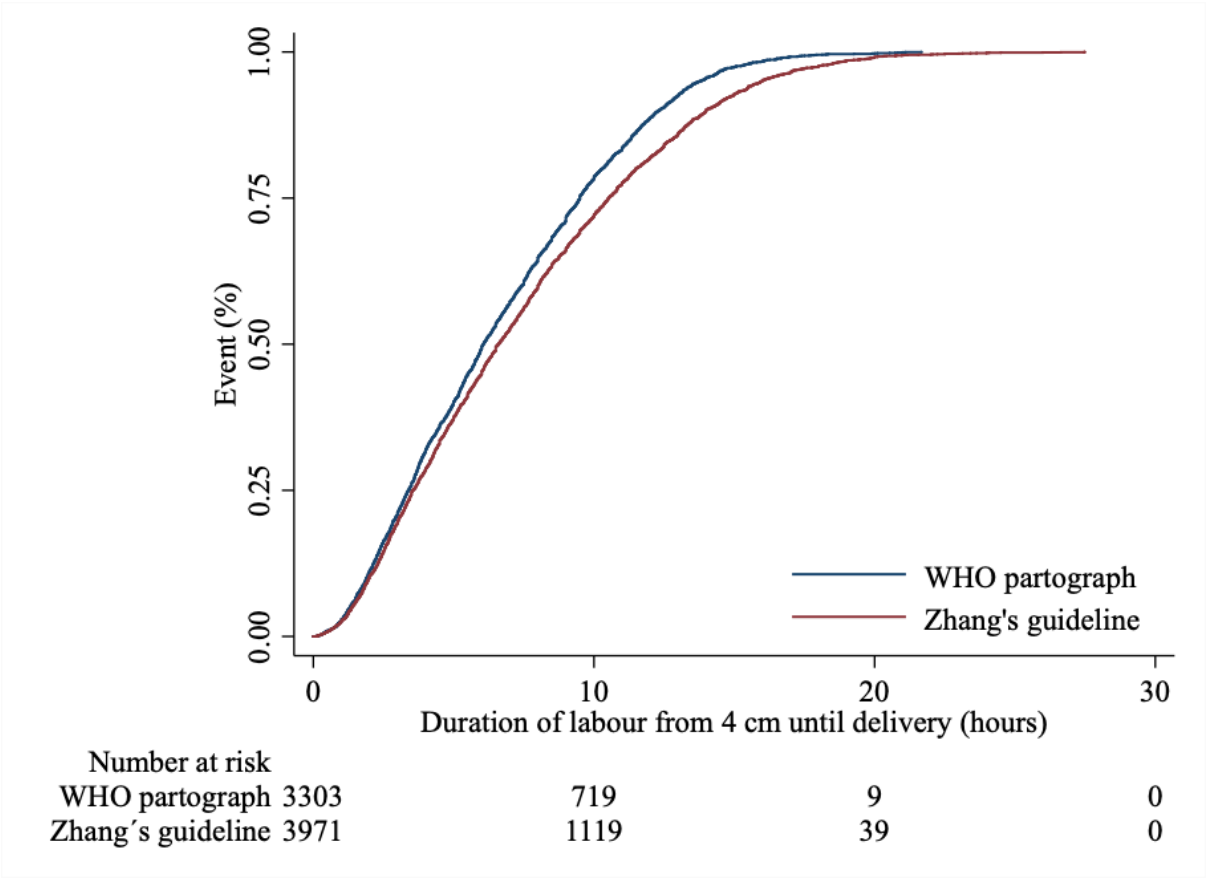
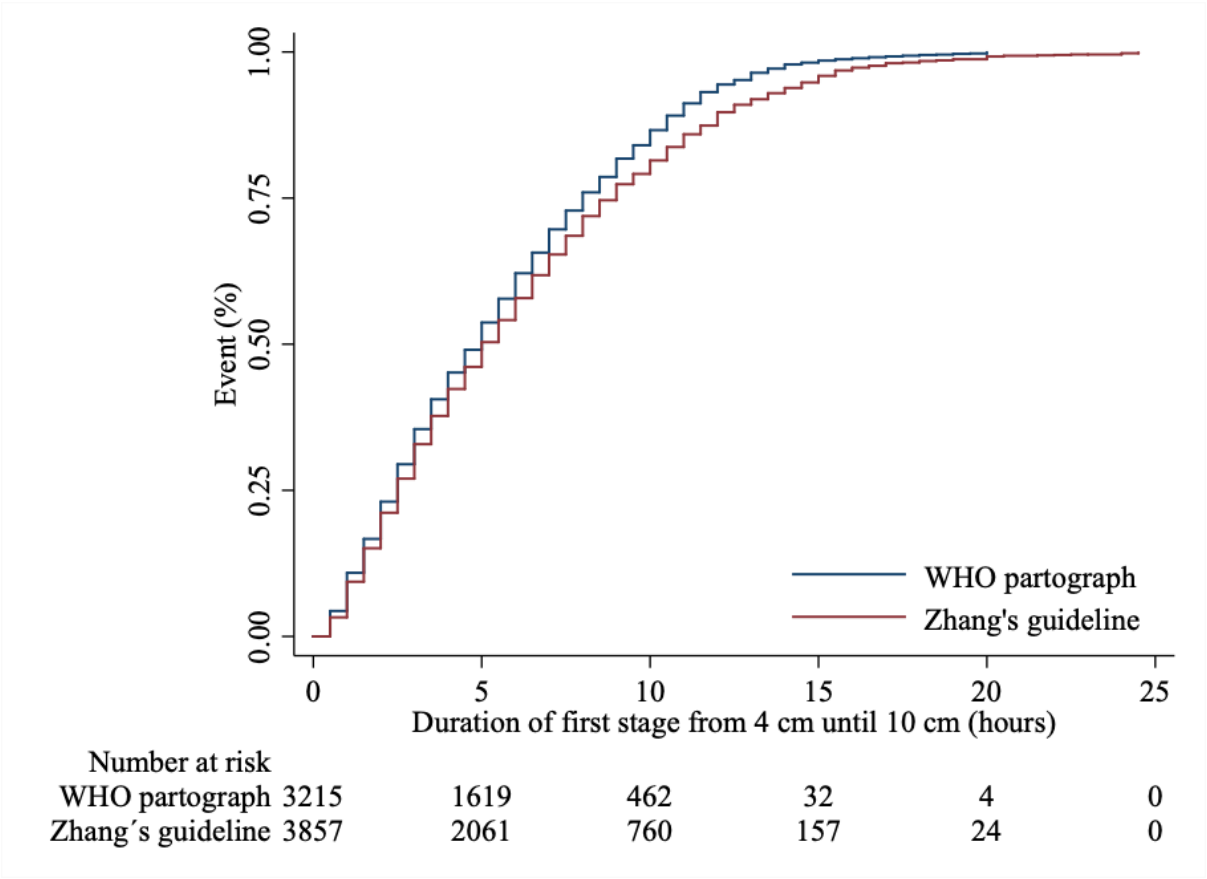
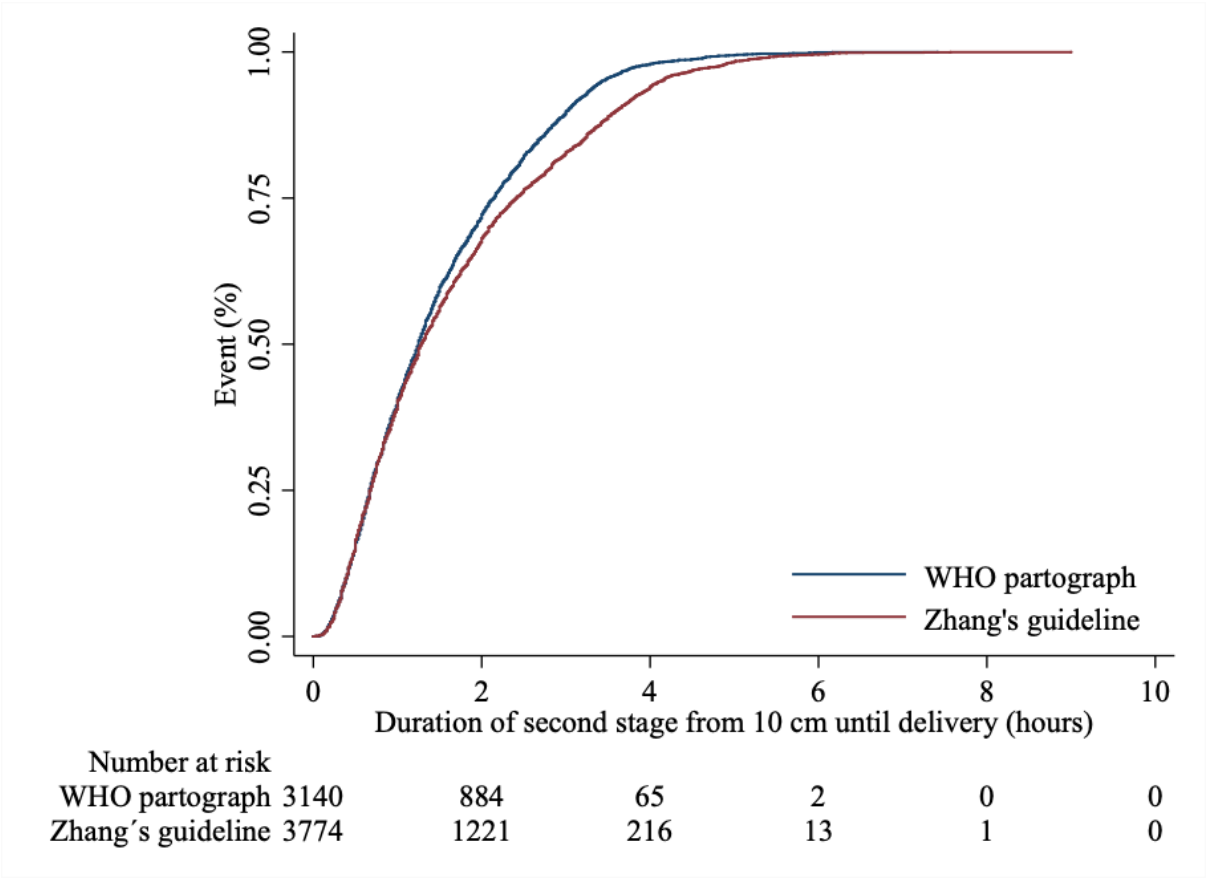


Figure S2. Unadjusted Kaplan-Meier plots for women adhering to Zhang's guideline and women adhering to the WHO partograph for duration of 1st stage, from 4 cm until 10 cm



Number at risk						
WHO partograph	3215	1619	462	32	4	0
Zhang´s guideline	3857	2061	760	157	24	0

Figure S3. Unadjusted Kaplan-Meier plots for women adhering to Zhang's guideline and women adhering to the WHO partograph for duration of second stage from 10 cm until delivery



Number at risk						
WHO partograph	3140	884	65	2	0	0
Zhang´s guideline	3774	1221	216	13	1	0

Table S1. Baseline characteristics of the included and non-included women

	Included women n=7277	Missing	**Non-included women** n= 4338	Missing	P-value
Maternal characteristics					
Age at delivery (years)*	28 ± 4		28 ± 5	1	1.0
< 25	1755 (24.1)		1026 (23.7)		0.57
25-35	4954 (68.1)		2923 (67.4)		0.44
≥ 35	568 (7.8)		388 (8.9)		0.03
Cohabitant or married	6878 (94.5)	60	3976 (91.7)	24	<0.001
Higher education ≥ 12 years	4429 (60.9)		2387 (55.0)	70	<0.001
Smoking first trimester	440 (6.0)	67	224 (5.2)	10	0.05
Pre-pregnant body mass index *†	24 ± 4	24	24 ± 4	197	1.0
≤ 18·5	314 (4.3)		220 (5.1)		0.06
18·5-24·9	4870 (66.9)		2725 (62.8)		<0.001
25·0-29·9	1452 (20.0)		824 (19.0)		0.2
≥ 30·0	617 (8.5)		372 (8.6)		0.86
Gestational age at onset of active labour (days)*	281 ± 7		281 ± 8	7	1.0

Numbers are no. (%) unless otherwise stated. *Values are means ± SD. †The body-mass index is the weight in kilograms divided by the square of the height in meters. The body-mass index was missing for 4·5% of the non-included women, thus the percentages do not add up to 100%.

Sponsor name	Østfold Hospital Trust
Sponsor address	PO Box 300, 1714 Grålum, Norway
EudraCT number	NCT02221427
Trial ID	LaPS

The Labor Progression Study - LaPS

SIGNATURE PAGE

PRINCIPAL/COORDINATING INVESTIGATOR:

Stine Bernitz, Midwife, PhD

Department of Obstetric and Gynecology

Østfold Hospital Trust, po box 300, 1714 Grålum, Norway

Stine Bernitz — Signature

23/11 2018 — Date

TRIAL STATISTICIAN FOR LAPS:

Inge Christoffer Olsen Statistician PhD

Oslo Centre for Biostatistics & Epidemiology

Sogn Arena 3.etg Pb 4950 Nydalen 0424 Oslo

Norway

Inge Olsen — Signature

13 November 2018 — Date

Study Coinvestigators

Rebecka Dalbye, Midwife MSc

Department of Obstetric and Gynecology

Østfold Hospital Trust, po box 300, 1714 Grålum, Norway

Rebecka Dalbye — Signature

13. November 2018 — Date

Kathrine Frey Frøslie

Norwegian National Advisory Unit on Women's Health

Oslo University Hospital, Rikshospitalet

Pb 4950 Nydalen 0424 Oslo, Norway

Kathrine Frey Frøslie

Signature

13/11-2018

Date

ABBREVIATIONS

AE	Adverse Event
BD	Base Deficit
BMI	Body Mass Index
BPM	Beats Per Minute
CEQ	Childbirth Experiences Questionnaire
CI	Confidence Interval
CRF	Case Report Form
CTG	Cardiotocography
ECD	Emergency Cesarean Delivery
EDC	Electronic Data Capture
EDA	Epidural analgesia
MedDRA	Medical Dictionary for Regulatory Activities
NICU	Neonatal Intensive Care Unit
P0	Nulliparous women
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
STAN	ST ANalyzes
TGCS	Ten Group Classification System
TNS	Transcutaneous Nervous Stimulation
WHO	World Health Organization

TABLE OF CONENTS

AMENDMENTS TO THE SAP

This is the first version of the SAP for the labour duration in LaPS

1 STUDY OBJECTIVES of the analysis of endpoints related to labour duration in LaPS

The present statistical analysis plan (SAP) describes the analyses of secondary endpoints and exploratory analyses related to aspects of labour duration in the LaPS study,

1.1 Primary Objective of the analysis

To assess the impact of adhering to the guideline for labour progression presented by Zhang(1) on the duration of total time in active labour (active 1st stage and total 2nd stage) in nulliparous women compared to adhering to the WHO-partograph based on Friedman's curve(2)

1.2 Secondary Objectives of the analysis

To assess the impact of adhering to the guideline for labour progression presented by Zhang (1) on other time related aspects of duration of labour progress outcomes in nulliparous women and their neonates, compared to adhering to the WHO-partograph (3).

2 OVERALL STUDY DESIGN

This is a cluster randomized, multi center, strategy trial.

3 GENERAL STATISTICAL CONSIDERATIONS

All analyses described in the protocol and the original SAP, published as supplementary material to the article accepted for publication in Lancet (accept 16.08.2018) were considered *a priori* analyses. The present SAP describes and elaborates the analyses of time related aspects of labour progress, defined as secondary endpoints in the LaPS study, and exploratory analyses related to these. All analyses that are described in the present document, but that were not described in the main trial analysis plan will be regarded as post-hoc analyses.

All categorical (binary and ordinal) data will be summarized using frequency counts and percentages of patient characteristics. Percentages will be calculated using the study population (defined as "full analysis set" in section 8); any exceptions to this will be highlighted in the table footnote. The continuous variables will be summarized using number of patients (N), and range (minimum and maximum) in combination with mean and standard deviation (SD), if data are normally distributed, and median, lower and upper quartiles if data are skewedly distributed. Time-to-event variables will be presented by the median, quartiles, 5 and 95 percentiles, or median and the 95 percentile for the cervical dilatation data. In general, minimum and maximum will be presented to the same degree of precision as data is recorded, with mean, median and quartiles having 1 additional place after the decimal, and standard deviation having 1 or 2 additional places after the decimal, depending on the size of the mean. Percentages less than 100 will be displayed to 1 place after the decimal, where space permits.

Baseline characteristics are given without *p*-values.

p-values larger than 0.01 will be reported to two decimal places, those between 0.01 and 0.001 to three decimal places. *p*-values below 0.001 will be displayed as "<0.001".

Data will be presented, unless otherwise indicated, according to the two guideline strategy groups.

In general, analyses presented in the tables, listings, and figures will be confined to participants included in the full analysis set (defined in section 8).

4 HYPOTHESES AND DECISION RULES

4.1 Statistical Hypotheses

This analysis plan describes the analyses of time related aspects of labour duration in the LaPS trial, defined as secondary endpoints in the LaPS study.

Among these, the primary question of interest in the present SAP is if the duration of the total time in active labour (active 1st stage and total 2nd stage) in nulliparous women adhering to the guideline for labour progression presented by Zhang(1) differ from the duration of the total time in active labour (active 1st stage and total 2nd stage)) in nulliparous women adhering to the WHO-partograph(3) based on Friedman's curve (2). The main focus of the analyses will be on the differences between the two groups, i.e. the effect sizes with corresponding 95% confidence intervals.

This SAP also describes the analyses of the other secondary endpoints and exploratory analyses of time related aspects of labour duration in the LaPS trial. These analyses will not rely on confirmatory statistical hypotheses testing. Instead, the main focus of these analyses will also be on the differences between the two groups, i.e. the effect sizes with corresponding 95% confidence intervals. Hence, p-values from hypotheses tests for other secondary or exploratory outcomes (i.e. if the outcomes among women adhering to the guideline for labour progression presented by Zhang differ from outcomes among those adhering to the WHO-partograph) will therefore be interpreted as hypothesis supporting and not confirmatory.

4.2 Statistical Decision Rule

Group comparisons resulting in a p-value below 0.05 will be denoted as a statistical significant difference, but no claim of superiority either way will be made based on such findings.

5 DEFINITIONS AND DERIVED VARIABLES

5.1 Change from baseline

Not applicable

5.2 Other calculations

Age (years) = [(date of baseline – date of birth)/365.25].

BMI = weight in kilograms / (height in metres) x (height in metres)

BMI will be categorized according to the WHO definitions for underweight, normal, overweight and obese.

Different delivery phase/stage is defined as follows (Figure 1).

- Latent phase of first stage is defined as the time of the onset of labor (patient reported) until the cervix is dilated to 4 cm.
- Active phase of first stage of labor is defined as regular painful uterine contractions and cervical dilatation from 4 centimeters until the cervix is fully dilated, 10 cm, or until ECD.
- Descending phase of second stage is defined as the period from full dilatation of cervix until the expulsion phase starts, or until ECD.
- The expulsion phase of the second stage is defined as the period from expulsion starts until the baby is completely out of the birth canal, or until ECD.
- Total length of active labor is described as the period from the partograph registration (minimum 4 cm) until the baby is born (vaginally or by ECD).
- Length of active phase of first stage of labor, length of second stage, descending phase and expulsion phase will also be described.

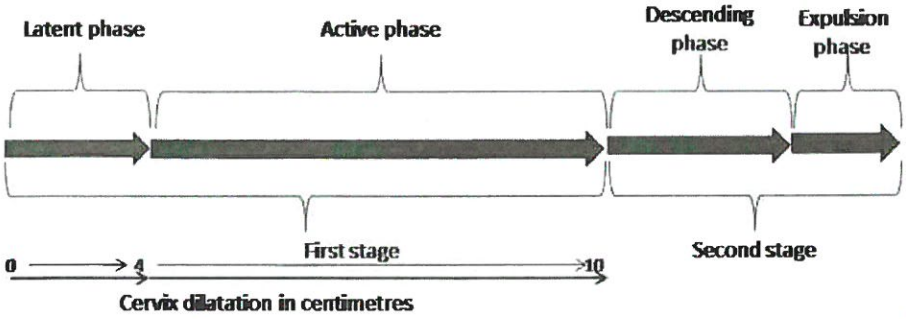


Fig 1

Computing of time variables for the different delivery phase/stage

The length of active phase of first stage of labor was recoded based on the cervix dilatation data in the CRF. In the CRF, dilatation data could be entered for every half hour from the start of the partograph registration. If no examination of the cervix dilatation was done, the corresponding data point in the CRF was not entered. The active phase of first stage was computed as time from 4cm cervix dilatation or first partograph registration to last partograph registration.

Descending and expulsion phase of second stage are directly registered in the CRF. The total length of second stage is computed as the sum of these. Total length of active labor is computed as the sum of the length of active phase of first stage, and the total length of second stage.

Estimated duration of progression from centimetre to the next centimetre

Women with at least two cervical dilatation measurements during the active labour were included in these calculations. The progression in labour dilatation was estimated as a maximum of 6 separate time intervals during the first stage of active phase (i.e, the time from 4 cm to 5 cm cervical

dilatation, the time from 5 cm to 6 cm cervical dilatation, the time from 6 cm to 7 cm cervical dilatation, the time from 7 cm to 8 cm cervical dilatation, the time from 8 cm to 9 cm cervical dilatation, and the time from 9 cm to 10 cm cervical dilatation), depending on the cervical dilatation at admission. That is, women who are admitted at 4 cm cervical dilatation and who reach 10 cm cervical dilatation will contribute with 6 time intervals, those admitted at 5 cm cervical dilatation and who reach 10 cm cervical dilatation will contribute with 5 time intervals etc.

For women who reach full cervical dilatation, the starting point of each time interval equals the first registration of a specific centimetre. The end point of each time interval is the first registration of the consecutive centimetre. If the consecutive cm is not observed but advanced cervical dilatation is observed at a later time point, the time to the consecutive cm is estimated by linear interpolation between two consecutive measurements. Also, the starting point of an interval is estimated in the same way if the specific cervical dilatation is not observed, but advanced cervical dilatation is observed at a later time point.

For women who had an ICS before full cervical dilatation were reached, the last cervical dilatation registered is the end point of the last time interval; i.e. this time interval is right-censored. Still, these women contribute with observation time in this interval. The observation time in this interval is set to the time from when the woman enters the interval, until ICS was done.

Labor dystocia is defined as follows:
Labor dystocia according to Zhang's guideline is diagnosed if the cervix dilatation rate according to the 95 % percentile, does not meet the expected progression from centimeter to the next centimeter. During second stage of labor, dystocia is diagnosed, if the time from full dilatation to active expulsion phase (passive second stage) exceeds 1 hour and 45 minutes (2 hours and 30 minutes for women with epidurals), or if the expulsion phase (active second stage) exceeds 60 minutes (see figure 2).

Dilation of the cervix	95 percentile * (dystocia)
From 4 to 5 cm	6 h 30 min
From 5 to 6 cm	3 h 15 min
From 6 to 7 cm	2 h 15 min
From 7 to 8 cm	1 h 30 min
From 8 to 9 cm	1 h 30 min
From 9 to 10 cm	1 h 45 min
2. stage without EDA Expulsion phase max 60 min	2 h 45 min
2. stage with EDA Expulsion phase max 60 min	3 h 30 min
Total time without EDA	19 h 30 min
Total time with EDA	20 h 15 min

Fig 2

Labor dystocia according to the WHO partograph/standard care guideline is diagnosed if cervix dilatation rate is slower than one centimeter per hour, assessed after four hours i.e. if the four-hours action line is crossed. During second stage of labor, dystocia is diagnosed if the time from full dilatation to active expulsion phase exceeds 1 hour (2 hours for women with epidurals), or if the expulsion phase (active second stage) exceeds 60 minutes (see figure 3).

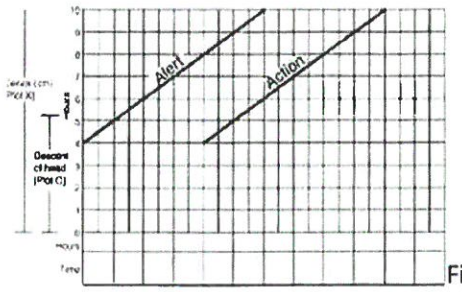


Fig 3

Operative vaginal delivery
Operative vaginal delivery is defined as a delivery of vacuum and/or forceps.

6 EFFICACY AND SAFETY ENDPOINTS / VARIABLES

6.1 Endpoints

The secondary endpoints as defined in the original LaPS protocol and presented in the SAP for the main publication, accepted 16.8 2018 in The Lancet are as follows:

- **Detailed information regarding time related aspects of labour in the different phases, including:**
  - active phase of first stage
  - descending phase of second stage
  - expulsion phase of second stage
  - total length of second stage
  - Total length of active phase of labour (1st and 2nd stage)

The primary endpoint of the present analysis is the total time of active phase of labour (1st and 2nd stage), described as the period from the first partograph registration (≥4 cm) until delivery, either vaginally or by ICS. This is a time-to-event endpoint.

6.1.1 Secondary and exploratory endpoints

The other secondary endpoints of time related aspects of labour duration in the LaPS trial, as described in the original SAP, will be considered as exploratory analyses.

6.1.1 Other endpoints from the original SAP

In the LaPS article published in Lancet, the primary and several secondary endpoints were presented in Table 2 and Table 3, respectively. In the present analysis, these data, and some of the secondary endpoints not presented in the Lancet publication, are treated as descriptive, e.g. as "Delivery characteristics". This applies to

- **Detailed information regarding time in different phases**
- **Duration of latent phase 1st stage**
- **Detailed information on labor dystocia**
  - Proportion of labor dystocia according to current guidelines

- Cervical dilatation when dystocia is diagnosed.
- Proportion of labor dystocia in the expulsion phase
- Stage of descending head when dystocia is diagnosed as follow: over spinae, stage spinae, below spinae or at pelvic flor. One possible option.

- **The proportion of spontaneous vaginal delivery rate (dichotomous)**
- **The proportion of operative vaginal delivery rate (dichotomous)**
- **The proportion of intrapartum caserean section**
- **The proportion of amniotomy (dichotomous)**
- **Detailed information on amniotomy**
  - The proportion of amniotomy (dichotomous)
  - Indications (dystocia, fetal distress and other reason), only one possible option
  - Cervical dilatation at amniotomy
- **The proportion of oxytocin augmentation in active labor (dichotomous)**
- **The proportion of epidural analgesia (dichotomous)**
- **Cervical dilatation at onset of EDA**
- **The proportion of episiotomies (dichotomous)**
- **The proportion of OASIS (dichotomous)**
- **The proportion of blood transfusions (dichotomous)**
- **The proportion of post partum haemorrhage ≥ 1000 ml (dichotomous)**
- **Detailed information on pH and BE in the umbilical cord**
  - The proportion of neonates with metabolic acidosis after birth

- **Detailed information on transfer neonates to Neonatal Intensive Care Unit after birth**
  - The proportion of transfer to the Neonatal Intensive Care Unit after birth(dichotomous)
  - Indications for transfer (four different indications: asphyxia, suspect infections, respiratory problems or other reasons). One possible option.
  - Length of stay, defined as more or less than 24 h.

- **Detailed information on perinatal tear as defined above.**

- **Detailed information on non invasive actions for stimulating of contractions describes as:**
  - none
  - change positions
  - emptied bladder
  - given food

- given liquid to drink

- **Detailed information on admission to the labor ward, including**
  - indication of admission
  - time from rupture of the membranes until admission
  - cervical dilatation when rupture of the membranes
  - characteristics of the amniotic fluid
  - rate of contractions before and upon admission
  - time of contractions until admission
  - cervical dilatation upon admission
  - fetal heart rate
  - if CTG was used
  - classification of the CTG

6.2 Safety Parameters

Not applicable

7 DETERMINATION OF SAMPLE SIZE

Sample size calculation is based to calculate the power for the overall primary endpoint for the LaPS described and presented both in the protocol, the original SAP, and the main publication (referanse eller "accepted 16.8 2018 in The Lancet"). The determination of the sample size (number of clusters and individuals) is based on a power calculation with the least occurring outcome; intrapartum cesarean delivery, which was 9.2% (at time of sample size calculation) in the study population (p1). Further, we expect that the intrapartum cesarean delivery rate will be 6.7% (p2) which is a 25% reduction, when using the new guideline. Formula (4) on page 320 in the article by Hayes et al. is used to calculate the needed number of clusters and participants(4). According to this formula, with a chosen significance level of 0.05, a power of 80% and p1 = 9.2% and p2 = 6.9%, we should include at least 14 clusters and 6582 individuals. The design allows flexibility, so that larger birth care units may contribute with more study subjects than smaller units.

8 DATA SETS TO BE ANALYZED

There will be four analyzes sets in this study.

- The **Eligible Analysis Set (EAS)** will include all eligible women within the inclusion period at each site

- The **Full Analysis Set (FAS)** will include all eligible women with signed informed consent.

- The **Vaginal Delivery Set (VDS)** will include all eligible women with signed informed consent delivering vaginally.

- The **Cesarean Delivery Set (CDS)** will include all eligible women with signed informed consent with emergency cesarean delivery.

- The **Descending Analysis Set (DAS)** will include eligible women in FAS minus women undergoing ICS during active phase of 1st stage

- The **Expulsion Analysis Set (ExAS)** will include eligible women in the Descending Analysis Set minus women undergoing ICS during descending phase.

9 PRESPECIFICATION OF ANALYSES

Although the allocation to each strategy has been revealed during the main article analyses, an effort will be made to keep decisions made in this document as unbiased as possible. This will be done by not performing any group comparison analyses prior to the finalization of this document, thus avoiding result-driven analyses.

10 STATISTICAL METHODOLOGY

The primary efficacy analyzes will be based on the Full Analysis Set (FAS) only. Secondary efficacy analyzes will be based on the Full Analysis Set (FAS), Descending Analysis Set (DAS) and the Expulsion Analysis Set (ExAS).

When random numbers are warranted for inference (such as for bootstrapping and multiple imputation), the seed will be set to the date the statistical analysis plan is signed-off (in the format yyyymmdd).

All efficacy analyzes will be presented by the size (point estimate) of the difference between the treatments and the associated 95% confidence interval, and p-values of the corresponding statistical hypothesis test as supporting information.

Statistical analyses will be done in Stata v15 (StataCorp. 2015. Stata Statistical Software: Release 15.1. College Station, TX, USA). Estimating of duration of progression from centimetre to the next centimetre will be analysed in R, version 3.5.0.

10.1 Adjustment for covariates

We will use the following covariates in all primary and secondary statistical models analyzes:

10.1.1 Maternal and neonatal characteristics

Maternal age
Maternal BMI
Civil status (single vs cohabitant/married)
Level of education (university/college education)
Cervical dilatation at first registration (time to event endpoints only)
Birth weight
Baby's head circumference

10.1.2 Hospital levels

Stratification variables

Annual emergency Cesarean delivery rate in Ten Group Classification System (TGCS) group 1 women in 2012

Annual number of deliveries in TGCS group 1 women in 2012

10.2 Center effect

As this is a cluster-randomized study with center as cluster, center will be included in the statistical models to adjust for within-cluster dependencies.

10.3 Multiplicity adjustments

There will be no adjustments for multiplicity in these sub-analyses. There will be no confirmatory hypothesis testing, and therefore there will be no need for formal adjustments for multiplicity.

10.4 Demographic and other baseline characteristics

Demographic and baseline characteristics, as well as cervical dilatation progress from centimetre to centimetre will be summarized descriptively by treatment group for women in the FAS. The median and 95th percentile duration from one centimetre to the next centimetre cervical dilatation will be presented both for each treatment group and subdivided into women with or without ICS within each treatment group. In addition, demographic and baseline data will be displayed separately for each of the study centres.

10.5 Efficacy analysis

The primary endpoint (the total time of active phase of labour (1st and 2nd stage), from the first partograph registration (≥4 cm) until delivery, either vaginally or by ICS) will be analysed using a Weibull regression with cluster as random intercept and treatment strategy as fixed effect, adjusted with covariates as given in section 10.1 in addition to first registration of cervical dilatation in cm. Unadjusted Kaplan-Meier plots will be presented. The primary analysis will be performed on the Full Analysis Set (FAS).

Time: Cervical dilatation ≥ 4 cm to delivery. Event of interest: Delivery FAS, no censoring

10.5.1 Analyses of secondary endpoints

The duration of active phase of 1st stage will be analysed using a Weibull regression with cluster as random intercept and treatment strategy as fixed effect, adjusted with covariates as given in section 10.1 in addition to first registration of cervical dilatation in cm, and with censoring for ICS. Unadjusted Kaplan-Meier plots will be presented. This analysis will be performed on the FAS.

Time: Cervical dilatation ≥ 4 cm to 10 cm. Event of interest: Cervical dilatation = 10 FAS, censoring for ICS

The duration of 2nd stage will be analysed using a Weibull regression with cluster as random intercept and treatment strategy as fixed effect, adjusted with covariates as given in section 10.1 in addition to first registration of cervical dilatation in cm, and with censoring for ICS. Unadjusted Kaplan-Meier plots will be presented. This analysis will be performed on the DAS.

Time: Cervical dilatation = 10 cm to delivery.
Event of interest: Delivery
DAS, censoring for ICS

10.5.2 Discussion regarding efficacy analyses

While Weibull regression relies on a two-parametric model for the distribution of survival times, the Cox model does not impose a parametric form for the distribution of survival times. Both methods allow for covariates and adjusting for cluster effects. In line with the analysis of binary data in the original SAP, we aim at using a parametric mixed model (Weibull), as this has good performance. (5, 6).

In the primary analysis, delivery is defined as the event of interest. Since the total time of active phase of labour (1st and 2nd stage), from the first partograph registration (≥4 cm) until delivery, either vaginally or by ICS, is registered for all included women, there will be no unobserved event in this analysis, and consequently no censoring.

In the secondary analyses, the event of interest is vaginal birth. Not all women will experience the event of interest, and the time is not observed. In traditional survival analysis, the registered time to an event, if the event does not occur during the observation period (e.g. if the patient is lost to follow-up), will often be considered to be censored. However, treating observation times as censored require the assumptions of independent and non-informative censoring (7). If, in contrast, the time to an event is not observed due to an event that either hinders the observation of the event of interest or modifies the chance that this event occurs, data should be treated as competing events (competing risk analysis), and not as censored (8). Although statistical methods for the analysis of competing risk in clustered data have been developed recently (9, 10)(11), we have chosen to present the traditional analyses with censoring for ICS, due to the low rate of ICS cases in the study.

10.6 Missing data imputation and sensitivity analyzes

Missing data assessments are based on a blinded review of the data prior to the primary publication.

All included women have been assessed for birth delivery method, and there are no missing data for the time-to-event outcomes.

There are no missing data in any of the covariates as described in section 10.1, except for BMI where 0.3% of the observations are missing and cohabitant with 0.8% missing values. Given the low missing data rate, we have decided to use a stochastic linear regression single imputation(12) for BMI and to

use cohabitant status not known as one of the categories in addition to cohabitant/married and single.

Additional robustness analyses will include non-adjusted models and models adjusted only for hospital level covariates.

10.7 Patient Characteristics

10.7.1 Patient Disposition

The disposition of all patients will be listed and summarised by treatment arm.

10.7.2 Background and Demographic Characteristics

Patient demographics and baseline characteristics will be summarized.

Patient demographics and baseline characteristics will be summarized by randomized treatment arm and overall using descriptive statistics as described in detail in section 3.

The maternal demographics and baseline characteristics include age at date of delivery, co-habitual status, education, smoking habits, body mass index (BMI) and cervical dilatation at first registration.

The birth and delivery demographics include rate of spontaneous vaginal delivery, operative vaginal delivery, intrapartum caserean section, amniotomy, oxytocin augmentation and epidural analgesia.

The neonatal characteristics include gestational age, birth weigth, head circumference and gender.

10.7.3 Treatment Compliance

To secure a thorough implementation of the trial, the management at all participating birth care units read and approved the trial protocol and signed a cooperation agreement committing to adhere to the protocol. All birth care units underwent a strict teaching program including information and allocated guideline instructions, securing that all birth attendants had profound knowledge about the guidelines. Throughout the whole trial period and on a regular basis, researchers from the LaPS group revisited the units to ensure that all units adhered to the allocated guideline. Written information about the trial and the guidelines was printed on posters and made visible and available for midwives and obstetricians at all times. No exceptional measurements of treatment compliance were performed.

10.7.4 Concomitant Medications and Other Therapies

Not applicable

10.7.5 Concomitant treatment

The only concomitant treatment registered in this trial is the use of oxytocin, which will be analyzed as an secondary endpoint.

11 Safety Analysis

11.1 Adverse events

There will be no additional analyzes of adverse events than those described as efficacy endpoints (episiotomies, OASIS, blood transfusions).

12 Interim analysis

No interim analysis was planned during the trial.

13 Data monitoring

There was no formal Data Monitoring Committee for this trial.

14 Table of Contents of Tables, Listings and Figures

14.1 List of Tables

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15 References

1. Zhang J, Landy HJ, Branch DW, Burkman R, Haberman S, Gregory KD, et al. Contemporary patterns of spontaneous labor with normal neonatal outcomes. Obstetrics and gynecology. 2010;116(6):1281-7.
2. Friedman E. The graphic analysis of labor. American journal of obstetrics and gynecology. 1954;68(6):1568-75.
3. World Health Organization partograph in management of labour. World Health Organization Maternal Health and Safe Motherhood Programme. Lancet. 1994;343(8910):1399-404.
4. Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. International journal of epidemiology. 1999;28(2):319-26.
5. Stedman MR, Lew RA, Losina E, Gagnon DR, Solomon DH, Brookhart MA. A comparison of statistical approaches for physician-randomized trials with survival outcomes. Contemp Clin Trials. 2012;33(1):104-15.
6. CRUMER AM. COMPARISON BETWEEN WEIBULL AND COX PROPORTIONAL HAZARDS MODELS: KANSAS STATE UNIVERSITY Manhattan, Kansas

2011.
7. Klein Ka. Survival analysis: A self-learning text. 3rd edition ed: Springer; 2011.

8. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant. 2013;28(11):2670-7.
9. Zhou B, Fine J, Latouche A, Labopin M. Competing risks regression for clustered data. Biostatistics. 2012;13(3):371-83.
10. Familusi MA. Analysis of Clustered Competing Risks with Application to a Multicentre Clinical Trial. Published by the University of Cape Town: University of Cape Town; 2016.
11. Latouche A. Competing risks regression for Stratified and Clustered data [Available from: https://www.rdocumentation.org/packages/crrSC/versions/1.1.
12. Buuren S. Flexible Imputation of Missing Data: Chapman and Hall/CRC. ; 2012 [Available from: http://doi.org/10.1201/b11826.