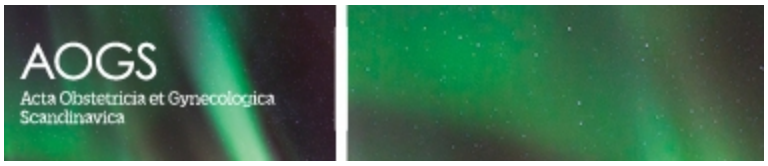

Induction of Labor and Nulliparity: A Nation-wide Clinical Practice Pilot Evaluation

Journal:	*Acta Obstetricia et Gynecologica Scandinavica*
Manuscript ID	AOGS-20-0223.R1
Wiley - Manuscript type:	Original Research Article
Date Submitted by the Author:	06-May-2020
Complete List of Authors:	Sørbye, Ingvil; Oslo University Hospital, National Resource Centre for Women's Health Oppegaard, Kevin Sunde; Helse Finnmark HF, Klinikk Hammerfest Weeks, Andrew; University of Liverpool, International Maternal Health Sanyu Research Unit ; Marsdal, Kjersti; Oslo universitetssykehus Rikshospitalet, Department of Obstetrics Jacobsen, Anne; Oslo University Hospital, Rikshospitalet, Dept of Obstetrics
Keywords:	Induction of labor, Cesarean, Delivery, Uterine scar

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May 6th 2020

Re: AOGS-20-0223: Induction of Labor and Nulliparity: A Nation-wide Clinical Practice Evaluation

Dear Sir,

Thank you very much for your letter dated 16th April 2020, attached with a detailed reviewers' report. We are grateful for the comments and analysis.

The changes to the manuscript are highlighted using tracked changes. We have tried to facilitate the review of the changes in the Point by Point Response for the editor by referring to the page numbers and lines in the manuscript. However, the format in a Word document can change, depending on the page format and printer selected, as well as if the Word document is accessed using the Mac or Windows version. We are submitting both the Manuscript with tracked changes and the Point by Point Response in PDF format.

We have addressed the comments from the reviewers as follows:

Review comment	Authors' response	Change to manuscript
Editor		
1. The rate of primary Caesarean section in women at term with a cephalic presentation is 21.9% in this cohort. This does not include women with a previous Caesarean section. Is this rate not too high? How can you explain it?	Thank you for your comment. We would like to clarify that our study only included pregnancies with induced labour. We apologize if this was unclear in the text. In the nulliparous term cephalic group (=Robson group 2; induced labor) the CS rate was 21.9%. This is slightly lower than national figures from The Medical Birth Registry of Norway for 2017. The proportions also correspond to international literature. We have clarified the inclusion criteria in the text.	See Methods Page 7, line 10.

2. Failed IOL was observed in 21.6% of this sub-group. How can you explain such a high percentage? Please discuss this issue.	We do not perceive a failed induction of labor rate of 21.6% in women without a previous vaginal birth to be particularly high, although we would clearly aim to have a lower failed induction rate in these groups. In comparison, a Finnish study published in 2015 showed a caesarean section rate of induced nulliparous women to be nearly double – 39.1% (Kruit H et al. Management of foley catheter induction among nulliparous women: a retrospective study. BMC 2015. doi: 10.1186/s12884-015-0715-9.	
Reviewer 1		
This was a multicenter prospective observational study among women who had an induction of labour and no previous vaginal birth. The primary outcome was caesarean section. The main study factors were indication for induction and method of induction. The study was well-written and addressed a topic likely to be of interest to AOGS readers. The data presented are interesting because the current literature surrounding caesarean section rates by indication for induction of labour is sparse.	Thank you for this comment.	
The authors have not explicitly stated that their manuscript was reported according the STROBE guidelines for reporting observational studies.	Thank for this observation. We have added a sentence that states that the manuscript followed the STOBE guidelines for cohort studies. We have added a reference.	Material and Methods, Page 7, lines 11-12 Reference no. 18.
A paper that may interest the authors is: DE VRIES BS, BARRATT A, MCGEECHAN K, et al. Outcomes of induction of labour in nulliparous women at 38 to 39 weeks pregnancy by clinical indication: An observational study. Aust N Z J Obstet Gynaecol 2019;59:484-92.	Thank you for drawing our attention to this paper. We have included the paper in the Reference list and in the Discussion.	Discussion, page 11, line 27. Reference no. 26.
A sample size calculation was performed based on comparing two groups of birth units with different methods for induction of labour. The calculation is based on a difference in caesarean section rates between two methods of 25% compared with 20% but does not specify an alpha-value or power/beta-value. It also does not specify a ratio for the prevalence of the two different methods ('allocation ratio'). The calculation (presumably performed before the study commenced) estimated 2500-3000 participants would be required but the investigators estimated they would recruit 2250 participants during the study period (and only 1818 were actually recruited). Thus, the study seems to have been planned to be underpowered. Additionally, the results of the primary analysis (for the primary study factor, primary outcome measure, and the results based on the sample	We planned this study as a pilot study, as we did not know the true proportions and variation of percentage of CS according to induction regime in women without a previous delivery. It was also a pilot study in terms of methods as we used a web-based e-CRF for gathering of data. Thus, we attempted a power calculation. We defined the significance level (alpha) as 0.05 and power (beta) at 0.80. We have erroneously reported a calculation of inclusion of 2500-3000 women as necessarily. The correct number of women is 2182 (1091 in each group). All 22 departments initially agreed to participate. However, one department (Bærum Hospital, n=1550 annual births) withdrew from participation after the study start, whilst one department (n=880 annual births) were not able to register until the last month of the inclusion period. In addition, birth numbers	We have added the term "pilot" in the Title, Abstract (line 13) , Introduction, Page 6, line 24 and Material and Methods, Page 7, line 3. We have specified the correct power calculation performed. See Material and methods, Page 8, lines 8-11.

size calculation) are presented in a supplementary table, not one of the main tables. I would suggest more details are provided for the sample size calculation and why the calculation exceeded the planned study size of 2250. I think the results currently in the supplementary table (S1) should be presented in the main paper given that they are the main results of the paper based on the stated aims and sample size calculation.	were unfortunately particularly low during the autumn of 2018, as part of a general downwards trend in birth numbers in Norway. Thus, we did not manage to recruit the target number. We agree that the results of the primary results should be presented in the main table and have accommodated this.	We now present the primary analysis in Table 5 (previously named Supporting Information Table S1).
Importantly, the investigators have described the results by Robson Group allowing comparisons with other settings.	Thank you for this comment. As the Robson classification allows for comparison across countries and departments, we believe it is a useful tool for our study.	
In the discussion the study was referred to as a pilot study (page 13 line 25) but I cannot see indication in the introduction or methods that this was a pilot study.	The study was planned as a pilot study, as we did not know the proportions of CS according to induction regime in women without a previous vaginal delivery.	We have added the term "pilot" in the Title, Abstract (line 13) , Introduction, Page 6, line 24 and Material and Methods, Page 7, line 3.
Methods: I miss a definition for failed induction of labour – this is very important as there is much variation in the literature about how this should be defined.	The departments used national and/or regional protocols for the definitions of indications for CS. In the guidelines for the Norwegian OBGYN Society that most birth departments follow, the chapter "Augmentation of labour" defines start of labour as regular contractions with a cervical dilatation of ≥4 cm. (https://www.legeforeningen.no/foreningsledd/fagmed/norsk-gynekologisk-forening/veiledere/veileder-i-fodselshjelp-2014/34.-stimulering-av-rier/). The diagnosis "failed induction" is normally used for women who did not reach this stage of labour.	This has been stated in Material and Methods, Page 7, lines 15-16.
Describing the two main groups as 'term cephalic' and 'VBAC' does not seem correct as many women in the VBAC group will have a term cephalic presenting fetus. Can the authors think of an alternative name for the 'term cephalic' group?	Thank you for this comment. We have struggled to name these groups. We have changed the classification to "Nulliparous term cephalic", "Previous CS" and "Other" Alternatively, the terms "Robson group 2" , "Robson group 5" and "Other Robson groups" could be used.	Nomenclature of classification has been changed throughout text and tables/figures.
Results: A lot of the results are reported in very general terms e.g. 'one in five', 'rates were doubled', 'around half'. These terms are imprecise, and it may be better to report actual percentages.	Thank you for this comment. We have changed the general terms to the specific percentages, as suggested throughout the text, except for in the 1st paragraph in the Discussion.	
A comparison between university and non-university hospitals is presented (page 11 line 42). However, this comparison is not mentioned in the methods so far as I could see. On the other hand, the methods and sample size calculation state a planned comparison between two groups based on different methods of induction of labour. The results of this planned comparison are not presented in the results except in the supplementary table which is only	Thank you for this observation. We have added a comparison of CS rates between university and non-university hospitals in the Material and Methods. As mentioned above, we have now included the results of the planned comparison between two groups based on different methods of induction of labour in Table 5.	Added information in Material and Methods, page 7, lines 16-17. We now present the primary analysis in Table 5 (previously

referred to in the discussion. I think that this comparison should be reported in the results.		Supporting Information Table S1).
For Figure 3, it would be interesting to see a breakdown by indication for caesarean section for each category of indication for induction of labour (e.g. prolonged labour/suspected hypoxia/failed induction)	We do have data on this and have supplied it in a Supporting Information table; however, cell numbers are small.	See Supporting Information Table S1. Results, Page 9, line 16.
The authors report 42 different combinations of methods of induction of labour (page 12 line 8) but I can only see 16 combinations in Table 4. Can the authors make the reason for this clearer in the manuscript?	Thank you for this observation. To clarify, we found 42 different combinations of methods; however, this included also method sequence and dosage. In Table 4 we have grouped the most important findings.	We have clarified this in Results, Page 9, lines 25-29.
Regarding the multivariable analysis: For the results in the supplementary table, I presume logistic regression was used. Can the authors confirm if the assumption of linearity of the regression was tested and if any tests for interaction were performed? I note the models are adjusted for birthweight and pre-pregnancy BMI as continuous variables which may not be appropriate if the assumption of linearity was not met. These details could be included in the statistical section of the methods. It is plausible that low birthweight is associated with caesarean section for suspected hypoxia and high birthweight is associated with caesarean section for prolonged labour in which case birthweight is not expected to have a linear relationship with the outcome. A major limitation of the multivariable analysis is that many variables that could be associated with the outcome of caesarean section are not adjusted for (e.g. indication for induction, maternal hypertension)	Thank you for this remark. We used general linear models in logistic regression analysis frameworks and have clarified this in the manuscript. To check for linearity regarding prepregnancy BMI and birthweight we also conducted analyses with log10-transformed variables; however, the results did not change. We agree with the stated limitations to the interpretation of findings in the regression analyses. Unfortunately, this study did not have the power to adjust for indication for induction and comorbidity.	See Material and Methods, Page 8, lines 13-15. We have added a sentence to the Material and Methods, Page 8, lines 16-18.
Page 12 line 30: would it make sense to remove the words “other administration forms of”?	Thank you for this suggestion which has been implemented.	Removed wording, page 10, line 1-2.
The authors state that maternal blood loss differed between groups (page 12 line 39). I presume the groups are term cephalic and VBAC – suggest this is stated explicitly. Also, a p-value of 0.049 is quoted but I can see no indication of what test of statistical significance was performed (e.g. ttest, Wilcoxon rank sum test, or chi-squared test based on the categories on the table). Suggest the methods used are included in the statistical analysis section of the methods and made clear in the text of the results.	We found differenced in blood loss between the three obstetric groups (nulliparous term cephalic, previous CS and other groups. We used the Chi-Square test.	Added information in Material and Methods, page 8, lines 12-13. Results, page 10, line 4.

Page 12 line 44: 'Among the 7 cases of umbilical artery pH<7.00, only 2 infants had an Apgar score of less than 7 at 5"; 6/7 cases in the term cephalic group and 1/7 case in the VBAC group (the latter case diagnosed with uterine rupture).' – I found this paragraph a little confusing. It may be clearer to report the total numbers of low pH and low Apgar score separately. I don't think it's necessary to report on the frequency of low Apgars among the 7 infants with a low umbilical cord pH.	Thank you for noticing this. We have changed the paragraph for better clarity.	See changes in Results, page 10, lines 7-9.
Discussion: Page 13 Suggest insert the word 'about' before 'two out of five' (line12) and 'one out of five' (line 14). Page 13 line 25 – if this is a pilot study, suggest stating this in the title and methods – otherwise remove the word 'pilot' from the discussion. This study seems large for a pilot study.	This has been changed. See comments above.	See changes in Discussion, page 10, lines 17-18.
Page 13 line 42 – I found the sentence starting 'Other birth unit characteristics…' difficult to understand – could the authors consider rewording this?	We agree. The sentence has been deleted.	Deleted sentence, Discussion, page 10, line 30.
Minor comments/typos: Page 11 line 31 replace 'common indication' with 'common indications'	The sentence has been reworded.	See changes, page 9, line 8.
Page 11 line 33 replace 'was indication' with 'was an indication'	The sentence has been reworded.	See changes, page 9, line 8.
Page 12 line 42 replace 'group' with 'Groups'	The sentence has been reworded.	See changes, page 10, line 6.
Page 12 line 46 – I am used to 5' referring to 5 minutes and 5" referring to 5 seconds.	Thank you for correcting this point. The sentence has been reworded.	See changes, page 10, line 7.
Page 14 line 3 – could remove the words: 'that explains these numbers'.	The sentence has been reworded	See changes, page 11, line 6.
Reviewer 2		
I read with an interest of this manuscript on different methods of induction at terms for women who did not have vaginal birth before. Authors have retrieved data over the period of four months and included 1874 women. Overall, they have presented data well and message is clear. I strongly recommend them to analyze data at least for a period of one year to refine these findings more. Good luck.	We thank you for this comment and agree that we would have preferred to continue the study for a longer period. Our study was concluded after four months. We have now changed our national guidelines in order to ensure standardized induction protocols. We hope that we will at a future opportunity be able to do a new prospective national registration using the same study design, to see if the results after induction of labour change significantly.	

All authors have reviewed and approved the revisions.
Yours sincerely,

Dr. Ingvil Krarup Sørbye

Title page

Induction of Labor and Nulliparity: A Nation-wide Clinical Practice Pilot Evaluation

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Conflict of interest:

The authors state that there are no conflicts of interest in connection with this article.

Funding information:

A grant of NOK 210 000 was received from the Norwegian Medical Association's fund for quality improvement and patient safety for a one-day seminar to present and discuss the project results for all participating birth units. The Research Council at Finnmark County Hospital, Hammerfest provided a grant of NOK 123 229 for KSO's travel expenses in connection with this project.

Abstract

Introduction

Induction of labor has become an increasingly common obstetric procedure. However, in nulliparous women or women with a previous c~~a~~esarean section, induction of labor can pose a clinical challenge. Despite an overall expansion of medical indications for labor induction, there is little international consensus regarding the criteria for induction of labor, or for the recommended methods among nulliparous women. In this light, we assessed variations in the practice of induction of labor among 21 birth units in a nation-wide cohort of women with no prior vaginal birth.

Material and methods

We carried out a prospective observational pilot study of women with induced labor, and no prior vaginal birth, across ~~21 of the~~ 22 Norwegian birth units. We registered induction indications, methods and outcomes from Sept 1st – Dec 31st 2018 using a web-based case record form. Women were grouped into '~~Term cephalic~~Nulliparous term cephalic', '~~VBAC~~Previous CS' ~~(attempted vaginal birth after caesarean section~~ and 'Other Robson' (Robson groups 6, 7, 8 or 10).

Results

More than 98% of eligible women (n=1818) were included. There was a wide variety of methods used for induction of labor. In ~~term cephalic~~nulliparous term cephalic pregnancies, c~~a~~esarean section rates ranged from 11.1 - 40.6% between birth units, whereas in the ~~VBAC~~previous CS group, rates ranged from 22.7 - 67.5%. The indications 'large fetus' and 'other fetal' indications were associated with the highest c~~a~~esarean rates. Failed inductions and failure to progress in labor contributed most to the c~~a~~esarean rates. Uterine rupture occurred in two women (0.11%), both in the ~~VBAC~~previous CS group. In neonates, 1.6% had Apgar <7 at 5 minutes, and 0.4% had an umbilical artery pH <7.00.

Conclusions

C~~a~~esarean rates and applied methods for induction of labor varied widely in this nation-wide cohort of women without a prior vaginal birth. Neonatal outcomes were similar to that of normal birth populations. Results could indicate the need to move towards more standardized induction protocols associated with optimal outcomes for mother and baby.

Keywords

Labor, Induced; C~~a~~esarean Section; Delivery, Obstetric; ~~Term cephalic~~Nulliparous term cephalic;~~VBA~~ Robson, Clinical Audit.

Abbreviations

CS	c~~a~~esarean section
BMI	body mass index
GDM	gestational diabetes mellitus
IQR	interquartile range

Key Message

In induction of labor among women without a prior vaginal birth, large variations in methods used and c~~a~~esarean rates were observed in this nation-wide clinical practice evaluation.

INTRODUCTION

The worldwide rate of induction of labor has been rising steadily over the last 15 years. Currently approximately 25 % of births in high-income countries are induced. (1, 2) When faced with unfavorable factors for the mother or the baby if pregnancy continues, induction of labor can be indicated. (3) In pregnancies complicated by maternal diabetes or preeclampsia, post-term pregnancies and prolonged prelabor rupture of membranes (PROM), induction of labor compared to expectant management reduces the risk of perinatal death and maternal complications. (3-7) Over the last decades an expansion of medical indications for labor induction has occurred, including such conditions as hypertensive disorders, (5) advanced maternal age, (8) gestational diabetes (GDM) (9) and suspected large fetus for gestation. (10) Newer studies have demonstrated the safety of induction of labor without a medical indication, with fetal outcomes and caesarean section (CS) rates comparable to rates among women awaiting spontaneous labor. (11)

However, there are some concerns as to the generalizations of these findings into routine practice. First, results produced in setting with relatively high overall CS rates cannot necessarily be extrapolated to settings with average low CS rates. A clinical challenge is also posed by the considerable number of nulliparous women and women with a previous uterine scar, (12) giving birth today. ~~, pose a clinical challenge.~~ Furthermore, induction of labor is not risk-free as more interventions are performed in induced compared to spontaneous labors. (13, 14) Finally, in recent studies of induction of labor, few have used standardized and consistent protocols in terms of the methods used. There is currently no international agreement as to what is the best induction method in women without a prior vaginal birth, (1, 15) and there is large diversity in clinical practice. (1, 2)

The authors of this study considered that assessing variation in induction practices in a national sample from a setting with free universal public delivery care and low average CS rates, (16) such as Norway, might be a good start to evaluate current practices and results. The aim of this pilot study was to examine variation in indications for induction of labor, methods and associated CS prevalence among women with no previous vaginal birth across 21 birth units nationwide. We used the Robson classification framework to distinguish women with ~~term cephalic~~nulliparous term cephalic pregnancies versus those with a previous uterine scar attempting a vaginal birth after caesarean section.~~V~~ (17) Ultimately, we aimed to identify practices associated with the best outcomes in terms of maternal and neonatal safety to inform obstetric providers.

MATERIAL AND METHODS

We carried out a prospective pilot registration of women undergoing induction of labor with a live fetus beyond 23 completed gestational weeks and with no prior vaginal birth between September 1st - December 31st 2018. We invited Norwegian obstetric departments with >1000 annual births to participate in the study. Out of 22 eligible units, 21 units were included (Supplementary Figure A). Participating units selected women whose labor was to be induced and decided upon the method(s) according to local practices, guidelines and definitions. Out-patient induction of labor was not practiced. Anonymous individual patient data were prospectively registered by clinicians in each department into a web-based electronic case record form. Only women with induction of labor were included. The number of nulliparous women without a previous birth and the induction rate during the period was also reported. The paper is reported using the STROBE guidelines for cohort studies.(18) Data were stored in Services for Sensitive Data, University of Oslo, Norway. The project is registered in ClinicalTrials.gov, no. NCT03730220.(19)

The primary outcome was the occurrence of caesarean section (CS) according to indication for induction and method of induction, stratified by ~~Robson~~obstetric group~~s~~. Indications for CS were defined according to national/regional guidelines. We also assessed CS rates according to level of birth unit (university hospital or not). Secondary outcomes included uterine rupture, estimated maternal blood loss, adverse neonatal outcomes and the time interval from drug administration to birth. Estimated postpartum blood loss ~~during labor and until 2 hours postpartum~~ in ml was reported in categories. Adverse neonatal outcomes were defined as a composite outcome of Apgar score <7 at 5 minutes and/or transfer to neonatal intensive care unit and/or pH in umbilical artery <7.10 within one hour of birth.

We categorized cases into three groups. These were: "Nulliparous ~~nulliparous~~ term cephalic" (Robson 2), "Previous CS" (classified as Robson 5: multiparous women with a previous uterine scar, ~~no previous vaginal birth and~~with a single cephalic term pregnancy; however with no previous vaginal birth), and "Other Robson" (including Robson groups 6 and 7: women with a single breech pregnancy; Robson group 8: women with multiple pregnancies, and Robson group 10: women with a single cephalic pregnancy < 37 weeks' gestation). ~~'Term cephalic' (Robson group 2); 'VBAC' (attempted vaginal birth after caesarean section; Robson group 5: multiparous women with previous uterine scars with a single cephalic term pregnancy) and 'Other Robson groups' (including Robson groups 6 and 7: women with a single breech pregnancy, including previous CS; Robson group 8: women with multiple pregnancies, including previous CS and Robson group 10: women with a single cephalic pregnancy < 37 weeks' gestation, including previous CS).~~

The indication for induction was categorized into 12 groups: Postdates (as defined locally; latest 42+0), PROM, preeclampsia/hypertension, intrauterine growth restriction (IUGR)/oligohydramnios, insulin-treated diabetes in pregnancy including insulin-treated GDM~~)~~, non-insulin treated GDM, suspected large fetus, reduced fetal movements, intrahepatic cholestasis of pregnancy, maternal request, 'other maternal' and 'other fetal'. The starting method for induction was categorized as Foley balloon catheter, misoprostol (oral, vaginal insert or vaginal tablet), or dinoprostone. As according to the protocol, we performed three comparisons: induction regime with Foley balloon catheter versus no catheter; induction regime including misoprostol vaginal insert versus other misoprostol administration forms, and induction regime including dinoprostone versus misoprostol.

Other covariates included maternal age in categories, pre-pregnancy body mass index (BMI) (< 30 or ~~BMI~~ ≥30), gestational age at induction, Bishop score at induction (≤5, >5 or missing), epidural, infant birthweight and tachysystole (>5 contractions per 10" with abnormal fetal tracing).

Statistical analysis

A statistical analysis plan ~~was completed before analysis.~~included a~~A~~ power analysis. A~~a~~ssuming two groups of birth units with different induction methods resulting in a difference in CS rate between 20 to 25%, a significance level (α) of 0.05, and 80% power (β), the study would ~~would~~ need ~~2500 – 3000~~2182 participants~~patients~~. Applying the inclusion criteria, we estimated 2250 births during the period. (20) Baseline characteristics and outcomes were summarized according to the obstetric group. Small cell numbers (n<10) were censored when calculating CS rates. For categorical outcomes we compared proportions with 95% CI with the Chi-Square test and/or Fisher's exact test. We estimated the risk of CS by logistic regression analysis in ~~in~~ generalized linear models adjusting for confounders as identified in the literature and according to biological plausibility, estimating crude and adjusted effect estimates as odds ratios (OR) with 95% CI with corresponding p-values. To check for linearity regarding continuous covariates, we also conducted analyses with log-transformed variables; however, the results did not change. We restricted analyses to ~~term cephalic~~nulliparous term cephalic and ~~VBAC~~previous CS only due to small cell numbers. In sub analyses of CS deliveries only, we determined indications for the procedure and the subtype (type 1- immediate delivery; type 2- within 20-30 minutes or type 3 - within a given timeframe >30 min < 8 hours). Calculated *P*-values were two-sided and compared to a 5% significance level. Statistical analyses were performed in SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.)

Ethical approval

All women received oral and written information about the study. As routine data were gathered anonymously, informed consent was waivered; however, women were able to opt out of the study upon

request. The project was approved by the Norwegian Ethics Board, Region Health South East C, reference 2018/1087 and each hospital's Data Protection Officer.

RESULTS

During the study period, a total of 7160 women without a prior vaginal birth gave birth in the 21 participating departments. Among these, labor was induced in 1874 women (26.2%; range 11.7-34.3% between hospitals). Of all 1874 eligible women for inclusion in the study,1818 (98.5%) were included (Figure 1). Most birth units had a written induction protocol; however, most were not differentiated according to their Robson group.

~~Term cephalic~~Nulliparous term cephalic pregnancies constituted 80.4% of births, followed by ~~VBAC~~previous CS pregnancies (12.2%) (Table 1). The "Other Robson' group included 52 twin pregnancies ~~classified in ((~~2.9%), 59 preterm births ~~classified in ((~~3.2%) and 25 planned breech births (1.4%). ~~One in five women~~Overall, 20.3% ~~were~~as aged 35 years or more and 18.4%~~. Similarly, one in five women~~ had a pre-pregnancy BMI of 30 or more. ~~The proportion of women with an unripe cervix did not differ between groups.~~ Of all women, 16.6% had a registered comorbidity where preeclampsia/hypertension was most prevalent. PROM, postdate pregnancy and preeclampsia/hypertension were the most common indications for induction~~, and comprised around half of all inductions.~~ Maternal request was an indication for induction in only 3.5% of women.

In the ~~term cephalic~~nulliparous term cephalic group, one in five women gave birth by CS, whereas rates were doubled in the ~~VBAC~~previous CS group and in the ~~"~~O~~O~~ther Robson~~"~~ group (Table 2). Hospital CS rates varied between 9.4% and 45.5% in the ~~term cephalic~~nulliparous term cephalic group and between 31.3% and 54.5% in the ~~VBAC~~previous CS group (Figure 2). In the whole cohort, university hospital CS rates did not differ significantly from non-university hospitals (24.2% vs 26.8%, *P*=0.22). In the ~~term cephalic~~nulliparous term cephalic group CS rates by indication for the induction of labor ranged from 11.1 to 40.6%, whereas in the ~~VBAC~~previous CS group rates were overall higher and ranged from 22.7 to 67.5% (Figure 3; Table S1.). In the ~~term cephalic~~nulliparous term cephalic group 'non-insulin GDM', 'other fetal' and 'large fetus' were the indications associated with the highest CS rates (40.6-33.3%). In the ~~VBAC~~previous CS group 'large fetus', 'insulin-treated diabetes' and 'other fetal' were associated with the highest CS rates (62.5-60.0%).

The most common CS indication was suspected fetal hypoxia in the ~~term cephalic~~nulliparous term cephalic group, and failed induction in the ~~VBAC~~previous CS group (Table 3). Of all c~~a~~esarean procedures, 9.2% were reported as grade 1 (immediate) (Table 3). Overall 2.1% of women in the ~~term cephalic~~nulliparous term cephalic group and 3.6% of the ~~VBAC~~previous CS group experienced an immediate CS. Suspected uterine rupture or abruptio placentae were indications for seven (0.4%) c~~a~~esarean procedures.

The most common methods for induction are presented in Table 4. ~~Altogether, more than 42 different combinations were registered among the 1818 women, not taking into account different modes of administration of misoprostol. The most common initial method was Foley catheter (59.7%) followed by misoprostol (28.2%) and amniotomy+/- oxytocin (7.2%).~~ In the ~~term cephalic~~nulliparous term cephalic group, a combination of Foley + ~~vaginal insert~~ misoprostol was the most common initiation method (37.3%), followed by Foley + ~~oral misoprostol~~amniotomy/~~oxytocine~~oxytocin (11.9%) (Table 4). In the ~~VBAC~~previous CS group, most women~~one third of women~~ received Foley + dinoprostone (34.4%), ~~as the most common method,~~ followed by Foley + amniotomy/~~ and/or~~ oxytocin.~~ Amniotomy as part of the induction was recorded in 46.9% in the term cephalic group and in 52.2% in the VBAC group, whereas oxytocin as an induction agent was used in 31.7% and 36.7% correspondingly.~~ However, altogether, more than 40 different method combinations and sequences were registered.

Use of Foley catheter was associated with birth by CS in the ~~term cephalic~~nulliparous term cephalic group (aOR 1.78, 95% CI 1.16-2.59, p=0.008), but not in the ~~VBAC~~previous CS group (aOR 0.63, 95% CI 0.19-2.07, *P*=0.45) (~~Supplementary~~ Table 5~~A~~). Use of dinoprostone showed a borderline significant association with birth by CS compared to ~~other administration forms of~~ misoprostol in crude, but not in adjusted analyses. There was no association between route of administration of misoprostol and risk of CS (data not shown).

Uterine rupture occurred in two women (0.11%), both in the ~~VBAC~~previous CS group (Table 6~~5~~). Maternal blood loss differed between groups (p=0.049, Chi-Square); however, tachysystole did not. The composite adverse infant outcome occurred in 9.5% and 10.0% in the ~~around one out of ten deliveries in term cephalic~~nulliparous term cephalic and the previous CS group respectively~~and VBAC births~~. A higher proportion (30.9%) was found in the Other Robson groups due to more transfers to the neonatal ward due to prematurity. Overall ~~Among the~~29 infants (1.6%) had an Apgar score of less than 7 at 5'. Seven infants (0.4%) had ~~7 cases of~~ an umbilical artery pH<7.00, of whom ~~, only 2 infants had an Apgar score of less than 7 at 5"; 6/7 cases in the term cephalic group and 1/7 case in the VBAC group (the latter case diagnosed with uterine rupture). Only~~ one infant ~~out of the seven infants with pH <7.00~~ was transferred to the neonatal ward. The method of induction was not ~~significantly~~ associated with adverse maternal or neonatal outcome.

Among ~~term cephalic~~nulliparous term cephalic births, 26.5% were still undelivered 48 hours after ~~start of~~ induction start, as were 31.6% in the ~~VBAC~~previous CS group and 26.5% in the Other Robson group (data not shown). In the three groups ~~M~~median duration from start of induction to birth ~~in the~~ were ~~term cephalic group was~~ 32.6 hours (IQR 31.8), ~~in the VBAC group~~ 34.1 hours (IQR 35.1) ~~and in the Other Robson group~~ and 30.6 hours (IQR 32.6), respectively.

DISCUSSION

Our study showed large variations in the practice and results of induction of labor in this nation-wide sample. The frequency of CS after induction of labor was highest in the ~~VBAC~~previous CS group, where about two out of five ~~-~~women gave birth by CS and lowest in the ~~term cephalic~~nulliparous term cephalic group, where about one out of five ~~-~~women gave birth by CS. CS rates after induction differed widely between units. CS performed due to failed induction of labor and prolonged first stage of labor accounted for nearly half of all CS ~~in our study group~~. Our study ~~also~~ found a wide variation of induction methods, with few units using standard induction protocols. Maternal and fetal safety outcomes were comparable to existing literature.

The strengths of this pilot study include the nation-wide prospective design with more than 98% of eligible women included. We had access to detailed information regarding indications, the ~~different~~ methods used, including the order and route of administration, as well as important safety and efficiency outcomes.

One of the limitations of the study is that we lacked control data from induced multiparous women as well as on spontaneous labors. For this reason, we cannot comment on whether induction increases the rate of CS or adverse outcomes compared to spontaneous birth. Furthermore, we lacked detailed data on the local birth units, such as the number of referrals, socioeconomic spread etc. that might influence outcomes in terms of mode of birth. In the ~~VBAC~~previous CS group we lacked information regarding the previous birth. ~~Other birth unit characteristics than methods diversities than induction methods might have affected CS rates, such as unregistered maternal or fetal comorbidities.~~ However, CS rates were slightly lower in tertiary referral university hospitals compared to non-university hospitals, where an accumulation of risks would be expected. Finally, our observational design does not warrant causal inference.

Induction by “large fetus” indication revealed high rates of CS in our study. However, the CS rate at 33.3% is similar to other studies of induction in woman with ‘large babies. In the comprehensive study by Boulvain et al, (10) there was a CS rate of 28%, even though 53% were parous. These rates might be the result of a high gestational age in combination with maternal diabetic comorbidity ~~that explains these numbers~~. GDM non-insulin comorbidity had the highest CS rate whereas insulin-treated pregestational or gestational diabetes comorbidity had a relatively low CS rate in ~~term cephalic~~nulliparous term cephalic pregnancies. In Norway, insulin users are induced between week 38 and 40, but non-insulin GDM are induced primarily on additional indications. (21)

“Other fetal indication” for induction of labor had one of the highest CS rates in both nulliparous term cephalic and previous CS pregnancies. This is a mixed group including fetal malformations,

polyhydramnios, non-reassuring antenatal fetal tracing and unknown gestational length. Polyhydramnios may give insufficient contractions due to an over distended uterus (22) and non-reassuring fetal tracing have to be handled with care; delivery, rather than expectant management is preferred, if it continues. The group "maternal request" was surprisingly low with 3.5 % of all inductions and we found a low CS rate both in the ~~term cephalic~~nulliparous term cephalic and the ~~VBAC~~previous CS group. This is lower than previously reported. (23) The distinction between 'maternal request' or 'medical problem' can be a fine one, especially when considering mental health and pregnancy complaints. However, this finding indicates a restrictive attitude among providers, in contrast to upcoming trends elsewhere. (24)

The overall proportion of failed induction and prolonged first stage was unexpectedly high in our sample. However, as 27-32% of women were undelivered 48 hours after the start of induction, this is not likely to reflect a use of rigid time limits. The 22-35% rate of failed induction/poor progress in the first stage that we found in our sample might imply a practice emphasizing safety rather than effectiveness. This is also reflected in a relatively low uterine rupture rate, a low tachysystole rate of 5% and few immediate CS procedures.

At present, there are conflicting reports of how and when induction of labor should be offered to women. Trials have been conducted among women at term with no medical indication. (11, 25, 26) These randomized trials indicate no major safety concerns in terms of the CS risk or adverse infant or maternal outcomes. In addition, although the ARRIVE trial has been criticized as including many overweight and obese women, (27) the 18.6% CS rate in the ~~ARRIVE~~ trial's ~~-~~induced group (who were all low risk nulliparous women) is similar to the 16.7% rate seen in 'maternal request' in the ~~term cephalic~~nulliparous term cephalic group in our study. A Cochrane review looking at induction at 40 weeks versus expectant management found improved outcomes in the induction group, except for a higher operative vaginal delivery rate. (3) However, a prerequisite in generalizing findings is that the induction process and labor is well managed with the necessary staff at hand. Like most high-resource countries, Norway has a rapidly increasing induction rate that reached 23% of all births in 2018 (20), but at the same time, overall CS rates - 16.0% in 2017 – are ~~very low,~~ the second lowest rate across the OECD area (16). However, CS rates vary considerably between regions beyond what can be expected due to case-mix. (28) A national induction guideline lists medical indications and methods, but leaves the choice among these methods to individual departments and staff. (21) In this clinical practice evaluation, we found that multiple induction protocols are used even within ~~term cephalic~~nulliparous term cephalic and ~~VBAC~~previous CS groups. What this means is that women across the country do not have similar treatment when undergoing induction of labor.

Translating RCT evidence into practical clinical protocols can be challenging in obstetric units facing logistical restraints such as delays in timely administration of uterotonics and performing rupture of

membranes. (29) Results from practice evaluations are therefore important to inform decisions in induction regimes tailored to specific groups. Women should be offered joint decision making based on these facts. Careful selection of women for induction who have previously had a caesarean section, as well as taking women's personal preferences into account, are important factors in a pragmatic induction of labor protocol.

CONCLUSION

A wide variation of induction methods and CS rates after induction, as well as a high rate of failed inductions in women without a prior vaginal birth, points to a potential for improvement by moving towards more standardized protocols. The Robson groups provide a framework for the counselling of women about particular risks and benefits regarding induction of labor while working towards shared decision-making.

Acknowledgements

We are indebted to our dedicated obstetrician and midwife collaborators in the National Induction Group at the participating birth units who made this study possible: Ines Panadero at Akershus University Hospital, Nina Marie Albretsen at Arendal Hospital, Kristin Hestvold at Drammen Hospital, Mette Kristine Hjertaas at Førde Hospital, Anja Holstad at Gjøvik Hospital, Line Olufsen-Melhus at Hammerfest Hospital, Kristin Urnes at Haugesund Hospital, Chen Sun at Haukeland University Hospital, Marte Eline Ween-Velken at Kristiansand Hospital, Dordi Bogfjellmo at Levanger Hospital, Jakob Nakling and Ida Olsen Hokland at Lillehammer Hospital, Kristin Skogøy at Nordland Hospital, Bodø, Anja Halleraker and Marianne Omland at Oslo University Hospital Rikshospitalet, Hilde Sellevoll and Marit Småvik Johansen at Oslo University Hospital Ullevål, Kjersti Skoe at Telemark Hospital, Ewa Margas at Tønsberg Hospital, Åse Torunn Pettersen at University Hospital of North Norway, Malin Dögl at St. Olavs University Hospital, Trondheim , Erik Andreas Torkildsen at Stavanger University Hospital, Katrine Sjøborg Dønvold and Lotte Martine Jacobsen at Østfold Hospital and Åse Turid Rossevatn Svoren at Ålesund Hospital.

Tweetable abstract:

There is considerable variation in outcomes after induction of labor, depending on where a primiparous woman chooses to have her birth.

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Legends of supporting information

~~Supporting Information Table S1 Method and risk of caesarean section among women in the term cephalic and VBAC groups.~~

Supporting Information Figure 1 Map of participating birth units in Norway.

Legends of Tables and Figures

Table 1 Maternal characteristics in 1818 women with no prior vaginal birth undergoing induction of labor.

Table 2 Delivery mode after induction of labor in 1818 women with no prior vaginal birth according to obstetric group.

~~Table 2 Delivery mode in term cephalic, VBAC and Other Robson groups in women with no prior vaginal delivery~~

Table 3 Main indication and subtype of 459 c~~a~~esarean sections[1] after induction of labor according to obstetric group.~~in term cephalic, VBAC and Other Robson groups.~~

Table 4 Induction methods in 1818 women with no prior vaginal birth according to obstetric group. ~~term cephalic, VBAC and Other Robson groups in 1818 women with no prior vaginal birth.~~

Table 5 Method and risk of cesarean section in nulliparous term cephalic and previous CS pregnancies after induction of labor.

Table 6 Maternal and fetal secondary outcomes after induction of labor according to obstetric groups.~~Table 5 Maternal and fetal secondary outcomes in term cephalic, VBAC and Other Robson groups for 1818 women with no prior vaginal birth.~~

Supporting information Table S1. Indication for induction according to indication for CS in three obstetric groups.

Figure 1 Flowchart of study participants

Figure 2 Proportions of caesarean section after induction of labor by delivery unit in the term cephalicnulliparous term cephalic (a) and VBACprevious CS pregnancies (b).

Figure 3 Caesarean section rates according to indication for induction of labor in Term cephalicnulliparous term cephalic and VBACprevious CS groupspregnancies.

Tables

Table 1 Maternal characteristics in 1818 women with no prior vaginal birth undergoing induction of labor.

	All		~~Term cephalic~~Nulliparous term cephalic		~~VBAC~~Previous CS		Other Robson	
	n	%	n=1461	%	n=221	%	n=136	%
Maternal age (years)								
16-24	246	13.5	222	15.2	15	6.8	9	6.6
25-34	1203	66.2	956	65.4	149	67.4	98	72.1
35-54	369	20.3	283	19.4	57	25.8	29	21.3
BMI prepregnancy[1]								
<30	1458	81.6	1185	82.3	160	74.8	113	85.0
>= 30	328	18.4	254	17.7	54	25.2	20	15.0
Bishops score[2]								
0-5	1366	82.8	1077	81.8	185	88.9	104	83.2
6-10	284	17.2	240	18.2	23	11.1	21	16.8
Birth at University hospital								
Yes	1173	64.5	957	65.5	124	56.1	93	68.4
Gest. age median (IQR)	40+1 (21)		40+3 (18)		40+0 (18)		36+5 (16)	
Maternal comorbidity[3]								
IDDM/GDM insulin	137	7.5	105	7.2	22	10.0	10	7.4
GDM, non-insulin	91	5.0	74	6.4	7	3.2	10	7.4
Preeclampsia/ hypertension	238	13.1	189	12.9	13	5.9	37	27.2
Intrahepatic cholestasis	34	1.9	25	1.7	6	2.7	3	2.2
Another comorbidity	272	15.0	210	14.4	39	17.6	23	5.9
Decision induction								
Consultant	1181	65.0	897	61.4	162	72.4	123	90.4
Resident	534	29.4	472	32.3	49	22.2	13	9.6
Midwife	103	5.7	93	6.4	10	4.5	0	0
Main indication for induction								
PROM	357	19.3	286	19.6	47	21.3	24	17.6
Postdates	336	18.5	299	20.5	33	14.9	4	2.9
Preeclampsia/hypertension	279	15.3	228	15.6	17	7.7	34	25.0
IUGR/oligohydramnios	280	15.4	231	15.8	24	10.9	25	18.4
IDDM/GDM - insulin	97	5.3	81	5.5	13	5.9	3	2.2
Large fetus	67	3.7	45	3.1	16	7.2	6	4.4
Maternal request	61	3.5	36	2.5	22	10.0	3	2.2
GDM, non-insulin	35	1.9	32	2.2	3	1.4	0	0
Intrahepatic cholestasis	43	2.4	35	2.4	5	2.3	3	2.2
Reduced fetal movements	40	2.2	36	2.5	3	1.4	1	0.7
Other maternal[4]	164	9.0	101	6.9	33	14.9	30	22.1
Other fetal[5]	59	3.2	51	3.5	5	2.3	3	2.2

~~Term cephalic~~Other Robson includes Robson groups 6, 7, 8 and 10. BMI= Body Mass Index. IQR=interquartile range. IDDM=insulin-dependent diabetes mellitus. GDM=gestational diabetes mellitus. PROM=prelabor rupture of membranes. IUGR=intrauterine growth restriction.[1]Missing 1.8%. [2]Not assessed in 9.2%. [3]More than one condition might be registered. [4]Incl. twin pregnancy, previous obstetric history, chronic disease, prolonged latency phase, vaginal bleeding. [5]incl. polyhydramnios, non-reassuring fetal tracing, known malformations, unknown gestational length.

Table 2 Delivery mode after induction of labor in 1818 women with no prior vaginal birth according to~~in term cephalic, VBAC and Other Robson groups in women with no prior vaginal delivery~~ obstetric group.

		Caesarean section[1]			Operative vaginal			Spontaneous vaginal		
	N	n	%	95% CI	n	%	95% CI	n	%	95% CI
~~Term cephalie~~Nulliparous term cephalic	1461	320	21.9	19.8-24.1	314	21.5	19.4-23.7	827	56.6	54.0-59.2
~~VBAC~~Previous CS	221	89	40.3	33.7-47.1	40	18.1	13.3-23.8	92	41.6	35.1-48.4
Other Robson	136	50	36.8	28.9-45.8	28	20.6	14.2-28.6	60	44.1	35.9-53.2
All	1818	459	25.2	23.3-27.3	382	21.0	19.2-23.0	979	53.9	51.5-56.2

~~"Term cephalic"~~Other~~"~~ Robson includes Robson groups 6, 7, 8 and 10. [1]Including caesarean section second twin.

Table 3 Main indication and subtype of 459 cesarean sections[1] after induction of labor according to obstetric group.~~Table 3 Main indication and subtype of 459 caesarean sections[1] in term cephalic, VBAC and Other Robson groups.~~

	All		~~Term cephalie~~Nulliparous term cephalic		~~VBAC~~Previous CS		Other Robson	
	n=459	%	n=320	%	n=89	%	n=50	%
Main caesarean indication								
Prolonged 1.stage	117	25.5	85	26.6	23	25.8	9	18.8
Prolonged 2. stage	26	5.7	19	5.9	4	4.5	3	6.5
Susp. fetal hypoxia	143	31.2	112	35.0	19	21.3	12	25.0
Failed induction	109	23.7	69	21.6	31	34.8	9	18.8
Uterine rupture	2	0.4	0	0	2	2.2	0	0
Abruptio placentae	5	1.1	3	0.9	1	1.1	1	2.1
Other	55	12.0	31	9.7	10	11.2	14	29.2
Subtype								
Type 1 (immediate)	42	9.2	30	9.4	8	9.0	6	12.0
Type 2 (<20 minutes)	234	51.0	172	53.8	36	40.4	26	52.0
Type 3 (>20 minutes)	181	39.4	118	36.9	45	50.6	18	36.0

[1]Including caesarean section of second twin only (n=2). ~~"Term cephalic"~~Other~~"~~ Robson includes Robson groups 6, 7, 8 and 10.

Table 4 Induction methods in 1818 women with no prior vaginal birth according to obstetric group. ~~Table 4 Induction methods in term cephalic, VBAC and Other Robson groups in 1818 women with no prior vaginal birth.~~

	All		~~Term cephalic~~Nulliparous term cephalic		~~VBAC~~Previous CS		Other	
Induction method	N=1818	%	N=1461	%	N=221	%	N=136	%
Foley start combinations								
Foley alone	135	7.4	102	7.0	19	8.6	14	10.3
Foley + oral misoprostol ± AT/oxytocin	191	10.5	178	12.2	4	1.8	9	6.6
Foley + insert misoprostol ± AT/oxytocin	198	10.9	190	13.0	1	0.5	7	5.1
Foley + vaginal misoprostol ± AT/oxytocin	213	11.7	177	12.1	11	5.0	25	18.4
Foley + dinoprostone ± AT/oxytocin	108	5.9	28	1.9	76	34.4	4	2.9
Foley ± AT/oxytocin	241	13.3	174	11.9	49	22.2	18	13.2
Misoprostol start combinations								
Oral misoprostol alone	118	6.5	107	7.3	1	0.5	10	7.4
Oral misoprostol ± AT/oxytocin	45	2.5	41	2.8	0	0	4	2.9
Insert misoprostol alone	67	3.7	66	4.5	0	0	1	0.7
Insert misoprostol ± AT/oxytocin	29	1.6	28	1.9	0	0	1	0.7
Vaginal misoprostol alone	165	9.0	148	10.1	3	1.4	14	10.3
Vaginal misoprostol ± AT/oxytocin	88	4.8	79	5.4	1	0.5	8	5.9
Other combinations								
Dinoprostone alone	39	2.1	9	0.6	26	11.8	4	2.9
Dinoprostone ± AT/oxytocin	11	0.6	2	0.1	8	3.6	1	0.7
Amniotomy ±oxytocin	130	7.2	103	7.0	19	8.6	8	5.9
Any misoprostol/dinoprostone + successive Foley ± AT/oxytocin	24	1.3	17	1.2	3	1.4	4	2.9
Other	16	0.9	12	0.8	0	0	4	2.9

~~Term cephalic~~Other Robson includes= Robson groups 6, 7, 8 and 10. AT=amniotomy.

Table 5 Method and risk of cesarean section in nulliparous term cephalic and previous CS pregnancies after induction of labor.

	Proportion CS		Risk of Caesarean section					
	CS	%	OR	95% CI	p	aOR[2]	a95% CI[2]	P[2]
1. Foley[1] (n=1356)								
Nulliparous term cephalic								
Foley catheter	212	25.2	1.55	1.13-2.13	0.007	1.78	1.16-2.59	0.008
No Foley catheter	61	17.9	1			1		
Previous CS								
Foley catheter	60	40.3	1.08	0.46-2.54	0.86	0.63	0.19-2.07	0.45
No Foley catheter	10	38.5	1			1		
2. Dinoprostone vs misoprostol (n=1195)								
Nulliparous term cephalic								
Dinoprostone	14	34.1	1.80	0.93-3.49	0.082	1.49	0.74-3.01	0.26
Misoprostol	230	22.4	1			1		
Previous CS								
Dinoprostone	49	47.1	1.29	0.51-3.27	0.60	1.47	0.54-3.99	0.46
Misoprostol	9	40.9	1			1		

[1]Excluding women with prelabor rupture of membranes. [2]Adjusted for maternal age groups 16-24, 25-34 (ref), ≥35; prepregnancy BMI, Bishop score ≤5 (ref), >5 and missing; Foley catheter yes/no, and birthweight in grams.

Table 6 Maternal and fetal secondary outcomes after induction of labor according to obstetric groups. ~~Table 5 Maternal and fetal secondary outcomes in term cephalic, VBAC and Other Robson groups for 1818 women with no prior vaginal birth.~~

	All		~~Term cephalic~~Nulliparous term cephalic		~~VBAC~~Previous CS		Other	
Maternal	n	%	N	%	n	%	n	%
Uterine rupture	2	0.1	0	0	2	0.9	0	0
Tachysystole	96	5.3	79	5.4	10	4.5	7	5.1
Epidural	1355	74.5	1090	74.6	157	71.0	108	79.4
Blood loss in ml								
<500	1051	57.8	863	59.1	120	54.3	68	50.0
500-999	552	30.4	439	30.0	69	31.2	44	32.4
1000-1999	178	9.8	135	9.2	24	10.9	19	14.0
2000-2999	33	1.8	22	1.5	6	2.7	5	3.7
3000+	4	0.2	2	0.1	2	0.9	0	0
Fetal[1]								
Mean birthweight in grams(SD)	3485	(597)	3513	(550)	3664	(522)	2887	(808)
Adverse neonatal outcome[2]	203	11.2	139	9.5	22	10.0	42	30.9
Transfer NICU	132	7.4	85	5.9	10	4.6	37	27.6
Apgar <~~7~~5 at ~~5~~7 minutes	29	1.6	20	1.4	7	3.2	2	1.5
pH art umb <7.10[3]	72	4.0	59	4.0	9	4.0	4	2.9
pH art umb <7.00[3]	7	0.4	6	0.4	1	0.5	0	0

~~Term cephalic~~Other Robson includes ~~=~~ Robson groups 6.7.8.and 10. [1]Outcomes for first twin only. SD= standard deviation. [2]Adverse neonatal outcome incl. pH arteria umbilicalis <7.10 and/or Apgar score at 5~~'~~'' <7 and/or transfer neonatal intensive care unit. NICU= neonatal intensive care unit excluding planned transfers (n=18). [3]Missing 19.5%.

Figures

Figure 1 Flowchart of study participants

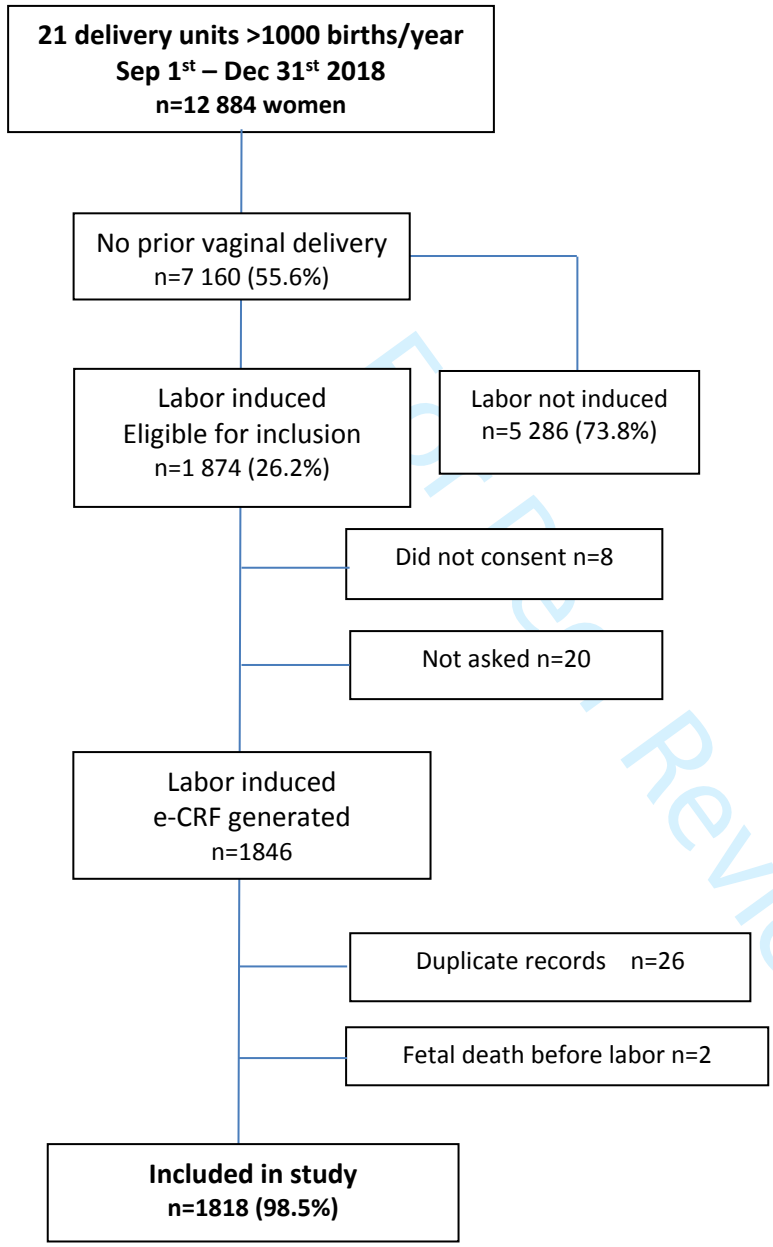
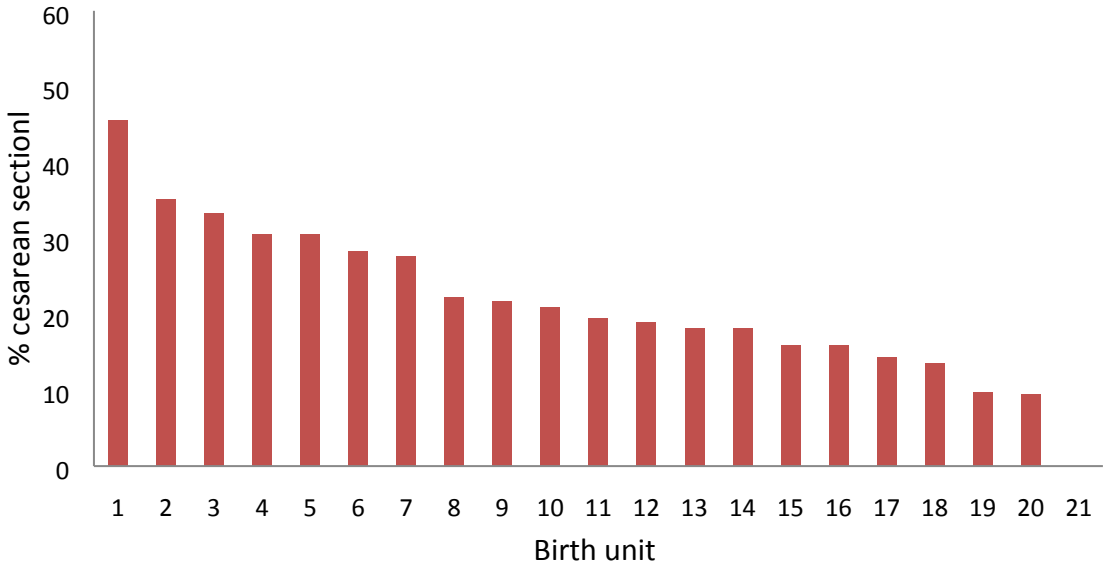
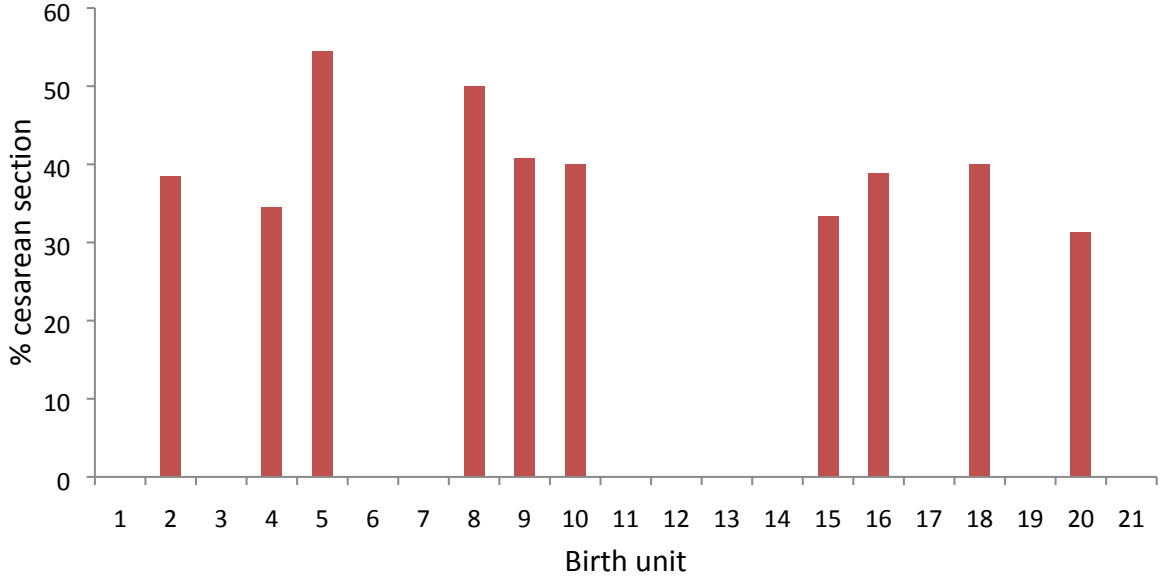


Figure 2 Proportions of cesarean section after induction of labor by delivery unit in nulliparous term cephalic (a) and previous CS pregnancies (b).~~Figure 2.~~
~~Proportions of caesarean section by delivery unit in the term cephalic (a) and VBAC pregnancies (b).~~

(a) ~~Term cephalic~~Nulliparous term cephalic

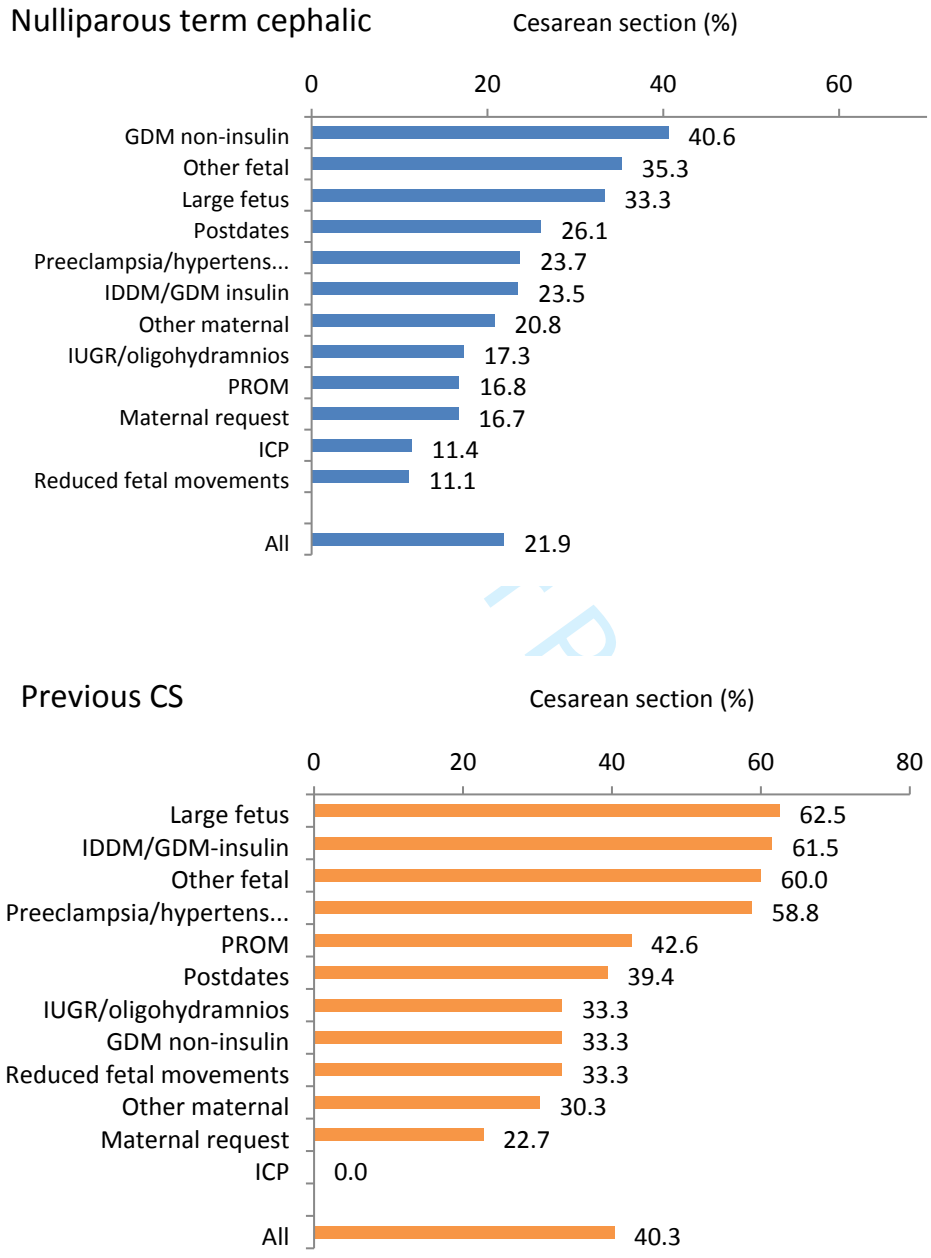


(b) ~~VBAC~~Previous CS



~~Term cephalic~~Other Robson includes~~=~~ Robson groups 6, 7,8 and 10. Results from delivery units with n<10 deliveries per cell are censored.

Figure 3 Cesarean section rates according to indication for induction of labor in nulliparous term cephalic and previous CS pregnancies. ~~Figure 3 Caesarean section rates according to indication for induction of labor in Term cephalic and VBAC groups~~



~~Term cephalic~~GDM= gestational diabetes mellitus; IDDM= insulin-dependent diabetes mellitus; IUGR=intrauterine growth restriction; PROM=prelabor rupture of membranes; ICP= intrahepatic cholestasis of pregnancy.

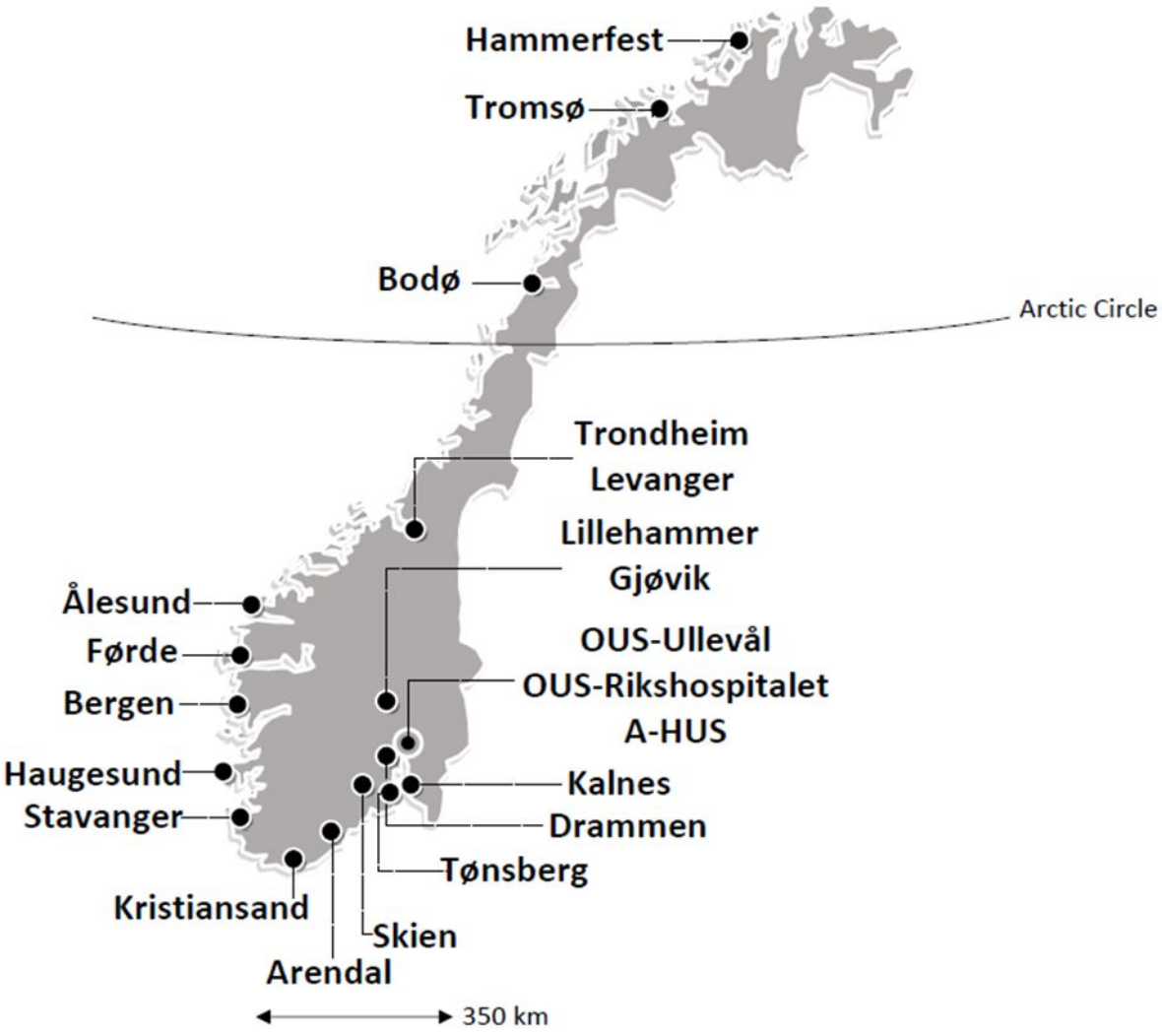
Supporting information Table S1. Indication for induction according to indication for CS in three obstetric groups.

Nulliparous term cephalic		Prolonged 1st stage	Prolonged 2nd stage	Fetal hypoxia	Failed induction	Uterine rupture	Abruptio placenta	Other	Total
Indication	Postdates	27	6	24	13	1	1	6	78
	PROM	14	5	17	6	0	0	6	48
	Preeclampsia/hypertension	10	4	17	13	0	0	10	54
	IUGR/oligohydramnios	9	0	19	9	0	2	1	40
	IDDM/GDM-insulin	1	1	6	11	0	0	0	19
	GDM, non-insulin	5	0	6	1	0	0	1	13
	Other maternal	4	1	8	6	0	0	2	21
	Reduced fetal movements	0	0	3	1	0	0	0	4
	Intrahepatic cholestasis	2	0	1	0	0	0	1	4
	Maternal request	2	1	1	0	0	0	2	6
	Suspected large fetus	6	1	3	4	0	0	1	15
	Other fetal	5	0	7	5	0	0	1	18
	Total	**85**	**19**	**112**	**69**	**1**	**3**	**31**	**320**
Previous CS		Prolonged 1st stage	Prolonged 2nd stage	Fetal hypoxia	Failed induction	Uterine rupture	Abruptio placenta	Other	Total
Indication	Postdates	4	0	3	4	0	0	2	13
	PROM	5	0	3	8	0	0	4	20
	Preeclampsia/hypertension	3	0	2	4	1	0	0	10
	IUGR/oligohydramnios	2	0	3	3	0	0	0	8
	IDDM/GDM-insulin	1	1	2	3	0	1	0	8
	GDM, non-insulin	1	0	0	0	0	0	0	1
	Other maternal	3	0	1	5	0	0	1	10
	Reduced fetal movements	1	0	0	0	0	0	0	1
	Maternal request	2	0	1	1	0	0	1	5
	Suspected large fetus	1	3	2	2	0	0	2	10
	Other fetal	0	0	2	1	0	0	0	3
Total		**23**	**4**	**19**	**31**	**1**	**1**	**10**	**89**
Other (Robson 6,7,8,10)		Prolonged 1st stage	Prolonged 2nd stage	Fetal hypoxia	Failed induction	Uterine rupture	Abruptio placenta	Other	Total
Indications	Postdates	0	0	2	1	0	0	1	4
	PROM	2	1	0	0	0	1	2	6
	Preeclampsia/hypertension	1	0	3	1	0	0	4	9
	IUGR/oligohydramnios	0	0	4	1	0	0	4	9
	IDDM/GDM-insulin	2	0	0	1	0	0	0	3
	Other maternal	2	2	2	2	0	0	3	11
	Reduced fetal movements	0	0	0	1	0	0	0	1
	Maternal request	0	0	0	1	0	0	0	1
	Suspected large fetus	2	0	1	1	0	0	0	4
Total		**9**	**3**	**12**	**9**	**0**	**1**	**14**	**48**

PROM=prelabor rupture of membranes. IUGR=intrauterine growth restriction. IDDM/GDM=insulin-dependent/gestational diabetes.

~~Term cephalic = Robson group 2; VBAC =attempted vaginal birth after caesarean delivery, includes Robson group 5.~~
~~[1]Excluding women with prelabor rupture of membranes.~~
~~[2]Adjusted for maternal age groups 16-24, 25-34 (ref), ≥35; prepregnancy BMI, Bishop score ≤5 (ref), >5 and missing; Foley catheter yes/no, and birthweight in grams.~~

Supporting Information Figure 1 Map of participating birth units in Norway.



Tables

Table 1 Maternal characteristics in 1818 women with no prior vaginal birth undergoing induction of labor.

	All		Nulliparous term cephalic		Previous CS		Other Robson	
	n	%	n=1461	%	n=221	%	n=136	%
Maternal age (years)								
16-24	246	13.5	222	15.2	15	6.8	9	6.6
25-34	1203	66.2	956	65.4	149	67.4	98	72.1
35-54	369	20.3	283	19.4	57	25.8	29	21.3
BMI prepregnancy[1]								
<30	1458	81.6	1185	82.3	160	74.8	113	85.0
>= 30	328	18.4	254	17.7	54	25.2	20	15.0
Bishops score[2]								
0-5	1366	82.8	1077	81.8	185	88.9	104	83.2
6-10	284	17.2	240	18.2	23	11.1	21	16.8
Birth at University hospital								
Yes	1173	64.5	957	65.5	124	56.1	93	68.4
Gest. age median (IQR)	40+1 (21)		40+3 (18)		40+0 (18)		36+5 (16)	
Maternal comorbidity[3]								
IDDM/GDM insulin	137	7.5	105	7.2	22	10.0	10	7.4
GDM, non-insulin	91	5.0	74	6.4	7	3.2	10	7.4
Preeclampsia/ hypertension	238	13.1	189	12.9	13	5.9	37	27.2
Intrahepatic cholestasis	34	1.9	25	1.7	6	2.7	3	2.2
Another comorbidity	272	15.0	210	14.4	39	17.6	23	5.9
Decision induction								
Consultant	1181	65.0	897	61.4	162	72.4	123	90.4
Resident	534	29.4	472	32.3	49	22.2	13	9.6
Midwife	103	5.7	93	6.4	10	4.5	0	0
Main indication for induction								
PROM	357	19.3	286	19.6	47	21.3	24	17.6
Postdates	336	18.5	299	20.5	33	14.9	4	2.9
Preeclampsia/hypertension	279	15.3	228	15.6	17	7.7	34	25.0
IUGR/oligohydramnios	280	15.4	231	15.8	24	10.9	25	18.4
IDDM/GDM - insulin	97	5.3	81	5.5	13	5.9	3	2.2
Large fetus	67	3.7	45	3.1	16	7.2	6	4.4
Maternal request	61	3.5	36	2.5	22	10.0	3	2.2
GDM, non-insulin	35	1.9	32	2.2	3	1.4	0	0
Intrahepatic cholestasis	43	2.4	35	2.4	5	2.3	3	2.2
Reduced fetal movements	40	2.2	36	2.5	3	1.4	1	0.7
Other maternal[4]	164	9.0	101	6.9	33	14.9	30	22.1
Other fetal[5]	59	3.2	51	3.5	5	2.3	3	2.2

Other Robson includes Robson groups 6, 7, 8 and 10. BMI= Body Mass Index. IQR=interquartile range. IDDM=insulin-dependent diabetes mellitus. GDM=gestational diabetes mellitus. PROM=prelabor rupture of membranes. IUGR=intrauterine growth restriction.[1]Missing 1.8%. [2]Not assessed in 9.2%. [3]More than one condition might be registered. [4]Incl. twin pregnancy, previous obstetric history, chronic disease, prolonged latency phase, vaginal bleeding. [5]incl. polyhydramnios, non-reassuring fetal tracing, known malformations, unknown gestational length.

Table 2 Delivery mode after induction of labor in 1818 women with no prior vaginal birth according to obstetric group.

		Cesarean section[1]			Operative vaginal			Spontaneous vaginal		
	N	n	%	95% CI	n	%	95% CI	n	%	95% CI
Nulliparous term cephalic	1461	320	21.9	19.8-24.1	314	21.5	19.4-23.7	827	56.6	54.0-59.2
Previous CS	221	89	40.3	33.7-47.1	40	18.1	13.3-23.8	92	41.6	35.1-48.4
Other Robson	136	50	36.8	28.9-45.8	28	20.6	14.2-28.6	60	44.1	35.9-53.2
All	1818	459	25.2	23.3-27.3	382	21.0	19.2-23.0	979	53.9	51.5-56.2

Other Robson includes Robson groups 6, 7, 8 and 10. [1]Including cesarean section second twin.

Table 3 Main indication and subtype of 459 cesarean sections[1] after induction of labor according to obstetric group.

	All		Nulliparous term cephalic		Previous CS		Other Robson	
	n=459	%	n=320	%	n=89	%	n=50	%
Main cesarean indication								
Prolonged 1.stage	117	25.5	85	26.6	23	25.8	9	18.8
Prolonged 2. stage	26	5.7	19	5.9	4	4.5	3	6.5
Susp. fetal hypoxia	143	31.2	112	35.0	19	21.3	12	25.0
Failed induction	109	23.7	69	21.6	31	34.8	9	18.8
Uterine rupture	2	0.4	0	0	2	2.2	0	0
Abruptio placentae	5	1.1	3	0.9	1	1.1	1	2.1
Other	55	12.0	31	9.7	10	11.2	14	29.2
Subtype								
Type 1 (immediate)	42	9.2	30	9.4	8	9.0	6	12.0
Type 2 (<20 minutes)	234	51.0	172	53.8	36	40.4	26	52.0
Type 3 (>20 minutes)	181	39.4	118	36.9	45	50.6	18	36.0

[1]Including cesarean section of second twin only (n=2). Other Robson includes Robson groups 6, 7, 8 and 10.

Table 4 Induction methods in 1818 women with no prior vaginal birth according to obstetric group.

	All		Nulliparous term cephalic		Previous CS		Other	
Induction method	N=1818	%	N=1461	%	N=221	%	N=136	%
Foley start combinations								
Foley alone	135	7.4	102	7.0	19	8.6	14	10.3
Foley + oral misoprostol ± AT/oxytocin	191	10.5	178	12.2	4	1.8	9	6.6
Foley + insert misoprostol ± AT/oxytocin	198	10.9	190	13.0	1	0.5	7	5.1
Foley + vaginal misoprostol ± AT/oxytocin	213	11.7	177	12.1	11	5.0	25	18.4
Foley + dinoprostone ± AT/oxytocin	108	5.9	28	1.9	76	34.4	4	2.9
Foley ± AT/oxytocin	241	13.3	174	11.9	49	22.2	18	13.2
Misoprostol start combinations								
Oral misoprostol alone	118	6.5	107	7.3	1	0.5	10	7.4
Oral misoprostol ± AT/oxytocin	45	2.5	41	2.8	0	0	4	2.9
Insert misoprostol alone	67	3.7	66	4.5	0	0	1	0.7
Insert misoprostol ± AT/oxytocin	29	1.6	28	1.9	0	0	1	0.7
Vaginal misoprostol alone	165	9.0	148	10.1	3	1.4	14	10.3
Vaginal misoprostol ± AT/oxytocin	88	4.8	79	5.4	1	0.5	8	5.9
Other combinations								
Dinoprostone alone	39	2.1	9	0.6	26	11.8	4	2.9
Dinoprostone ± AT/oxytocin	11	0.6	2	0.1	8	3.6	1	0.7
Amniotomy ±oxytocin	130	7.2	103	7.0	19	8.6	8	5.9
Any misoprostol/dinoprostone + successive Foley ± AT/oxytocin	24	1.3	17	1.2	3	1.4	4	2.9
Other	16	0.9	12	0.8	0	0	4	2.9

Other Robson includes Robson groups 6, 7, 8 and 10. AT=amniotomy.

Table 5 Method and risk of cesarean section in nulliparous term cephalic and previous CS pregnancies after induction of labor.

	Proportion CS		Risk of Caesarean section					
	CS	%	OR	95% CI	p	aOR[2]	a95% CI[2]	P[2]
1. Foley[1] (n=1356)								
Nulliparous term cephalic								
Foley catheter	212	25.2	1.55	1.13-2.13	0.007	1.78	1.16-2.59	0.008
No Foley catheter	61	17.9	1			1		
Previous CS								
Foley catheter	60	40.3	1.08	0.46-2.54	0.86	0.63	0.19-2.07	0.45
No Foley catheter	10	38.5	1			1		
2. Dinoprostone vs misoprostol (n=1195)								
Nulliparous term cephalic								
Dinoprostone	14	34.1	1.80	0.93-3.49	0.082	1.49	0.74-3.01	0.26
Misoprostol	230	22.4	1			1		
Previous CS								
Dinoprostone	49	47.1	1.29	0.51-3.27	0.60	1.47	0.54-3.99	0.46
Misoprostol	9	40.9	1			1		

[1]Excluding women with prelabor rupture of membranes. [2]Adjusted for maternal age groups 16-24, 25-34 (ref), ≥35; prepregnancy BMI, Bishop score ≤5 (ref), >5 and missing; Foley catheter yes/no, and birthweight in grams.

Table 6 Maternal and fetal secondary outcomes after induction of labor according to obstetric groups.

	All		Nulliparous term cephalic		Previous CS		Other	
Maternal	n	%	N	%	n	%	n	%
Uterine rupture	2	0.1	0	0	2	0.9	0	0
Tachysystole	96	5.3	79	5.4	10	4.5	7	5.1
Epidural	1355	74.5	1090	74.6	157	71.0	108	79.4
Blood loss in ml								
<500	1051	57.8	863	59.1	120	54.3	68	50.0
500-999	552	30.4	439	30.0	69	31.2	44	32.4
1000-1999	178	9.8	135	9.2	24	10.9	19	14.0
2000-2999	33	1.8	22	1.5	6	2.7	5	3.7
3000+	4	0.2	2	0.1	2	0.9	0	0
Fetal[1]								
Mean birthweight in grams (SD)	3485	(597)	3513	(550)	3664	(522)	2887	(808)
Adverse neonatal outcome[2]	203	11.2	139	9.5	22	10.0	42	30.9
Transfer NICU	132	7.4	85	5.9	10	4.6	37	27.6
Apgar <7 at 5 minutes	29	1.6	20	1.4	7	3.2	2	1.5
pH art umb <7.10[3]	72	4.0	59	4.0	9	4.0	4	2.9
pH art umb <7.00[3]	7	0.4	6	0.4	1	0.5	0	0

Other Robson includes Robson groups 6.7.8.and 10. [1]Outcomes for first twin only. SD= standard deviation. [2]Adverse neonatal outcome incl. pH arteria umbilicalis <7.10 and/or Apgar score at 5' <7 and/or transfer neonatal intensive care unit. NICU= neonatal intensive care unit excluding planned transfers (n=18). [3]Missing 19.5%.

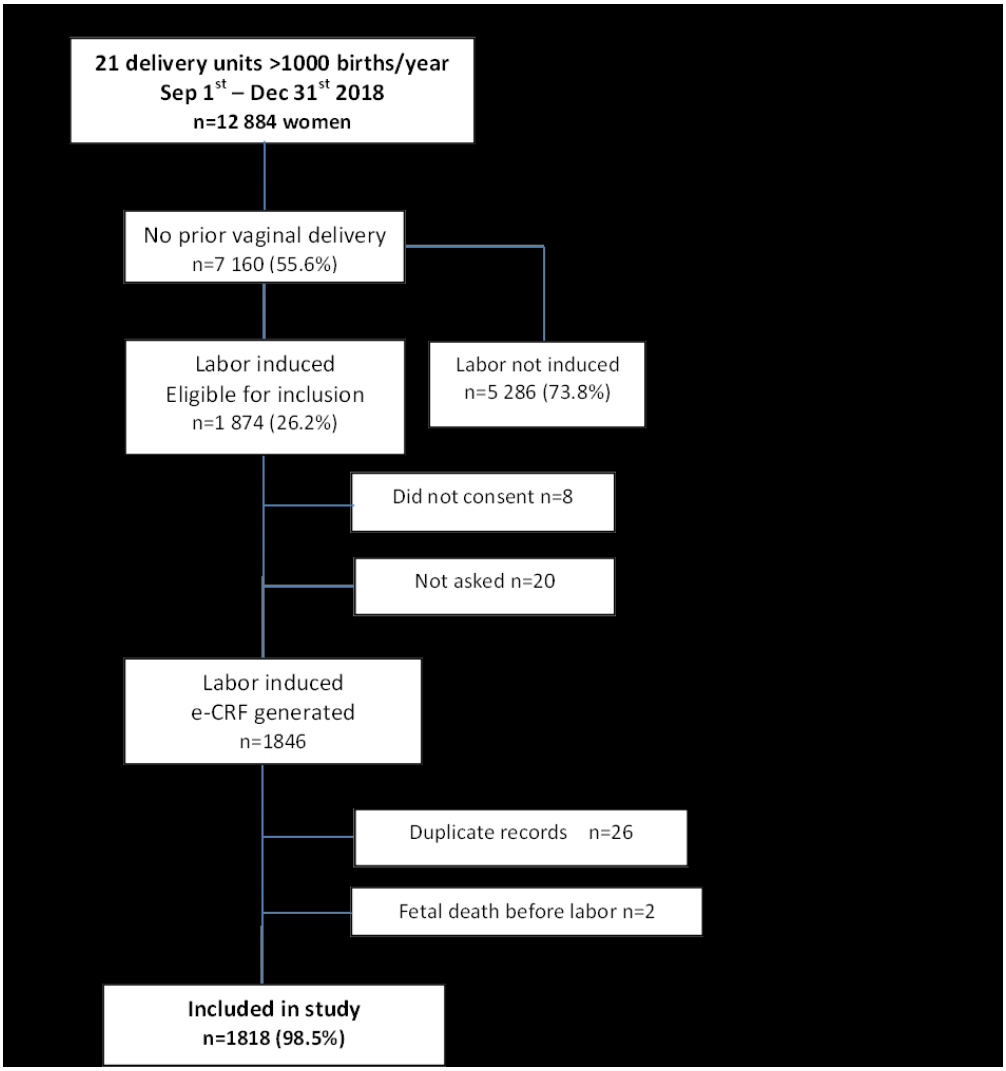
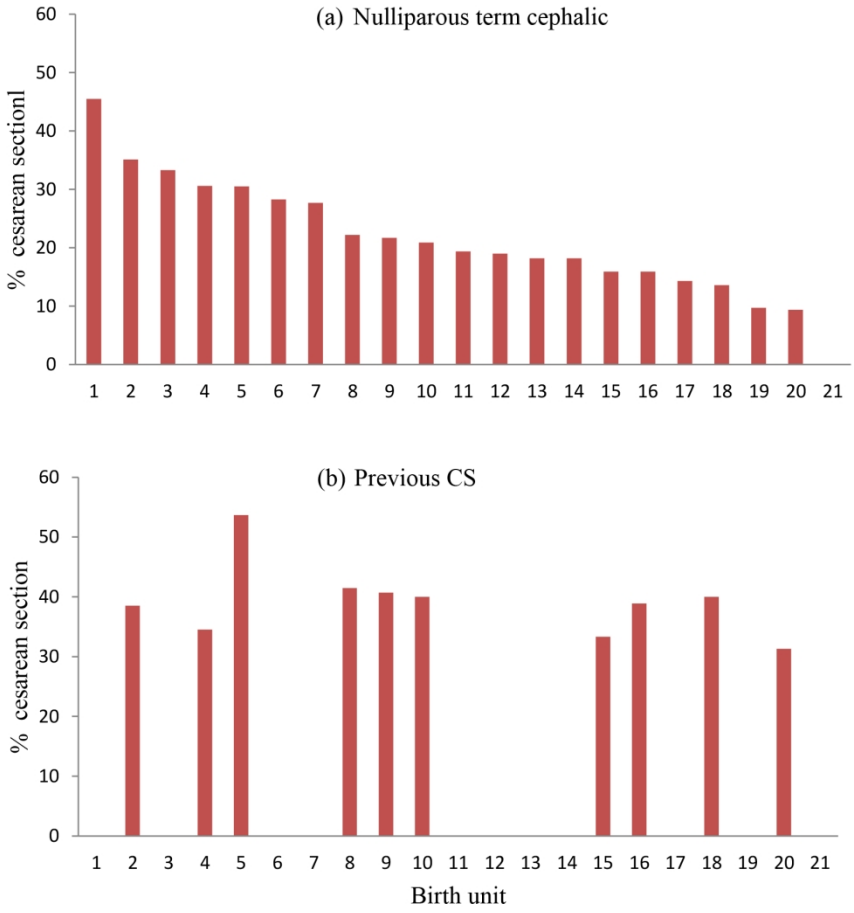


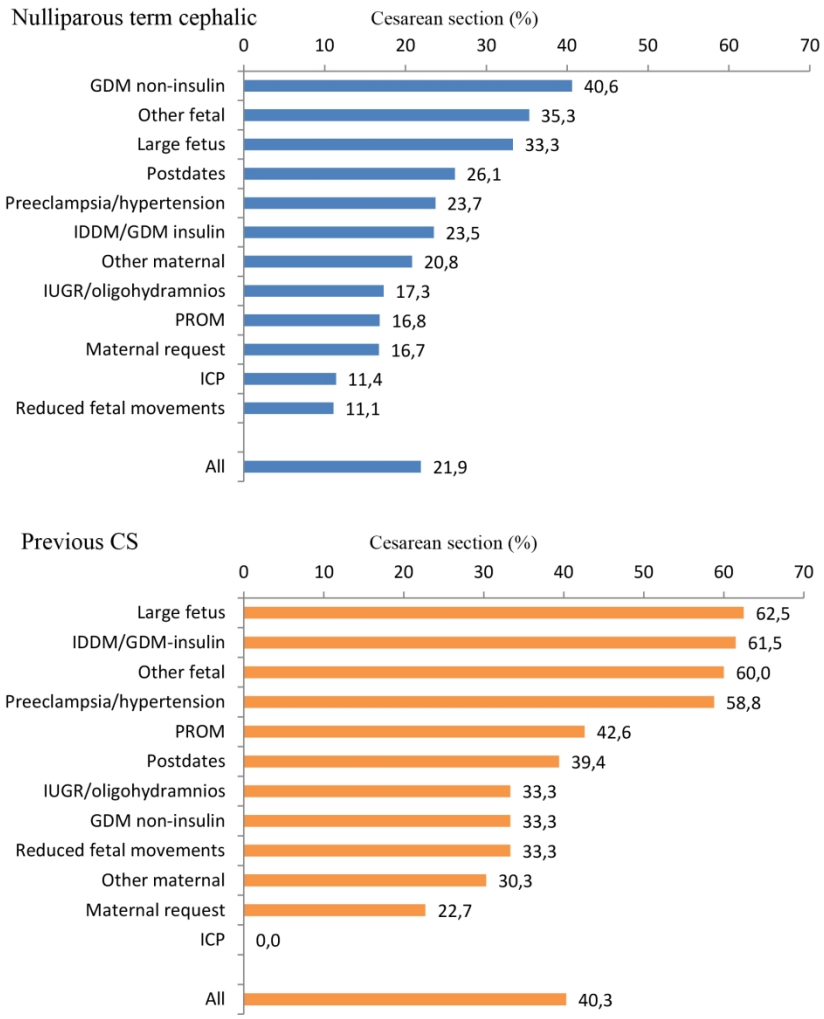
Figure 1 Flowchart of participants

160x170mm (150 x 150 DPI)



Other Robson includes Robson groups 6, 7, 8 and 10. Results from delivery units with n<10 deliveries per cell are censored.

Figure 2



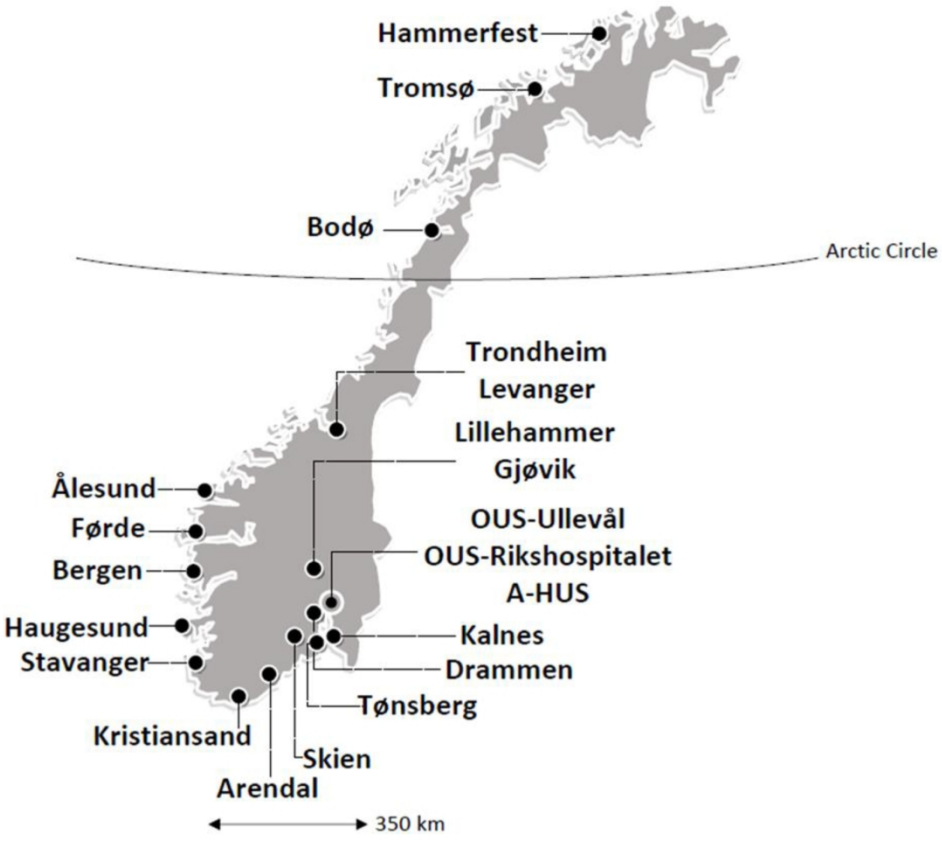
GDM= gestational diabetes mellitus; IDDM= insulin-dependent diabetes mellitus; IUGR=intrauterine growth restriction; PROM=prelabor rupture of membranes; ICP= intrahepatic cholestasis of pregnancy.

Figure 3

Supporting information Table S1. Indication for induction according to indication for CS in three obstetric groups.

Nulliparous term cephalic		Prolonged 1st stage	Prolonged 2nd stage	Fetal hypoxia	Failed induction	Uterine rupture	Abruptio placenta	Other	Total
Indication	Postdates	27	6	24	13	1	1	6	78
	PROM	14	5	17	6	0	0	6	48
	Preeclampsia/hypertension	10	4	17	13	0	0	10	54
	IUGR/oligohydramnios	9	0	19	9	0	2	1	40
	IDDM/GDM, insulin	1	1	6	11	0	0	0	19
	GDM, non-insulin	5	0	6	1	0	0	1	13
	Other maternal	4	1	8	6	0	0	2	21
	Reduced fetal movements	0	0	3	1	0	0	0	4
	Intrahepatic cholestasis	2	0	1	0	0	0	1	4
	Maternal request	2	1	1	0	0	0	2	6
	Suspected large fetus	6	1	3	4	0	0	1	15
	Other fetal	5	0	7	5	0	0	1	18
	Total	**85**	**19**	**112**	**69**	**1**	**3**	**31**	**320**
Previous CS		Prolonged 1st stage	Prolonged 2nd stage	Fetal hypoxia	Failed induction	Uterine rupture	Abruptio placenta	Other	Total
Indication	Postdates	4	0	3	4	0	0	2	13
	PROM	5	0	3	8	0	0	4	20
	Preeclampsia/hypertension	3	0	2	4	1	0	0	10
	IUGR/oligohydramnios	2	0	3	3	0	0	0	8
	IDDM/GDM, insulin	1	1	2	3	0	1	0	8
	GDM, non-insulin	1	0	0	0	0	0	0	1
	Other maternal	3	0	1	5	0	0	1	10
	Reduced fetal movements	1	0	0	0	0	0	0	1
	Maternal request	2	0	1	1	0	0	1	5
	Suspected large fetus	1	3	2	2	0	0	2	10
	Other fetal	0	0	2	1	0	0	0	3
Total		**23**	**4**	**19**	**31**	**1**	**1**	**10**	**89**
Other (Robson 6,7,8,10)		Prolonged 1st stage	Prolonged 2nd stage	Fetal hypoxia	Failed induction	Uterine rupture	Abruptio placenta	Other	Total
Indications	Postdates	0	0	2	1	0	0	1	4
	PROM	2	1	0	0	0	1	2	6
	Preeclampsia/hypertension	1	0	3	1	0	0	4	9
	IUGR/oligohydramnios	0	0	4	1	0	0	4	9
	IDDM/GDM, insulin	2	0	0	1	0	0	0	3
	Other maternal	2	2	2	2	0	0	3	11
	Reduced fetal movements	0	0	0	1	0	0	0	1
	Maternal request	0	0	0	1	0	0	0	1
	Suspected large fetus	2	0	1	1	0	0	0	4
Total		**9**	**3**	**12**	**9**	**0**	**1**	**14**	**48**

PROM=prelabor rupture of membranes. IUGR=intrauterine growth restriction. IDDM=insulin-dependent diabetes mellitus. GDM=gestational diabetes mellitus.



Supporting Figure 1

Title page

Induction of Labor and Nulliparity: A Nation-wide Clinical Practice Pilot Evaluation

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Conflict of interest:

The authors state that there are no conflicts of interest in connection with this article.

Funding information:

A grant of NOK 210 000 was received from the Norwegian Medical Association's fund for quality improvement and patient safety for a one-day seminar to present and discuss the project results for all participating birth units. The Research Council at Finnmark County Hospital, Hammerfest provided a grant of NOK 123 229 for KSO's travel expenses in connection with this project.

Abstract

Introduction

Induction of labor has become an increasingly common obstetric procedure. However, in nulliparous women or women with a previous cesarean section, induction of labor can pose a clinical challenge. Despite an overall expansion of medical indications for labor induction, there is little international consensus regarding the criteria for induction of labor, or for the recommended methods among nulliparous women. In this light, we assessed variations in the practice of induction of labor among 21 birth units in a nation-wide cohort of women with no prior vaginal birth.

Material and methods

We carried out a prospective observational pilot study of women with induced labor, and no prior vaginal birth, across 21 Norwegian birth units. We registered induction indications, methods and outcomes from Sept 1st – Dec 31st 2018 using a web-based case record form. Women were grouped into 'Nulliparous term cephalic', 'Previous CS' and 'Other Robson' (Robson groups 6, 7, 8 or 10).

Results

More than 98% of eligible women (n=1818) were included. There was a wide variety of methods used for induction of labor. In nulliparous term cephalic pregnancies, cesarean section rates ranged from 11.1 - 40.6% between birth units, whereas in the previous CS group, rates ranged from 22.7 - 67.5%. The indications 'large fetus' and 'other fetal' indications were associated with the highest cesarean rates. Failed inductions and failure to progress in labor contributed most to the cesarean rates. Uterine rupture occurred in two women (0.11%), both in the previous CS group. In neonates, 1.6% had Apgar <7 at 5 minutes, and 0.4% had an umbilical artery pH <7.00.

Conclusions

Cesarean rates and applied methods for induction of labor varied widely in this nation-wide cohort of women without a prior vaginal birth. Neonatal outcomes were similar to that of normal birth populations. Results could indicate the need to move towards more standardized induction protocols associated with optimal outcomes for mother and baby.

Keywords

Labor, Induced; Cesarean Section; Delivery, Obstetric; Nulliparous term cephalic; Robson, Clinical Audit.

Abbreviations

CS	cesarean section
BMI	body mass index
GDM	gestational diabetes mellitus
IQR	interquartile range

Key Message

In induction of labor among women without a prior vaginal birth, large variations in methods used and cesarean rates were observed in this nation-wide clinical practice evaluation.

INTRODUCTION

The worldwide rate of induction of labor has been rising steadily over the last 15 years. Currently approximately 25 % of births in high-income countries are induced. (1, 2) When faced with unfavorable factors for the mother or the baby if pregnancy continues, induction of labor can be indicated. (3) In pregnancies complicated by maternal diabetes or preeclampsia, post-term pregnancies and prolonged prelabor rupture of membranes (PROM), induction of labor compared to expectant management reduces the risk of perinatal death and maternal complications. (3-7) Over the last decades an expansion of medical indications for labor induction has occurred, including such conditions as hypertensive disorders, (5) advanced maternal age, (8) gestational diabetes (GDM) (9) and suspected large fetus for gestation. (10) Newer studies have demonstrated the safety of induction of labor without a medical indication, with fetal outcomes and cesarean section (CS) rates comparable to rates among women awaiting spontaneous labor. (11)

However, there are some concerns as to the generalizations of these findings into routine practice. First, results produced in setting with relatively high overall CS rates cannot necessarily be extrapolated to settings with average low CS rates. A clinical challenge is also posed by the considerable number of nulliparous women and women with a previous uterine scar, (12) giving birth today. Furthermore, induction of labor is not risk-free as more interventions are performed in induced compared to spontaneous labors. (13, 14) Finally, in recent studies of induction of labor, few have used standardized and consistent protocols in terms of the methods used. There is currently no international agreement as to what is the best induction method in women without a prior vaginal birth, (1, 15) and there is large diversity in clinical practice. (1, 2)

The authors of this study considered that assessing variation in induction practices in a national sample from a setting with free universal public delivery care and low average CS rates, (16) such as Norway, might be a good start to evaluate current practices and results. The aim of this pilot study was to examine variation in indications for induction of labor, methods and associated CS prevalence among women with no previous vaginal birth across 21 birth units nationwide. We used the Robson classification framework to distinguish women with nulliparous term cephalic pregnancies versus those with a previous uterine scar attempting a vaginal birth after cesarean section. (17) Ultimately, we aimed to identify practices associated with the best outcomes in terms of maternal and neonatal safety to inform obstetric providers.

MATERIAL AND METHODS

We carried out a prospective pilot registration of women undergoing induction of labor with a live fetus beyond 23 completed gestational weeks and with no prior vaginal birth between September 1st - December 31st 2018. We invited Norwegian obstetric departments with >1000 annual births to participate in the study. Out of 22 eligible units, 21 units were included (Supplementary Figure A). Participating units selected women whose labor was to be induced and decided upon the method(s) according to local practices, guidelines and definitions. Out-patient induction of labor was not practiced. Anonymous individual patient data were prospectively registered by clinicians in each department into a web-based electronic case record form. Only women with induction of labor were included. The number of nulliparous women without a previous birth and the induction rate during the period was also reported. The paper is reported using the STROBE guidelines for cohort studies.(18) Data were stored in Services for Sensitive Data, University of Oslo, Norway. The project is registered in ClinicalTrials.gov, no. NCT03730220.(19)

The primary outcome was the occurrence of cesarean section (CS) according to indication for induction and method of induction, stratified by obstetric group. Indications for CS were defined according to national/regional guidelines. We also assessed CS rates according to level of birth unit (university hospital or not). Secondary outcomes included uterine rupture, estimated maternal blood loss, adverse neonatal outcomes and the time interval from drug administration to birth. Estimated postpartum blood loss in ml was reported in categories. Adverse neonatal outcomes were defined as a composite outcome of Apgar score <7 at 5 minutes and/or transfer to neonatal intensive care unit and/or pH in umbilical artery <7.10 within one hour of birth.

We categorized cases into three groups. These were: “Nulliparous term cephalic” (Robson 2), "Previous CS" (classified as Robson 5: multiparous women with a previous uterine scar, with a single cephalic term pregnancy; however with no previous vaginal birth), and “Other Robson” (including Robson groups 6 and 7: women with a single breech pregnancy; Robson group 8: women with multiple pregnancies, and Robson group 10: women with a single cephalic pregnancy < 37 weeks’ gestation).
The indication for induction was categorized into 12 groups: Postdates (as defined locally; latest 42+0), PROM, preeclampsia/hypertension, intrauterine growth restriction (IUGR)/oligohydramnios, insulin-treated diabetes in pregnancy including insulin-treated GDM, non-insulin treated GDM, suspected large fetus, reduced fetal movements, intrahepatic cholestasis of pregnancy, maternal request, ‘other maternal’ and ‘other fetal’. The starting method for induction was categorized as Foley balloon catheter, misoprostol (oral, vaginal insert or vaginal tablet), or dinoprostone. As according to the protocol, we performed three comparisons: induction regime with Foley balloon catheter versus no catheter; induction regime including

misoprostol vaginal insert versus other misoprostol administration forms, and induction regime including dinoprostone versus misoprostol.

Other covariates included maternal age in categories, pre-pregnancy body mass index (BMI) (< 30 or ≥30), gestational age at induction, Bishop score at induction (≤5, >5 or missing), epidural, infant birthweight and tachysystole (>5 contractions per 10" with abnormal fetal tracing).

Statistical analysis

A statistical analysis plan included a power analysis. Assuming two groups of birth units with different induction methods resulting in a difference in CS rate between 20 to 25%, a significance level (α) of 0.05, and 80% power (β), the study would need 2182 participants. Applying the inclusion criteria, we estimated 2250 births during the period. (20) Baseline characteristics and outcomes were summarized according to the obstetric group. Small cell numbers (n<10) were censored when calculating CS rates. For categorical outcomes we compared proportions with 95% CI with the Chi-Square test and/or Fisher's exact test. We estimated the risk of CS by logistic regression analysis in generalized linear models adjusting for confounders as identified in the literature and according to biological plausibility, estimating crude and adjusted effect estimates as odds ratios (OR) with 95% CI with corresponding p-values. To check for linearity regarding continuous covariates, we also conducted analyses with log-transformed variables; however, the results did not change. We restricted analyses to nulliparous term cephalic and previous CS only due to small cell numbers. In sub analyses of CS deliveries only, we determined indications for the procedure and the subtype (type 1- immediate delivery; type 2- within 20-30 minutes or type 3 - within a given timeframe >30 min < 8 hours). Calculated *P*-values were two-sided and compared to a 5% significance level. Statistical analyses were performed in SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.)

Ethical approval

All women received oral and written information about the study. As routine data were gathered anonymously, informed consent was waivered; however, women were able to opt out of the study upon request. The project was approved by the Norwegian Ethics Board, Region Health South East C, reference 2018/1087 and each hospital's Data Protection Officer.

RESULTS

During the study period, a total of 7160 women without a prior vaginal birth gave birth in the 21 participating departments. Among these, labor was induced in 1874 women (26.2%; range 11.7-34.3% between hospitals). Of all 1874 eligible women for inclusion in the study,1818 (98.5%) were included

(Figure 1). Most birth units had a written induction protocol; however, most were not differentiated according to their Robson group.

Nulliparous term cephalic pregnancies constituted 80.4% of births, followed by previous CS pregnancies (12.2%) (Table 1). The "Other Robson' group included 52 twin pregnancies (2.9%), 59 preterm births (3.2%) and 25 planned breech births (1.4%). Overall, 20.3% were aged 35 years or more and 18.4% had a pre-pregnancy BMI of 30 or more. Of all women, 16.6% had a registered comorbidity where preeclampsia/hypertension was most prevalent. PROM, postdate pregnancy and preeclampsia/hypertension were the most common indications for induction. Maternal request was an indication for induction in only 3.5% of women.

In the nulliparous term cephalic group, one in five women gave birth by CS, whereas rates were doubled in the previous CS group and in the Other Robson group (Table 2). Hospital CS rates varied between 9.4% and 45.5% in the nulliparous term cephalic group and between 31.3% and 54.5% in the previous CS group (Figure 2). In the whole cohort, university hospital CS rates did not differ significantly from non-university hospitals (24.2% vs 26.8%, *P*=0.22). In the nulliparous term cephalic group CS rates by indication for the induction of labor ranged from 11.1 to 40.6%, whereas in the previous CS group rates were overall higher and ranged from 22.7 to 67.5% (Figure 3; Table S1.). In the nulliparous term cephalic group 'non-insulin GDM', 'other fetal' and 'large fetus' were the indications associated with the highest CS rates (40.6-33.3%). In the previous CS group 'large fetus', 'insulin-treated diabetes' and 'other fetal' were associated with the highest CS rates (62.5-60.0%).

The most common CS indication was suspected fetal hypoxia in the nulliparous term cephalic group, and failed induction in the previous CS group (Table 3). Of all cesarean procedures, 9.2% were reported as grade 1 (immediate) (Table 3). Overall 2.1% of women in the nulliparous term cephalic group and 3.6% of the previous CS group experienced an immediate CS. Suspected uterine rupture or abruptio placentae were indications for seven (0.4%) cesarean procedures.

The most common methods for induction are presented in Table 4. In the nulliparous term cephalic group, a combination of Foley + misoprostol was the most common initiation method (37.3%), followed by Foley + amniotomy/oxytocin (11.9%) (Table 4). In the previous CS group, most women received Foley + dinoprostone (34.4%), followed by Foley + amniotomy/oxytocin. However, altogether, more than 40 different method combinations and sequences were registered.

Use of Foley catheter was associated with birth by CS in the nulliparous term cephalic group (aOR 1.78, 95% CI 1.16-2.59, p=0.008), but not in the previous CS group (aOR 0.63, 95% CI 0.19-2.07, *P*=0.45) (Table 5). Use of dinoprostone showed a borderline significant association with birth by CS compared to

misoprostol in crude, but not in adjusted analyses. There was no association between route of administration of misoprostol and risk of CS (data not shown).

Uterine rupture occurred in two women (0.11%), both in the previous CS group (Table 6). Maternal blood loss differed between groups (p=0.049, Chi-Square); however, tachysystole did not. The composite adverse infant outcome occurred in 9.5% and 10.0% in the nulliparous term cephalic and the previous CS group respectively. A higher proportion (30.9%) was found in the Other Robson groups due to more transfers to the neonatal ward due to prematurity. Overall 29 infants (1.6%) had an Apgar score of less than 7 at 5'. Seven infants (0.4%) had an umbilical artery pH<7.00, of whom one infant was transferred to the neonatal ward. The method of induction was not associated with adverse maternal or neonatal outcome.

Among nulliparous term cephalic births, 26.5% were still undelivered 48 hours after induction start, as were 31.6% in the previous CS group and 26.5% in the Other Robson group (data not shown). In the three groups median duration from start of induction to birth were 32.6 hours (IQR 31.8), 34.1 hours (IQR 35.1) and 30.6 hours (IQR 32.6), respectively.

DISCUSSION

Our study showed large variations in the practice and results of induction of labor in this nation-wide sample. The frequency of CS after induction of labor was highest in the previous CS group, where about two out of five women gave birth by CS and lowest in the nulliparous term cephalic group, where about one out of five women gave birth by CS. CS rates after induction differed widely between units. CS performed due to failed induction of labor and prolonged first stage of labor accounted for nearly half of all CS. Our study found a wide variation of induction methods, with few units using standard induction protocols. Maternal and fetal safety outcomes were comparable to existing literature.

The strengths of this pilot study include the nation-wide prospective design with more than 98% of eligible women included. We had access to detailed information regarding indications, the methods used, including the order and route of administration, as well as important safety and efficiency outcomes.

One of the limitations of the study is that we lacked control data from induced multiparous women as well as on spontaneous labors. For this reason, we cannot comment on whether induction increases the rate of CS or adverse outcomes compared to spontaneous birth. Furthermore, we lacked detailed data on the local birth units, such as the number of referrals, socioeconomic spread etc. that might influence outcomes in terms of mode of birth. In the previous CS group we lacked information regarding the previous birth. However, CS rates were slightly lower in tertiary referral university hospitals compared to non-university hospitals, where

an accumulation of risks would be expected. Finally, our observational design does not warrant causal inference.

Induction by "large fetus" indication revealed high rates of CS in our study. However, the CS rate at 33.3% is similar to other studies of induction in woman with 'large babies. In the comprehensive study by Boulvain et al, (10) there was a CS rate of 28%, even though 53% were parous. These rates might be the result of a high gestational age in combination with maternal diabetic comorbidity. GDM non-insulin comorbidity had the highest CS rate whereas insulin-treated pregestational or gestational diabetes comorbidity had a relatively low CS rate in nulliparous term cephalic pregnancies. In Norway, insulin users are induced between week 38 and 40, but non-insulin GDM are induced primarily on additional indications. (21)

"Other fetal indication" for induction of labor had one of the highest CS rates in both nulliparous term cephalic and previous CS pregnancies. This is a mixed group including fetal malformations, polyhydramnios, non-reassuring antenatal fetal tracing and unknown gestational length. Polyhydramnios may give insufficient contractions due to an over distended uterus (22) and non-reassuring fetal tracing have to be handled with care; delivery, rather than expectant management is preferred, if it continues. The group "maternal request" was surprisingly low with 3.5 % of all inductions and we found a low CS rate both in the nulliparous term cephalic and the previous CS group. This is lower than previously reported. (23) The distinction between 'maternal request' or 'medical problem' can be a fine one, especially when considering mental health and pregnancy complaints. However, this finding indicates a restrictive attitude among providers, in contrast to upcoming trends elsewhere. (24)

The overall proportion of failed induction and prolonged first stage was unexpectedly high in our sample. However, as 27-32% of women were undelivered 48 hours after the start of induction, this is not likely to reflect a use of rigid time limits. The 22-35% rate of failed induction/poor progress in the first stage that we found in our sample might imply a practice emphasizing safety rather than effectiveness. This is also reflected in a relatively low uterine rupture rate, a low tachysystole rate of 5% and few immediate CS procedures.

At present, there are conflicting reports of how and when induction of labor should be offered to women. Trials have been conducted among women at term with no medical indication. (11, 25, 26) These randomized trials indicate no major safety concerns in terms of the CS risk or adverse infant or maternal outcomes. In addition, although the ARRIVE trial has been criticized as including many overweight and obese women, (27) the 18.6% CS rate in the trial's induced group (who were all low risk nulliparous women) is similar to the 16.7% rate seen in 'maternal request' in the nulliparous term cephalic group in our study. A Cochrane review looking at induction at 40 weeks versus expectant management found improved outcomes in the induction group, except for a higher operative vaginal delivery rate. (3) However, a

prerequisite in generalizing findings is that the induction process and labor is well managed with the necessary staff at hand. Like most high-resource countries, Norway has a rapidly increasing induction rate that reached 23% of all births in 2018 (20), but at the same time, overall CS rates - 16.0% in 2017 – are the second lowest rate across the OECD area (16). However, CS rates vary considerably between regions beyond what can be expected due to case-mix. (28) A national induction guideline lists medical indications and methods, but leaves the choice among these methods to individual departments and staff. (21) In this clinical practice evaluation, we found that multiple induction protocols are used even within nulliparous term cephalic and previous CS groups. What this means is that women across the country do not have similar treatment when undergoing induction of labor.

Translating RCT evidence into practical clinical protocols can be challenging in obstetric units facing logistical restraints such as delays in timely administration of uterotonics and performing rupture of membranes. (29) Results from practice evaluations are therefore important to inform decisions in induction regimes tailored to specific groups. Women should be offered joint decision making based on these facts. Careful selection of women for induction who have previously had a cesarean section, as well as taking women's preferences into account, are important factors in a pragmatic induction of labor protocol.

CONCLUSION

A wide variation of induction methods and CS rates after induction, as well as a high rate of failed inductions in women without a prior vaginal birth, points to a potential for improvement by moving towards more standardized protocols. The Robson groups provide a framework for the counselling of women about particular risks and benefits regarding induction of labor while working towards shared decision-making.

Acknowledgements

We are indebted to our dedicated obstetrician and midwife collaborators in the National Induction Group at the participating birth units who made this study possible: Ines Panadero at Akershus University Hospital, Nina Marie Albretsen at Arendal Hospital, Kristin Hestvold at Drammen Hospital, Mette Kristine Hjertaas at Førde Hospital, Anja Holstad at Gjøvik Hospital, Line Olufsen-Melhus at Hammerfest Hospital, Kristin Urnes at Haugesund Hospital, Chen Sun at Haukeland University Hospital, Marte Eline Ween-Velken at Kristiansand Hospital, Dordi Bogfjellmo at Levanger Hospital, Jakob Nakling and Ida Olsen Hokland at Lillehammer Hospital, Kristin Skogøy at Nordland Hospital, Bodø, Anja Halleraker and Marianne Omland at Oslo University Hospital Rikshospitalet, Hilde Sellevoll and Marit Småvik Johansen at Oslo University Hospital Ullevål, Kjersti Skoe at Telemark Hospital, Ewa Margas at Tønsberg Hospital, Åse Torunn Pettersen at University Hospital of North Norway, Malin Dögl at St. Olavs University Hospital, Trondheim , Erik Andreas Torkildsen at Stavanger University Hospital, Katrine Sjøborg Dønvold and Lotte Martine Jacobsen at Østfold Hospital and Åse Turid Rossevatn Svoren at Ålesund Hospital.

Tweetable abstract:

There is considerable variation in outcomes after induction of labor, depending on where a primiparous woman chooses to have her birth.

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Legends of supporting information

Supporting Information Figure 1 Map of participating birth units in Norway.

Legends of Tables and Figures

Table 1 Maternal characteristics in 1818 women with no prior vaginal birth undergoing induction of labor.

Table 2 Delivery mode after induction of labor in 1818 women with no prior vaginal birth according to obstetric group.

Table 3 Main indication and subtype of 459 cesarean sections[1] after induction of labor according to obstetric group.

Table 4 Induction methods in 1818 women with no prior vaginal birth according to obstetric group.

Table 5 Method and risk of cesarean section in nulliparous term cephalic and previous CS pregnancies after induction of labor.

Table 6 Maternal and fetal secondary outcomes after induction of labor according to obstetric groups.

Supporting information Table S1. Indication for induction according to indication for CS in three obstetric groups.

Figure 1 Flowchart of study participants

Figure 2 Proportions of cesarean section after induction of labor by delivery unit in nulliparous term cephalic (a) and previous CS pregnancies (b).

Figure 3 Cesarean section rates according to indication for induction of labor in nulliparous term cephalic and previous CS pregnancies.

Tables

Table 1 Maternal characteristics in 1818 women with no prior vaginal birth undergoing induction of labor.

	All		Nulliparous term cephalic		Previous CS		Other Robson	
	n	%	n=1461	%	n=221	%	n=136	%
Maternal age (years)								
16-24	246	13.5	222	15.2	15	6.8	9	6.6
25-34	1203	66.2	956	65.4	149	67.4	98	72.1
35-54	369	20.3	283	19.4	57	25.8	29	21.3
BMI prepregnancy[1]								
<30	1458	81.6	1185	82.3	160	74.8	113	85.0
>= 30	328	18.4	254	17.7	54	25.2	20	15.0
Bishops score[2]								
0-5	1366	82.8	1077	81.8	185	88.9	104	83.2
6-10	284	17.2	240	18.2	23	11.1	21	16.8
Birth at University hospital								
Yes	1173	64.5	957	65.5	124	56.1	93	68.4
Gest. age median (IQR)	40+1 (21)		40+3 (18)		40+0 (18)		36+5 (16)	
Maternal comorbidity[3]								
IDDM/GDM insulin	137	7.5	105	7.2	22	10.0	10	7.4
GDM, non-insulin	91	5.0	74	6.4	7	3.2	10	7.4
Preeclampsia/ hypertension	238	13.1	189	12.9	13	5.9	37	27.2
Intrahepatic cholestasis	34	1.9	25	1.7	6	2.7	3	2.2
Another comorbidity	272	15.0	210	14.4	39	17.6	23	5.9
Decision induction								
Consultant	1181	65.0	897	61.4	162	72.4	123	90.4
Resident	534	29.4	472	32.3	49	22.2	13	9.6
Midwife	103	5.7	93	6.4	10	4.5	0	0
Main indication for induction								
PROM	357	19.3	286	19.6	47	21.3	24	17.6
Postdates	336	18.5	299	20.5	33	14.9	4	2.9
Preeclampsia/hypertension	279	15.3	228	15.6	17	7.7	34	25.0
IUGR/oligohydramnios	280	15.4	231	15.8	24	10.9	25	18.4
IDDM/GDM - insulin	97	5.3	81	5.5	13	5.9	3	2.2
Large fetus	67	3.7	45	3.1	16	7.2	6	4.4
Maternal request	61	3.5	36	2.5	22	10.0	3	2.2
GDM, non-insulin	35	1.9	32	2.2	3	1.4	0	0
Intrahepatic cholestasis	43	2.4	35	2.4	5	2.3	3	2.2
Reduced fetal movements	40	2.2	36	2.5	3	1.4	1	0.7
Other maternal[4]	164	9.0	101	6.9	33	14.9	30	22.1
Other fetal[5]	59	3.2	51	3.5	5	2.3	3	2.2

Other Robson includes Robson groups 6, 7, 8 and 10. BMI= Body Mass Index. IQR=interquartile range. IDDM=insulin-dependent diabetes mellitus. GDM=gestational diabetes mellitus. PROM=prelabor rupture of membranes. IUGR=intrauterine growth restriction.[1]Missing 1.8%. [2]Not assessed in 9.2%. [3]More than one condition might be registered. [4]Incl. twin pregnancy, previous obstetric history, chronic disease, prolonged latency phase, vaginal bleeding. [5]incl. polyhydramnios, non-reassuring fetal tracing, known malformations, unknown gestational length.

Table 2 Delivery mode after induction of labor in 1818 women with no prior vaginal birth according to obstetric group.

		Cesarean section[1]			Operative vaginal			Spontaneous vaginal		
	N	n	%	95% CI	n	%	95% CI	n	%	95% CI
Nulliparous term cephalic	1461	320	21.9	19.8-24.1	314	21.5	19.4-23.7	827	56.6	54.0-59.2
Previous CS	221	89	40.3	33.7-47.1	40	18.1	13.3-23.8	92	41.6	35.1-48.4
Other Robson	136	50	36.8	28.9-45.8	28	20.6	14.2-28.6	60	44.1	35.9-53.2
All	1818	459	25.2	23.3-27.3	382	21.0	19.2-23.0	979	53.9	51.5-56.2

Other Robson includes Robson groups 6, 7, 8 and 10. [1]Including cesarean section second twin.

Table 3 Main indication and subtype of 459 cesarean sections[1] after induction of labor according to obstetric group.

	All		Nulliparous term cephalic		Previous CS		Other Robson	
	n=459	%	n=320	%	n=89	%	n=50	%
Main cesarean indication								
Prolonged 1.stage	117	25.5	85	26.6	23	25.8	9	18.8
Prolonged 2. stage	26	5.7	19	5.9	4	4.5	3	6.5
Susp. fetal hypoxia	143	31.2	112	35.0	19	21.3	12	25.0
Failed induction	109	23.7	69	21.6	31	34.8	9	18.8
Uterine rupture	2	0.4	0	0	2	2.2	0	0
Abruptio placentae	5	1.1	3	0.9	1	1.1	1	2.1
Other	55	12.0	31	9.7	10	11.2	14	29.2
Subtype								
Type 1 (immediate)	42	9.2	30	9.4	8	9.0	6	12.0
Type 2 (<20 minutes)	234	51.0	172	53.8	36	40.4	26	52.0
Type 3 (>20 minutes)	181	39.4	118	36.9	45	50.6	18	36.0

[1]Including cesarean section of second twin only (n=2). Other Robson includes Robson groups 6, 7, 8 and 10.

Table 4 Induction methods in 1818 women with no prior vaginal birth according to obstetric group.

	All		Nulliparous term cephalic		Previous CS		Other	
Induction method	N=1818	%	N=1461	%	N=221	%	N=136	%
Foley start combinations								
Foley alone	135	7.4	102	7.0	19	8.6	14	10.3
Foley + oral misoprostol ± AT/oxytocin	191	10.5	178	12.2	4	1.8	9	6.6
Foley + insert misoprostol ± AT/oxytocin	198	10.9	190	13.0	1	0.5	7	5.1
Foley + vaginal misoprostol ± AT/oxytocin	213	11.7	177	12.1	11	5.0	25	18.4
Foley + dinoprostone ± AT/oxytocin	108	5.9	28	1.9	76	34.4	4	2.9
Foley ± AT/oxytocin	241	13.3	174	11.9	49	22.2	18	13.2
Misoprostol start combinations								
Oral misoprostol alone	118	6.5	107	7.3	1	0.5	10	7.4
Oral misoprostol ± AT/oxytocin	45	2.5	41	2.8	0	0	4	2.9
Insert misoprostol alone	67	3.7	66	4.5	0	0	1	0.7
Insert misoprostol ± AT/oxytocin	29	1.6	28	1.9	0	0	1	0.7
Vaginal misoprostol alone	165	9.0	148	10.1	3	1.4	14	10.3
Vaginal misoprostol ± AT/oxytocin	88	4.8	79	5.4	1	0.5	8	5.9
Other combinations								
Dinoprostone alone	39	2.1	9	0.6	26	11.8	4	2.9
Dinoprostone ± AT/oxytocin	11	0.6	2	0.1	8	3.6	1	0.7
Amniotomy ±oxytocin	130	7.2	103	7.0	19	8.6	8	5.9
Any misoprostol/dinoprostone + successive Foley ± AT/oxytocin	24	1.3	17	1.2	3	1.4	4	2.9
Other	16	0.9	12	0.8	0	0	4	2.9

Other Robson includes Robson groups 6, 7, 8 and 10. AT=amniotomy.

Table 5 Method and risk of cesarean section in nulliparous term cephalic and previous CS pregnancies after induction of labor.

	Proportion CS		Risk of Caesarean section					
	CS	%	OR	95% CI	p	aOR[2]	a95% CI[2]	P[2]
1. Foley[1] (n=1356)								
Nulliparous term cephalic								
Foley catheter	212	25.2	1.55	1.13-2.13	0.007	1.78	1.16-2.59	0.008
No Foley catheter	61	17.9	1			1		
Previous CS								
Foley catheter	60	40.3	1.08	0.46-2.54	0.86	0.63	0.19-2.07	0.45
No Foley catheter	10	38.5	1			1		
2. Dinoprostone vs misoprostol (n=1195)								
Nulliparous term cephalic								
Dinoprostone	14	34.1	1.80	0.93-3.49	0.082	1.49	0.74-3.01	0.26
Misoprostol	230	22.4	1			1		
Previous CS								
Dinoprostone	49	47.1	1.29	0.51-3.27	0.60	1.47	0.54-3.99	0.46
Misoprostol	9	40.9	1			1		

[1]Excluding women with prelabor rupture of membranes. [2]Adjusted for maternal age groups 16-24, 25-34 (ref), ≥35; prepregnancy BMI, Bishop score ≤5 (ref), >5 and missing; Foley catheter yes/no, and birthweight in grams.

Table 6 Maternal and fetal secondary outcomes after induction of labor according to obstetric groups.

	All		Nulliparous term cephalic		Previous CS		Other	
Maternal	n	%	N	%	n	%	n	%
Uterine rupture	2	0.1	0	0	2	0.9	0	0
Tachysystole	96	5.3	79	5.4	10	4.5	7	5.1
Epidural	1355	74.5	1090	74.6	157	71.0	108	79.4
Blood loss in ml								
<500	1051	57.8	863	59.1	120	54.3	68	50.0
500-999	552	30.4	439	30.0	69	31.2	44	32.4
1000-1999	178	9.8	135	9.2	24	10.9	19	14.0
2000-2999	33	1.8	22	1.5	6	2.7	5	3.7
3000+	4	0.2	2	0.1	2	0.9	0	0
Fetal[1]								
Mean birthweight in grams(SD)	3485	(597)	3513	(550)	3664	(522)	2887	(808)
Adverse neonatal outcome[2]	203	11.2	139	9.5	22	10.0	42	30.9
Transfer NICU	132	7.4	85	5.9	10	4.6	37	27.6
Apgar <7 at 5 minutes	29	1.6	20	1.4	7	3.2	2	1.5
pH art umb <7.10[3]	72	4.0	59	4.0	9	4.0	4	2.9
pH art umb <7.00[3]	7	0.4	6	0.4	1	0.5	0	0

Other Robson includes Robson groups 6.7.8.and 10. [1]Outcomes for first twin only. SD= standard deviation. [2]Adverse neonatal outcome incl. pH arteria umbilicalis <7.10 and/or Apgar score at 5' <7 and/or transfer neonatal intensive care unit. NICU= neonatal intensive care unit excluding planned transfers (n=18). [3]Missing 19.5%.

Figures

Figure 1 Flowchart of study participants

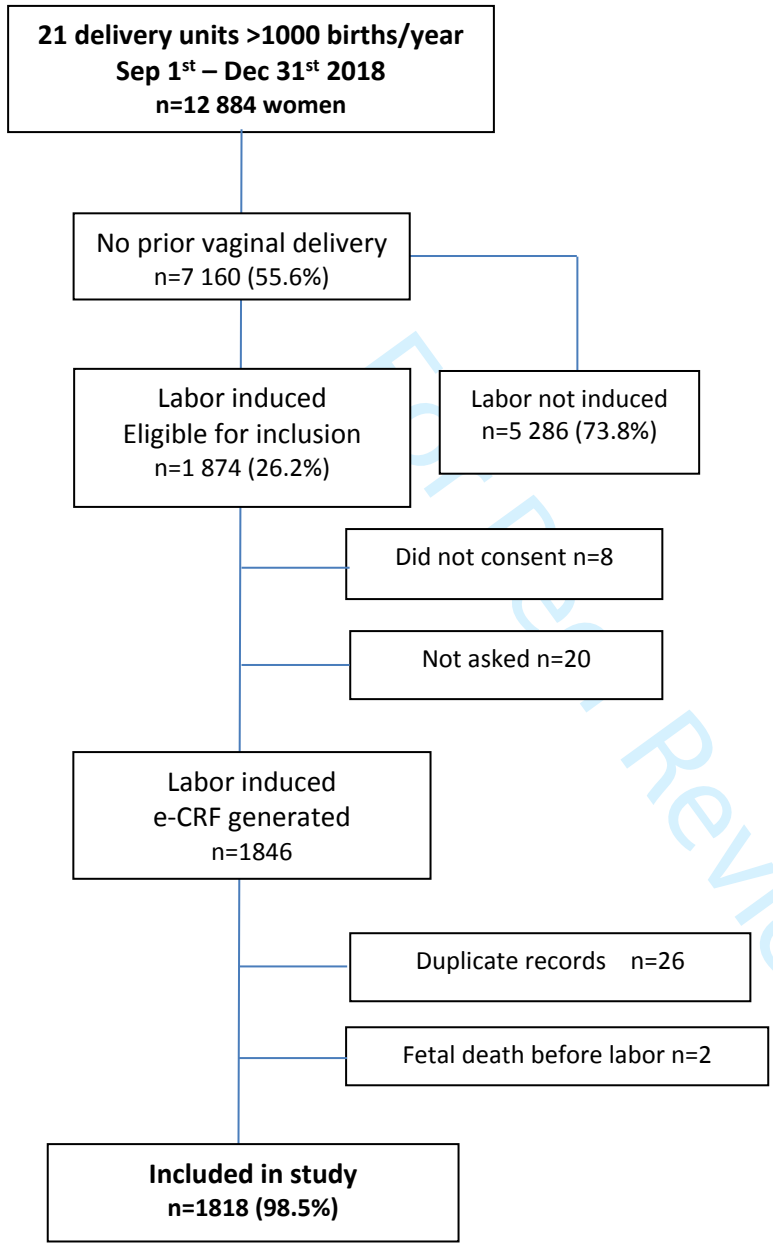
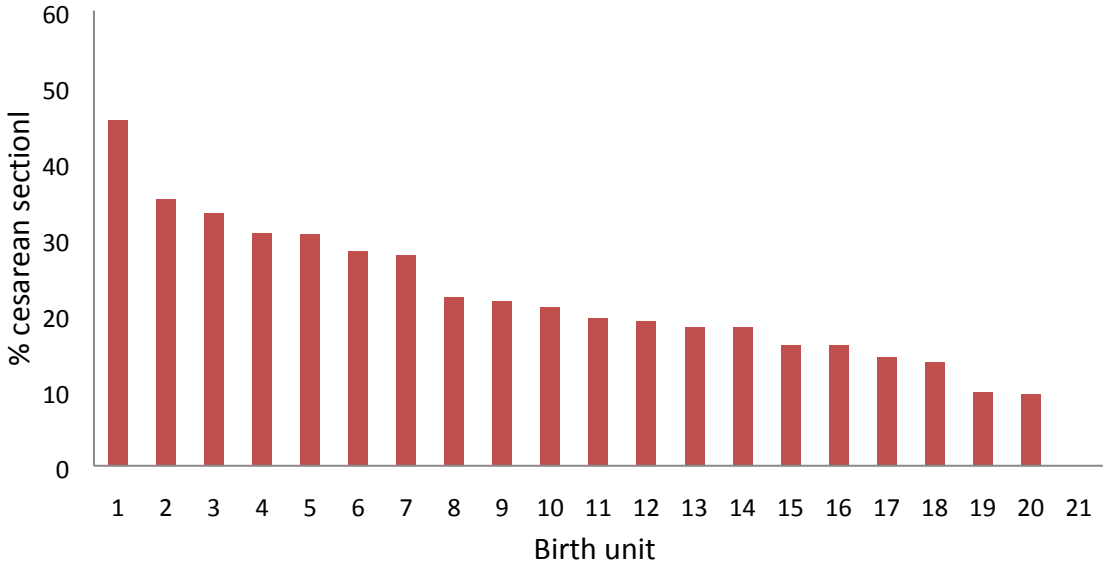
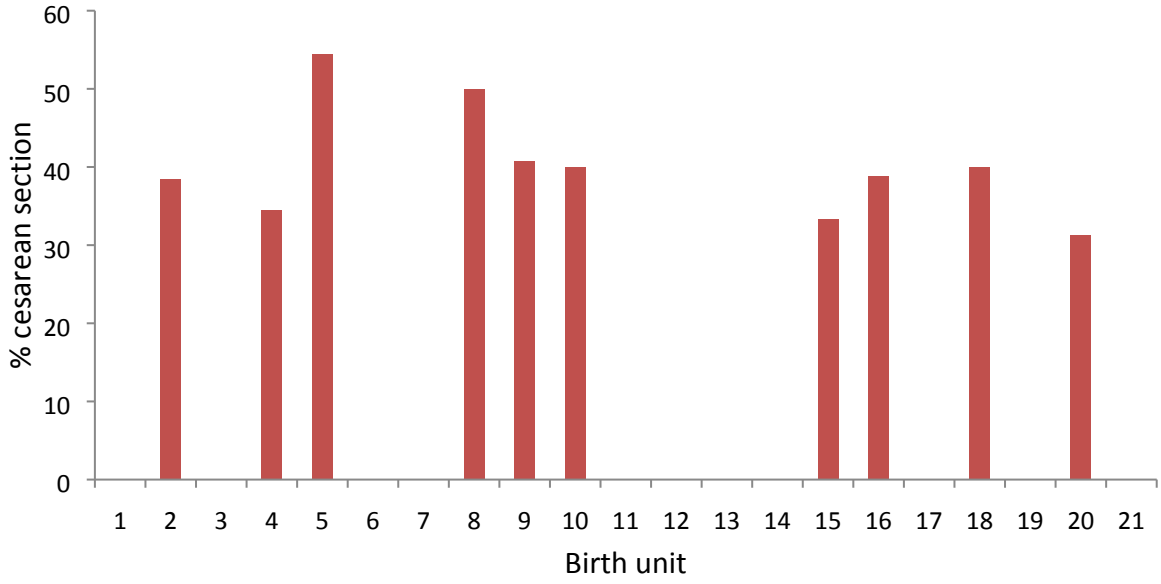


Figure 2 Proportions of cesarean section after induction of labor by delivery unit in nulliparous term cephalic (a) and previous CS pregnancies (b).

(a) Nulliparous term cephalic

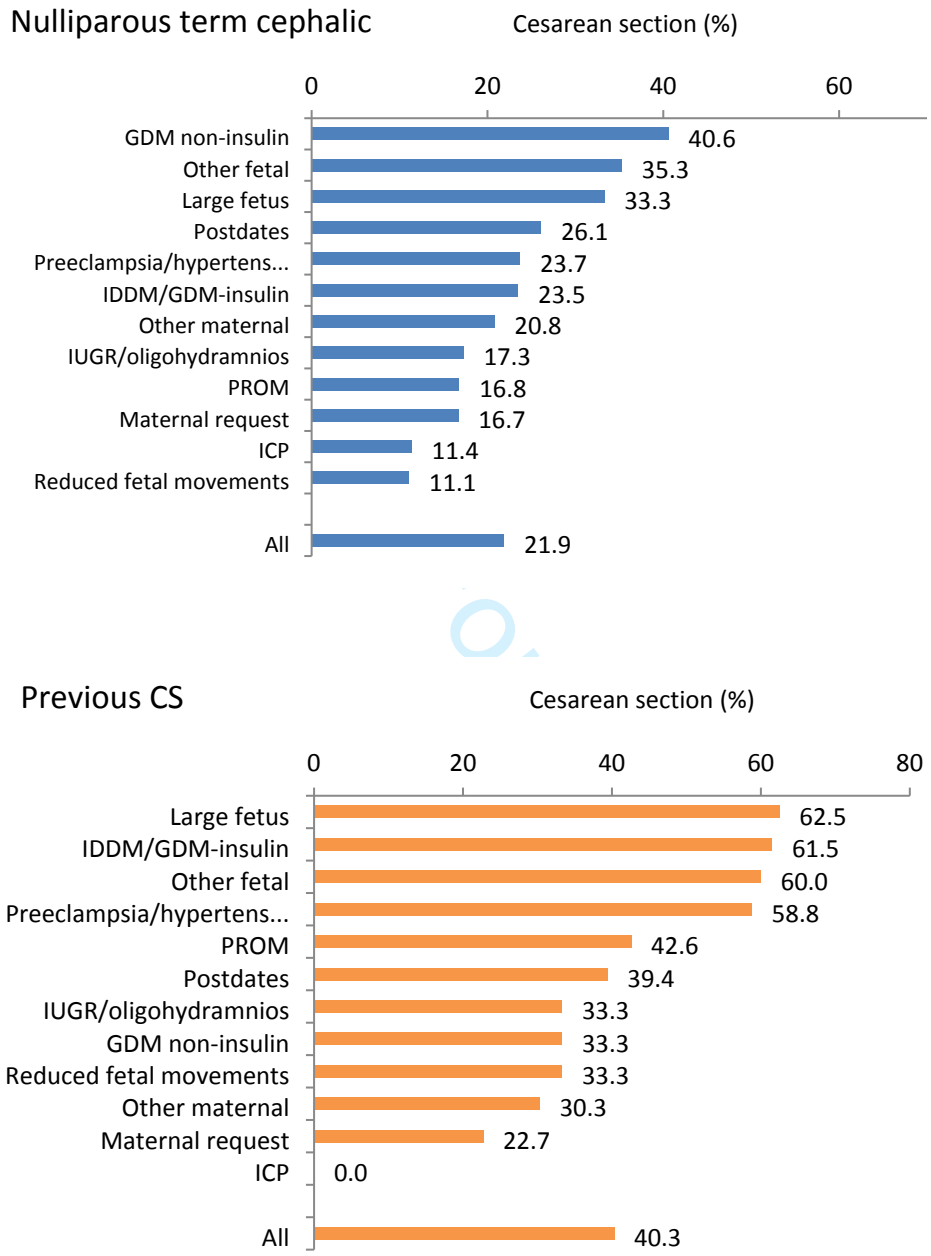


(b) Previous CS



Other Robson includes Robson groups 6, 7,8 and 10. Results from delivery units with n<10 deliveries per cell are censored.

Figure 3 Cesarean section rates according to indication for induction of labor in nulliparous term cephalic and previous CS pregnancies.



GDM= gestational diabetes mellitus; IDDM= insulin-dependent diabetes mellitus; IUGR=intrauterine growth restriction; PROM=prelabor rupture of membranes; ICP= intrahepatic cholestasis of pregnancy.

Supporting information Table S1. Indication for induction according to indication for CS in three obstetric groups.

Nulliparous term cephalic		Prolonged 1st stage	Prolonged 2nd stage	Fetal hypoxia	Failed induction	Uterine rupture	Abruptio placenta	Other	Total
Indication	Postdates	27	6	24	13	1	1	6	78
	PROM	14	5	17	6	0	0	6	48
	Preeclampsia/hypertension	10	4	17	13	0	0	10	54
	IUGR/oligohydramnios	9	0	19	9	0	2	1	40
	IDDM/GDM-insulin	1	1	6	11	0	0	0	19
	GDM, non-insulin	5	0	6	1	0	0	1	13
	Other maternal	4	1	8	6	0	0	2	21
	Reduced fetal movements	0	0	3	1	0	0	0	4
	Intrahepatic cholestasis	2	0	1	0	0	0	1	4
	Maternal request	2	1	1	0	0	0	2	6
	Suspected large fetus	6	1	3	4	0	0	1	15
	Other fetal	5	0	7	5	0	0	1	18
	Total	**85**	**19**	**112**	**69**	**1**	**3**	**31**	**320**
Previous CS		Prolonged 1st stage	Prolonged 2nd stage	Fetal hypoxia	Failed induction	Uterine rupture	Abruptio placenta	Other	Total
Indication	Postdates	4	0	3	4	0	0	2	13
	PROM	5	0	3	8	0	0	4	20
	Preeclampsia/hypertension	3	0	2	4	1	0	0	10
	IUGR/oligohydramnios	2	0	3	3	0	0	0	8
	IDDM/GDM-insulin	1	1	2	3	0	1	0	8
	GDM, non-insulin	1	0	0	0	0	0	0	1
	Other maternal	3	0	1	5	0	0	1	10
	Reduced fetal movements	1	0	0	0	0	0	0	1
	Maternal request	2	0	1	1	0	0	1	5
	Suspected large fetus	1	3	2	2	0	0	2	10
	Other fetal	0	0	2	1	0	0	0	3
Total		**23**	**4**	**19**	**31**	**1**	**1**	**10**	**89**
Other (Robson 6,7,8,10)		Prolonged 1st stage	Prolonged 2nd stage	Fetal hypoxia	Failed induction	Uterine rupture	Abruptio placenta	Other	Total
Indications	Postdates	0	0	2	1	0	0	1	4
	PROM	2	1	0	0	0	1	2	6
	Preeclampsia/hypertension	1	0	3	1	0	0	4	9
	IUGR/oligohydramnios	0	0	4	1	0	0	4	9
	IDDM/GDM-insulin	2	0	0	1	0	0	0	3
	Other maternal	2	2	2	2	0	0	3	11
	Reduced fetal movements	0	0	0	1	0	0	0	1
	Maternal request	0	0	0	1	0	0	0	1
	Suspected large fetus	2	0	1	1	0	0	0	4
Total		**9**	**3**	**12**	**9**	**0**	**1**	**14**	**48**

PROM=prelabor rupture of membranes. IUGR=intrauterine growth restriction. IDDM/GDM=insulin-dependent/gestational diabetes.

Supporting Information Figure 1 Map of participating birth units in Norway.