AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

Can oxytocin augmentation modify the risk of epidural analgesia by maternal age in cesarean sections?

JANNE ROSSEN[1,2], KARI KLUNGSØYR[3,4], SUSANNE ALBRECHTSEN[5,6], ELLEN LØKKEGÅRD[7], STEEN RASMUSSEN[7], THOMAS BERGHOLT[8] & FINN E. SKJELDESTAD[9]

[1]Department of Obstetrics and Gynecology, Sørlandet Hospital Kristiansand, Kristiansand, [2]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, [3]Department of Global Public Health and Primary Care, University of Bergen, Bergen, [4]Medical Birth Registry of Norway, Norwegian Institute of Public Health, Bergen, Norway, [5]Department of Obstetrics and Gynecology, Haukeland University Hospital, Haukeland, Denmark, [6]Department of Clinical Medicine, University of Bergen, Bergen, Norway, [7]Clinical Research Unit, Department of Obstetrics and Gynecology, Nordsjællands Hospital, University of Copenhagen, Hillerød, [8]Department of Obstetrics, Rigshospitalet University Hospital, University of Copenhagen, Copenhagen, Denmark, and [9]Research Group Epidemiology of Chronic Diseases, Department of Community Medicine, Faculty of Health Sciences, UiT the Arctic University of Norway, Tromsø, Norway

Key words
Maternal medicine, cesarean section, maternal age, epidural analgesia, oxytocin augmentation, medical management

Correspondence
Finn Egil Skjeldestad, Department of Community Medicine, Research Group Epidemiology of Chronic Diseases, UiT The Arctic University of Norway, Tromsø 7037, Norway.
E-mail: eskjelde@online.no

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

Please cite this article as: Rossen J, Klungsøyr K, Albrechtsen S, Løkkegård E, Rasmussen S, Bergholt T, Skjeldestad FE. Can oxytocin augmentation modify the risk of epidural analgesia by maternal age in cesarean sections? Acta Obstet Gynecol Scand 2018; https://doi.org/10.1111/aogs.13341

Received: 3 September 2017
Accepted: 21 February 2018

DOI: 10.1111/aogs.13341

Abstract

Introduction. Maternal age is an established risk factor for cesarean section; epidural analgesia and oxytocin augmentation may modify this association. We investigated the effects and interactions of oxytocin augmentation, epidural analgesia and maternal age on the risk of cesarean section. *Material and methods.* In all, 416 386 nulliparous women with spontaneous onset of labor, ≥37 weeks of gestation and singleton infants with a cephalic presentation during 2000–2011 from Norway and Denmark were included [Ten-group classification system (Robson) group 1]. In this case-control study the main exposure was maternal age; epidural analgesia, oxytocin augmentation, birthweight and time period were explanatory variables. Chi-square test and logistic regression were used to estimate associations and interactions. *Results.* The cesarean section rate increased consistently with advancing maternal age, both overall and in strata of epidural analgesia and oxytocin augmentation. We observed strong interactions between maternal age, oxytocin augmentation and epidural analgesia for the risk of cesarean section. Women with epidural analgesia generally had a reduced adjusted odds ratio when oxytocin was used compared with when it was not used. In Norway, this applied to all maternal age groups but in Denmark only for women ≥30 years. Among women without epidural, oxytocin augmentation was associated with an increased odds ratio for cesarean section in Denmark, whereas no difference was observed in Norway. *Conclusions.* Oxytocin augmentation in nulliparous women with epidural analgesia is associated with a reduced risk of cesarean section in labor with spontaneous onset.

Abbreviations: CI, confidence interval; CS, cesarean section; RR, risk ratio.

Introduction

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

Changes in maternal risk factors and obstetric practice have contributed to a rising rate of cesarean section (CS) (5). Maternal age at first delivery has increased steadily

during the last decades (since the late 1990ies), and the risk of CS increases with maternal age (6). Use of epidural analgesia has increased, and its use is associated with longer duration of labor, especially among nulliparous women (7). Oxytocin augmentation is more prevalent among women who receive epidural analgesia (2,7). Oxytocin use may modify the effect of epidural analgesia on maternal age as a risk factor for CS, despite the finding of no difference in CS rates between oxytocin-exposed and non-exposed women in two randomized trials (8).

Using a case-control design we investigated the effects and interactions of epidural analgesia, oxytocin augmentation and maternal age on CS among nulliparous women in spontaneous labor delivering singleton infants with a cephalic presentation at term.

Material and methods

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

Variables were harmonized across the birth registers in the merged database. Maternal age was defined as the difference in completed years between date of delivery and maternal date of birth and was categorized into six groups (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years). Parity and previous cesarean delivery were defined as the highest number of births based on information in the registers (linkage of births to their mothers by the unique national identification numbers) or maternal information provided at first delivery. Gestational age was estimated from ultrasound screening of biparietal diameter in second trimester, but from 2004 and onwards a first trimester scan for crown–rump length was the basis for assessment of gestational age in Denmark (10). Fetal lie was classified as longitudinal or transverse, and presentation as cephalic or breech. Start of delivery was defined as spontaneous onset of birth, induction or CS. Mode of delivery comprised spontaneous vaginal delivery, instrumental vaginal delivery (vacuum extraction or forceps) or CS. Emergency CSs encompassed all CS not reported as elective. Since 1998, the Medical Birth Registry of Norway has gathered information about mothers and their corresponding pregnancies, deliveries and infants via check boxes supplemented with free text information on the birth notification form. Use of oxytocin and epidural analgesia is based on check boxes, and a sample of this information was validated against medical records at reporting hospitals by one of the authors (K.K.). The validation showed a positive predictive value of oxytocin augmentation above 98%. Oxytocin augmentation is defined as oxytocin used to accelerate labor progress. For Denmark, information about pregnancy and delivery, including use of oxytocin augmentation and epidural analgesia during labor, was captured from the Danish National Patient Register. We categorized three-year periods as 2000–2002, 2003–2005, 2006–2008 and 2009–2011. Included in the original database were women who delivered after the 22nd gestational week, or, if gestational age was missing, women who gave birth to infants with a birthweight of ≥500 g.

Statistical analyses

All analyses were done in Statistical Package for Social Sciences version 21 (IBM, Armonk, NY, USA). A Chi-square test was used to evaluate linear trends and logistic regression analysis was used to estimate odds of CS in relation to maternal age, use of epidural analgesia and oxytocin augmentation, when adjusting for potential confounding factors such as birthweight (>4000 g: yes/no) and period. We tested interactions using multiplicative models. Age standardization was done by the direct method, using the total and age-specific subpopulations of the entire database as the reference populations.

Ethical approval

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

Results

The merged database comprised all deliveries from 1 January 2000 to 31 December 2011, totaling 757 257 and 699 754 deliveries in Denmark and Norway, respectively. The proportion of unclassifiable cases due to missing information on variables comprising the Ten-group classification system increased slightly from the first to the

Key Message

Oxytocin augmentation is an effect modifier of epidural analgesia when studying maternal age as risk for cesarean section.

final study period in Denmark (from 0.4 to 0.9%) but decreased in Norway (from 1.8 to 0.7%).

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

Table 1 displays characteristics of the study population. Maternal age increased in both countries but Danish parturients were in general older. Use of epidural analgesia increased with maternal age in both countries. Its use also increased during the period, but to a larger degree in Denmark, whereas the overall use was more prevalent in Norway. Oxytocin augmentation also increased consistently with maternal age in both countries, but the age-specific use of oxytocin demonstrated generally larger increases over time in Denmark (Table 1). However, the overall use of oxytocin augmentation was more prevalent in Norway than in Denmark.

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

Table 3 presents the observed CS rates. Across the study the age-standardized overall CS rate increased from 9.4 to 10.5% in Denmark and from 8.0 to 9.3% in Norway. The CS rate in both countries and all periods increased with maternal age in the strata of epidural analgesia and oxytocin augmentation. The increase by age was more apparent when epidural analgesia was used (Figure 1). In both countries the overall CS rate among women with epidural analgesia and augmentation with oxytocin was significantly higher than among those not exposed to either epidural analgesia or oxytocin augmentation (data not shown). Among women with epidural

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

	Denmark				Norway			
	n = 225 678				*n* = 203 420			
Time period	2000–2002 *n* = 61 401 %	2003–2005 *n* = 57 172 %	2006–2008 *n* = 57 343 %	2009–2011 *n* = 49 762 %	2000–2002 *n* = 49 515 %	2003–2005 *n* = 49 071 %	2006–2008 *n* = 51 718 %	2009–2011 *n* = 53 116 %
Maternal age								
<20	3.5	3.1	3.4	3.4	6.4	5.2	5.5	5.2
20–24	20.8	17.7	18.1	19.1	26.9	25.4	25.5	25.8
25–29	45.6	44.8	42.2	40.7	40.6	38.7	38.0	38.1
30–34	23.6	27.2	28.1	27.3	20.6	24.0	23.7	23.4
35–39	5.7	6.4	7.1	8.3	4.8	6.1	6.5	6.7
≥40	0.7	0.8	1.1	1.2	0.6	0.7	0.9	0.9
Use of epidural by maternal age								
<20	8.0	25.6	32.5	37.3	38.5	41.2	45.8	46.4
20–24	8.7	22.2	33.1	36.5	36.9	38.9	43.3	44.6
25–29	8.4	20.7	31.6	34.2	37.1	39.0	41.9	43.5
30–34	10.8	23.2	35.5	37.5	40.6	42.7	46.3	47.8
35–39	14.5	27.1	41.2	40.6	43.9	44.0	49.7	52.6
≥40	15.2	32.4	43.3	44.3	44.6	51.2	48.9	53.0
In total*	10.2	23.1	34.8	36.9	39.4	41.2	44.9	46.6
Use of oxytocin by maternal age								
<20	30.0	36.9	34.1	32.0	38.1	38.6	42.6	38.9
20–24	34.9	39.9	41.4	40.5	39.8	43.2	46.0	43.0
25–29	38.8	43.9	46.0	44.8	44.3	47.3	48.4	47.5
30–34	44.1	48.6	51.1	49.5	46.3	51.6	54.9	53.0
35–39	51.6	55.1	56.5	55.4	51.4	54.5	59.0	58.4
≥40	50.0	59.4	61.5	58.6	54.1	55.7	55.6	56.7
In total*	41.8	46.6	48.5	47.7	45.4	49.1	51.0	50.1

*Age-standardized.

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

	Denmark				Norway			
Time period	2000–2002 *n* = 61 401 %	2003–2005 *n* = 57 172 %	2006–2008 *n* = 57 343 %	2009–2011 *n* = 49 762 %	2000–2002 *n* = 49 515 %	2003–2005 *n* = 49 071 %	2006–2008 *n* = 51 718 %	2009–2011 *n* = 53 116 %
No use of epidural anal-gesia, use of oxytocin: Maternal age								
<20	27.0	25.9	20.9	17.5	26.5	21.9	26.1	22.8
20–24	31.5	30.1	27.1	25.2	29.3	28.2	28.4	26.2
25–29	36.0	35.3	32.4	30.5	33.1	31.9	32.0	30.6
30–34	40.3	39.0	36.3	33.8	33.9	35.6	35.0	33.3
35–39	48.1	45.4	40.0	38.7	39.7	40.5	42.8	39.6
≥40	45.9	51.7	47.3	40.6	44.8	39.0	39.7	39.2
In total	36.4	35.8	32.7	30.8	32.1	31.8	32.1	30.2
Use of epidural analgesia, use of oxytocin: Maternal age								
<20	64.5	68.9	61.5	56.3	56.7	62.3	62.2	57.5
20–24	70.1	73.8	70.4	66.3	57.8	66.7	69.1	63.9
25–29	70.3	76.9	75.3	72.4	63.3	71.3	71.3	69.5
30–34	75.9	80.6	78.1	75.6	64.4	73.2	73.7	74.4
35–39	72.7	81.1	80.0	79.8	66.3	72.4	75.3	75.4
≥40	73.1	75.5	80.1	81.4	65.6	71.5	72.1	72.2
In total	71.9	77.4	75.3	72.4	61.9	70.2	71.1	69.1

analgesia, the risk of CS decreased during the study period in Denmark but increased in Norway (Table 3). This, in addition to country-specific differences in prevalence of oxytocin augmentation, implies country-specific interactions, from exposure of epidural analgesia and oxytocin augmentation regarding our primary outcome variable, CS. As a consequence, country-specific stratified analyses were performed.

In both countries, significant associations between maternal age and use of epidural analgesia, and between maternal age and oxytocin augmentation, regarding CS risk were found. Accordingly, we created a new variable comprising maternal age, use of epidural analgesia and oxytocin augmentation. We defined women aged 20–24 years with no use of epidural analgesia or oxytocin as the common reference group, as we considered this subset to be the women with lowest risk of CS.

For all age groups in Norway, women who received epidural analgesia and oxytocin augmentation had significantly lower adjusted odds ratios than those who received epidural analgesia but not oxytocin, whereas in Denmark this association only held for women ≥30 years (Figure 2). For women in Norway who did not receive epidural analgesia, the adjusted odds ratios did not differ significantly by oxytocin augmentation in any age group except for those ≥40 years. In Denmark, on the other hand, the adjusted odds ratios among women without epidural analgesia were higher when oxytocin augmentation was administered, except in the oldest age group (≥40 years).

In predicting CS among the Norwegian study population, there was a minimal confounding of period on the stratified odds ratios of maternal age, epidural analgesia and oxytocin augmentation (Figure 2). In Denmark, period had a confounding effect on CS, as epidural analgesia increased over the periods and oxytocin use changed differently according to age and use of epidural analgesia (data not shown).

The overall prevalence of birthweight ≥4000 g decreased over the study year, from 16.1 to 12.7% in Denmark and from 17.0 to 12.4% in Norway. These changes were consistent across maternal age groups in both countries. Among women delivering a fetus with birthweight ≥4000 g, the CS rate increased from 15.8 to 19.5% in Denmark and from 12.6 to 16.2% in Norway during the period. Furthermore, the CS rate among these women increased with maternal age in all time periods in both countries (data not shown). However, in neither country did birthweight have any confounding effect on the associations between oxytocin augmentation, epidural analgesia and maternal age for CS.

Discussion

The overall use of oxytocin augmentation among nulliparous women with spontaneous onset of labor [Ten-group classification system (Robson) group 1] increased and reached 48% in Denmark and 50% in Norway in 2009–2011. Stratified by maternal age, use of oxytocin

Table 3. Prevalence of cesarean section by maternal age (in years), by epidural analgesia (No/Yes) and maternal age, and by oxytocin augmentation (No/Yes) and maternal age (%) in Denmark and Norway, 2000–2011.

	Denmark								Norway							
Time period	2000–2002 %		2003–2005 %		2006–2008 %		2009–2011 %		2000–2002 %		2003–2005 %		2006–2008 %		2009–2011 %	
Maternal age																
<20	3.8		5.1		4.9		6.0		4.0		4.5		3.9		4.7	
20–24	6.0		7.4		7.3		7.1		5.1		5.4		6.1		6.4	
25–29	7.7		8.6		8.8		8.4		6.2		6.7		7.2		8.1	
30–34	10.3		11.5		11.9		11.8		8.7		8.7		10.1		9.5	
35–39	14.8		14.7		15.5		15.2		12.2		11.3		12.8		14.0	
≥40	17.6		22.2		21.6		20.5		18.4		19.0		17.4		18.6	
In total*	9.4		10.5		10.8		10.5		8.0		8.1		8.9		9.3	
	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)	(No)	(Yes)
Epidural and maternal age																
<20	2.8	15.1	3.4	9.9	2.4	10.0	2.2	12.3	1.4	8.3	1.8	8.3	0.8	7.6	1.6	8.3
20–24	5.1	15.8	3.8	19.9	3.1	15.9	3.2	13.9	1.6	11.1	1.4	11.8	1.4	12.3	1.4	12.5
25–29	6.1	24.6	4.8	23.1	3.6	20.1	3.0	18.9	1.6	14.0	1.6	14.8	1.6	15.1	1.7	16.4
30–34	8.1	28.4	6.1	29.3	4.8	24.7	4.3	24.2	2.8	17.3	1.9	17.8	1.9	19.6	1.9	17.7
35–39	11.5	34.2	8.9	30.1	5.6	29.4	5.8	28.9	3.8	23.0	2.7	22.2	2.7	23.0	2.7	24.2
≥40	14.4	35.8	11.1	45.2	12.3	33.7	9.3	34.7	7.4	32.1	3.7	33.7	4.4	31.1	5.1	30.6
In total*	7.5	24.6	6.0	24.5	4.6	18.2	4.2	21.0	2.4	16.2	1.9	16.7	1.9	17.5	1.9	17.5
Oxytocin and maternal age																
<20	2.7	6.5	3.7	7.5	4.0	6.6	4.2	9.7	4.0	4.1	4.1	5.1	2.9	5.3	3.3	6.8
20–24	4.5	8.8	4.9	11.1	4.8	10.9	4.5	10.8	4.5	6.0	4.7	6.4	4.8	7.7	4.9	8.3
25–29	5.5	11.1	5.8	12.1	5.4	12.8	4.9	12.8	5.3	7.3	5.4	8.3	5.4	9.2	5.9	10.5
30–34	7.1	14.3	7.4	15.7	8.4	15.2	7.8	15.8	8.2	9.2	6.8	10.5	7.9	12.1	7.2	11.6
35–39	12.9	16.6	11.1	17.6	11.4	18.6	11.2	18.3	12.4	12.0	11.4	11.2	11.0	14.1	11.2	15.9
≥40	15.4	19.9	20.6	23.2	19.8	22.7	18.0	22.3	22.2	15.1	18.8	19.3	18.6	16.5	19.5	17.9
In total*	7.1	12.7	7.3	14.1	7.5	14.2	7.2	14.6	7.5	8.5	6.9	9.3	7.2	10.7	7.2	11.4

*Age-standardized.

(vs. no use of oxytocin) was associated with a reduced risk of CS among women with epidural analgesia in both countries. In Norway this applied to all maternal age groups, but in Denmark only to women ≥30 years. Among women without epidural analgesia, oxytocin augmentation showed minimal impact on the risk of CS in Norway, whereas its use was associated with an increased risk of CS in women <40 years in Denmark.

This study applied a stratified dynamic approach, which reflects the use of epidural analgesia and oxytocin augmentation by maternal age in daily clinical obstetric practice. We observed that CS rates increased with maternal age in both Denmark and Norway. However, the use of epidural analgesia and oxytocin augmentation seemed to modify the effects of maternal age on risk of CS in both countries.

In Norway, use of oxytocin augmentation and epidural analgesia was consistent across maternal age groups and periods. In Denmark, there was an increase in epidural analgesia use from the first to the second period, and oxytocin use varied more by maternal age and epidural analgesia use compared with Norway. This may explain the observed interaction between period and epidural/oxytocin use for Danish data.

We have not found other studies analyzing CS rates stratified by maternal age, use of epidural analgesia and use of oxytocin. A Cochrane review with data from 27 randomized controlled trials assessed the effect of epidural analgesia vs. non-epidural analgesia on women in labor and found no difference in the overall risk of CS (risk ratio, RR) 1.10 [95% confidence interval (CI): 0.97–1.25)] (11). The timing of epidural analgesia, early or late in the first stage of labor, did not influence the risk of CS (RR 1.02, 95% CI 0.96–1.08, from nine trials) (12). Use of epidural analgesia increases the use of oxytocin (11), but use of oxytocin among women with epidural analgesia has not yet been found to reduce the risk of CS (RR 0.95, 95% CI 0.42–2.12, from two trials) (8). A Cochrane review on early augmentation compared with expectant management in prevention of delayed labor found that

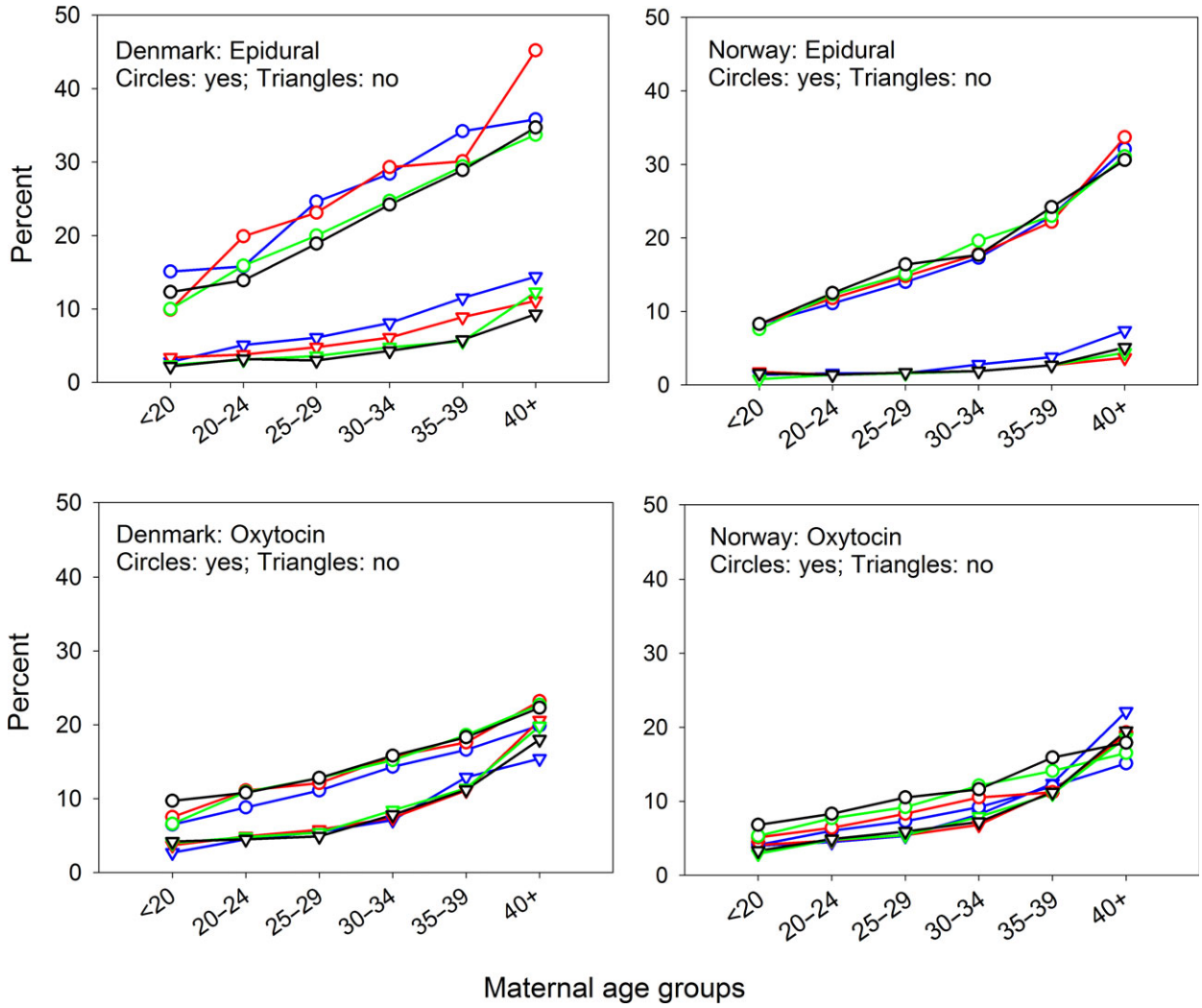

Figure 1. Cesarean section rates by use/no use of epidural, time period, age and country (upper panel). Cesarean section rates by use/no use of oxytocin augmentation, time period, age and country (lower panel) (%). Time period: Blue: 2000–2002; Red: 2003–2005; Green: 2006–2008; Black: 2009–2011. [Color figure can be viewed at wileyonlinelibrary.com].

early use of oxytocin was associated with a modest reduction in the risk of CS (RR 0.87, 95% CI 0.77–0.99, from 11 trials) (13). However, there was large heterogeneity related to use of epidural analgesia and oxytocin between the included studies, an issue the authors did not explore (13). Another Cochrane review with data from six trials revealed that active management of labor (defined as strict diagnosis of labor, routine amniotomy, oxytocin for slow progress and one-to-one support in labor) gave a modest, but significant, reduced risk of CS (RR 0.77, 95% CI 0.63–0.94) (14). The authors stated that there were no differences between the groups in use of epidural analgesia, but this does not rule out a possible effect modification of epidural analgesia caused by other variables, as shown in the present study. Furthermore, the authors of this review did not discuss the large variations in oxytocin use in relation to diverging CS rates (14), nor did they consider use of oxytocin as a possible modifier of the effect of maternal age and epidural analgesia, as observed in the present study. In addition, findings from an observational study may diverge from randomized controlled trials due to residual confounding in observational studies and lack of external validity in randomized controlled trial studies. Kotaska et al. (15) demonstrated that use of high oxytocin doses compared with low oxytocin doses among women with epidural analgesia reduced the risk of CS, whereas our associations are related to use or no use of oxytocin.

The effect of maternal age stratified by use of epidural analgesia and oxytocin has received little attention. Small sample sizes in most randomized clinical trials may explain this. Pooling of data from randomized trials, as

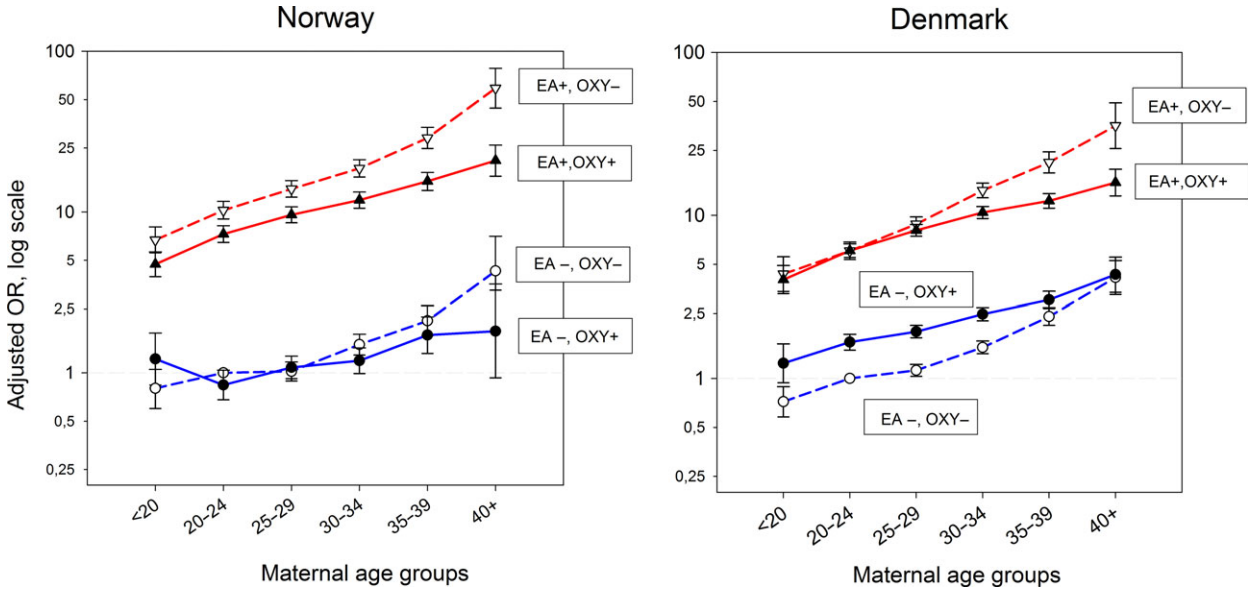

Figure 2. Adjusted odds ratio (OR; log. scale) for cesarean section, stratified by use/no use of epidural analgesia (EA) and use/no use of oxytocin (OXY), by age and country (age group 20–24 years is reference). [Color figure can be viewed at wileyonlinelibrary.com].

included in the various Cochrane reviews cited above (8,11–14), will probably still yield an insufficient sample size for valid conclusions. Therefore, in situations where randomized controlled trials may not be performed or will not achieve sample sizes large enough to answer complex obstetrical research questions, well conducted observational studies based on high-quality birth register data will be the best possible study design.

Other confounders that might have an independent effect on CS, such as maternal body mass index and length/arrest of labor, were not available for analysis. However, women receiving oxytocin are women with long duration of labor and/or arrest of labor. Indications for epidural analgesia and use of oxytocin have occurred before provision of the actual treatments. Thus, we argue that epidural analgesia and use of oxytocin captured the indications within the variables themselves (collinearity). We consider lack of information on these particular confounders to have had minor influence on the reported associations on CS.

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

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

In the present study we have explored how oxytocin augmentation and use of epidural analgesia may modify the effect of maternal age on CS rates in the Ten-group classification system (Robson) group 1. These women constitute nearly 30% of all women giving birth, and nearly 20% of all CS are carried out in this subset of parturients in the Nordic countries (16). Any efforts to prevent CS in Robson group 1 will inevitably decrease the overall CS rate, and will also have additional complementary effects on repeated CSs in other Robson groups that will reinforce the preventive measures of lowering the CS rate in Robson group 1 (16).

In conclusion, we have demonstrated consistent data suggesting that oxytocin augmentation in women with epidural analgesia is associated with a reduced risk of CS among nulliparous women with spontaneous onset of labor, especially those of advanced maternal age. High-quality routine data collected through medical birth registers, including information on administration of oxytocin, timing of epidural analgesia and the indication for CS, may add external validity to our results.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

1. Bugg GJ, Siddiqui F, Thornton JG. Oxytocin versus no treatment or delayed treatment for slow progress in the first stage of spontaneous labour. Cochrane Database Syst Rev. 2013;(6):CD007123.
2. Clark SL, Simpson KR, Knox GE, Garite TJ. Oxytocin: new perspectives on an old drug. Am J Obstet Gynecol. 2009;200:35.e1–6.
3. Rygh AB, Skjeldestad FE, Körner H, Eggebø TM. Assessing the association of oxytocin augmentation with obstetric anal sphincter injury in nulliparous women: a population-based, case–control study. BMJ Open. 2014;4:e004592.
4. Selin L, Almstrom E, Wallin G, Berg M. Use and abuse of oxytocin for augmentation of labor. Acta Obstet Gynecol Scand. 2009;88:1352–7.
5. Laughon SK, Branch DW, Beaver J, Zhang J. Changes in labor patterns over 50 years. Am J Obstet Gynecol. 2012;206:419.e1–9.
6. Herstad L, Klungsøyr K, Skjaerven R, Tanbo T, Forsén L, Åbyholm T, et al. Maternal age and emergency operative deliveries at term: a population-based registry study among low-risk primiparous women. BJOG. 2015;122:1642–51.
7. Cheng YW, Shaffer BL, Nicholson JM, Caughey AB. Second stage of labor and epidural use: a larger effect than previously suggested. Obstet Gynecol. 2014;123:527–35.
8. Costley PL, East CE. Oxytocin augmentation of labour in women with epidural analgesia for reducing operative deliveries. Cochrane Database Syst Rev. 2013;(7): CD009241.
9. Robson M. Classification of caesarean sections. Fetal Matern Med Rev. 2001;12:123–39.
10. Ekelund CK, Jørgensen FS, Petersen OB, Sundberg K, Tabor A. Impact of a new national screening policy for Down's syndrome in Denmark: population based cohort study. BMJ. 2008;337:a2547.
11. Anim-Somuah M, Smyth RMD, Jones L. Epidural versus non-epidural or no analgesia in labour. Cochrane Database Syst Rev. 2011;(12):CD000331.
12. Sng BL, Leong WL, Zeng Y, Siddiqui FJ, Assam PN, Lim Y, et al. Early versus late initiation of epidural analgesiafor labour. Cochrane Database Syst Rev. 2014; (10):CD007238.
13. Wei S, Wo BL, Qi HP, Xu H, Luo ZC, Roy C, et al. Early amniotomy and early oxytocin for prevention of, or therapy for, delay in first stage spontaneous labour compared with routine care. Cochrane Database Syst Rev. 2013;(8):CD006794.
14. Brown HC, Paranjothy S, Dowswell T, Thomas J. Package of care for active management in labour for reducing caesarean section rates in low-risk women. Cochrane Database Syst Rev. 2013;(9):CD004907.
15. Kotaska AJ, Klein MC, Liston RM. Epidural analgesia associated with low-dose oxytocin augmentation increases cesarean births: a critical look at the external validity of randomized trials. Am J Obstet Gynecol. 2006;194:809–14.
16. Pyykönen A, Gissler M, Løkkegaard E, Bergholt T, Rasmussen SC, Smárason A, et al. Cesarean section trends in the Nordic Countries – a comparative analysis with the Robson classification. Acta Obstet Gynecol Scand. 2017;96:607–16.