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

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Conflicts of interest

None of the authors have any conflict of interest

Abstract

Introduction: Maternal age is an established risk factor for cesarean section (CS), whereas 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 CS.

Material and methods: In all, 416 386 nulliparous women with spontaneous onset of labor, ≥ 37 weeks of gestation, 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, whereas epidural analgesia, oxytocin augmentation, birthweight and time period were explanatory variables. Chi-squared test and logistic regression were used to estimate associations and interactions.

Results: The CS 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 on the risk of CS. Women with epidural analgesia generally had a reduced adjusted odds ratio when oxytocin was used compared to when not used. In Norway, this applied to all maternal age groups, but in Denmark only for women ≥ 30 years. Among women without epidural, oxytocin augmentation was associated with an increased odds ratio for CS in Denmark, while no difference was observed in Norway.

Conclusions: Oxytocin augmentation in nulliparous women with epidural analgesia is associated with a reduced risk of CS in labors with spontaneous onset.

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

Abbreviations:

BW	Birthweight
CS	Cesarean section
EA	Epidural analgesia
MBRN	Medical birth registry of Norway
OA	Oxytocin augmentation
RCTs	Randomized clinical trials
RR	Relative risk

Key message:

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

Introduction

Oxytocin augmentation has for 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 cesarean section (CS) rate (5). Maternal age at first delivery has increased steadily during the last decades, 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 risk for CS, despite 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.

Materials and methods

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

Variables were harmonized across birth register in the merged database. Maternal age was defined as the difference in completed years between date of delivery and maternal date of birth, and categorized into six groups (< 20, 20–24, 25–29, 30–34, 35–39, ≥40 years). Parity and previous caesarean delivery were defined as the highest number of births based on information in the register (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 bi-parietal diameter in second trimester, but from 2004 and onwards a first trimester scan for crown-rump length was basis for assessment of

GA 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 CSs not reported as elective. Since 1998, the Medical Birth Registry of Norway (MBRN) has gathered information about mothers and their corresponding pregnancies, deliveries and infants, via check boxes supplemented with free text information on the birth notification form. Use of oxytocin and epidural analgesia are based on check boxes, and a sample of this information was validated against medical records at reporting hospitals by one of the authors (KK). The validation showed a positive predictive value of 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 2000–02, 2003–05, 2006–08 and 2009–11. Included in the original database were women who delivered after the 22nd gestational week, or, if gestational age was missing, women who gave birth to infants with a birthweight of 500 g or more.

Statistical analyses

All analyses were done in Statistical Package for Social Sciences (SPSS) version 21. Chi-squared 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 approvals

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 January 1st 2000 to December 31st 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 final study period in Denmark (0.4% to 0.9%), but decreased in Norway (1.8% to 0.7%).

The study population comprised 416 386 women, representing 29.8% (225 678/757 257) of all Danish and 29.1% (203 420/699 754) of all Norwegian women giving birth 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, while 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 from 72% to 75% in Denmark but increased moderately from 62% to 69% in Norway. 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 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 exposed to neither epidural analgesia nor oxytocin augmentation (data not shown). Among women with epidural 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, on 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 nor 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, while in Denmark this association held for women 30 years or older (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 groups 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 administrated compared to not administrated, except in the oldest age group (≥ 40 years).

In predicting CS among the Norwegian study population, there was 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 by age and use of epidural analgesia (data not shown).

The overall prevalence of birthweight ≥ 4000 g decreased over the study years, 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). In both countries, however, birthweight had no 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 2009-11. Stratified by maternal age, use of oxytocin versus no oxytocin use 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 or older. Among women without epidural analgesia, oxytocin augmentation showed minimal impact on the risk of CS in Norway, while its use was associated with an increased risk of CS in women less than 40 years old in Denmark.

This study applies 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 were 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 to 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 versus non-epidural analgesia on women in labor, and found no difference in the overall risk of CS (risk ratio (RR) 1.10 (95% CI: 0.97–1.25)) (13). 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 9 trials) (14). Use of epidural analgesia increases the use of oxytocin (13), but use of oxytocin among women with epidural analgesia is not yet 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 to expectant management in prevention of delayed labor found that 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) (15). There was, however, large heterogeneity related to use of epidural analgesia and oxytocin

between the included studies, an issue the authors did not explore (15). Another Cochrane review with data from six trials revealed that active management of labor (defined as strict diagnosis of labor, routine amniotomy, oxytocin for slow progress and one-to-one support in labor) gave a modest, but significant, reduced risk of CS (RR 0.77, 95% (CI: 0.63–0.94)) (16). 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 through other variables, as shown in the present study. Furthermore, the authors of this review did not discuss the large variations in oxytocin use in relation to diverging CS rates (16), nor did they consider use of oxytocin as a possible modifier on 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 (RCTs) due to residual confounding in observational studies and lack of external validity in RCT studies. Kotaska et al. (17) demonstrated that use of high oxytocin doses compared to low oxytocin doses among women with 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 included in the various Cochrane reviews cited above (8, 13–16), will probably still yield an insufficient sample size for valid conclusions. Therefore, in situations where RCTs may not be performed or will not achieve sample sizes large enough for answering 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 (co-linearity). 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 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's timeframe (Table 1). Because of the strong associations observed in our study, we argue that our findings are plausible and that they add knowledge on the use of oxytocin augmentation on a population level.

We have in the present study 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 comprise nearly 30% of all women giving birth, and nearly 20% of all CS are denoted this subset of parturients in the Nordic countries (18). Any efforts of preventing CS in Robson group 1, will inevitably decrease the overall CS rate, but 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 (18).

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 for 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 cesarean section, may add external validity to our results.

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Legends of figures

Figure 1: CS rates by use/no use of epidural, time period, age and country (upper panel). CS rates by use/no use of oxytocin augmentation, time period, age and country (lower panel) (%).

Time period: **Blue:** 2000-02 **Red**: 2003-05 **Green:** 2006-08 **Black:** 2009-11

Figure 2: Adjusted Odds Ratio (log. scale) for CS, stratified by use/no use of epidural analgesia and use/no use of oxytocin, by age and country (age group 20-24 years is reference).

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

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

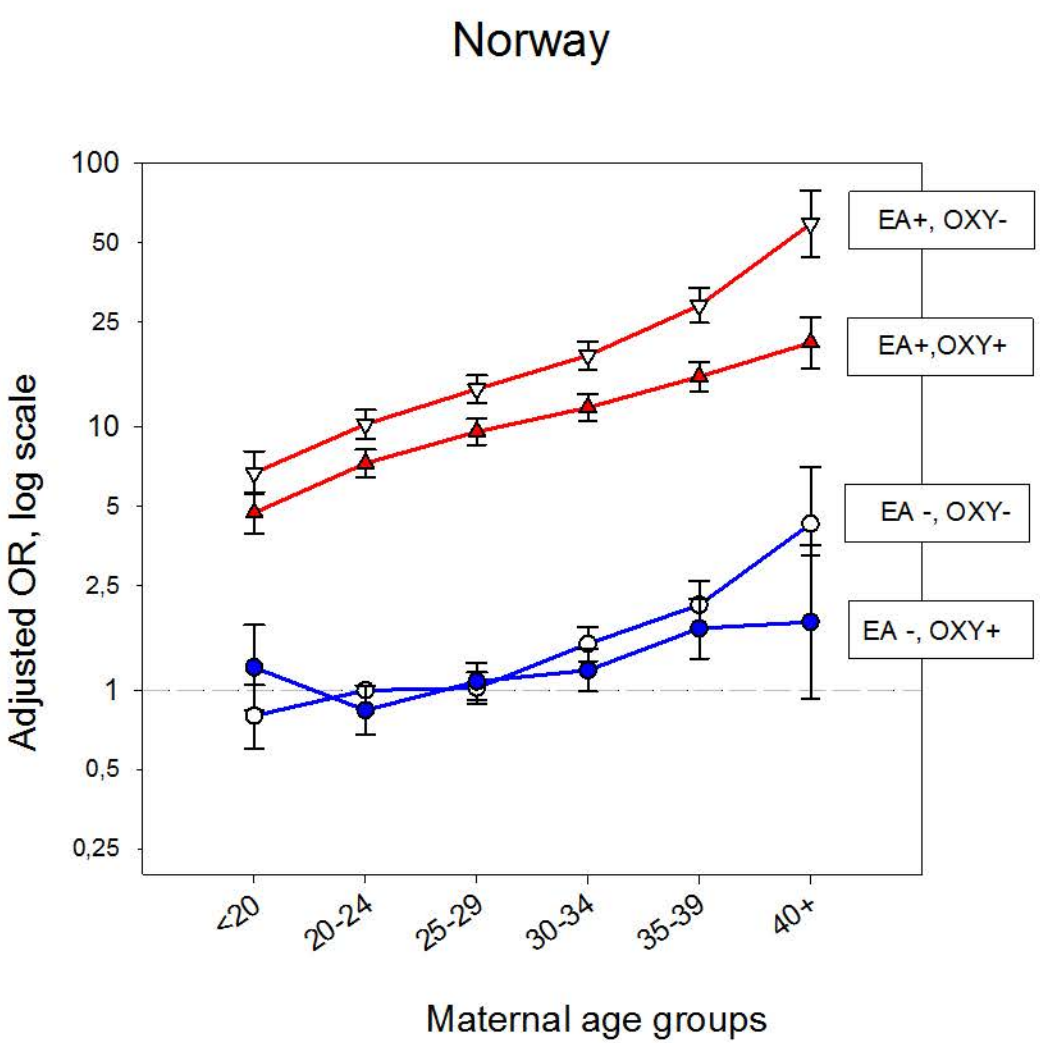
*Age-standardized

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

		Denmark				Norway			
Time-period		**2000-02**	**2003-05**	**2006-08**	**2009-11**	**2000-02**	**2003-05**	**2006-08**	**2009-11**
		N=61 401	N=57 172	N=57 343	N=49 762	N=49 515	N=49 071	N=51 718	N=53 116
		%	%	%	%	%	%	%	%
No use of epidural analgesia, 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

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. *Age-standardized

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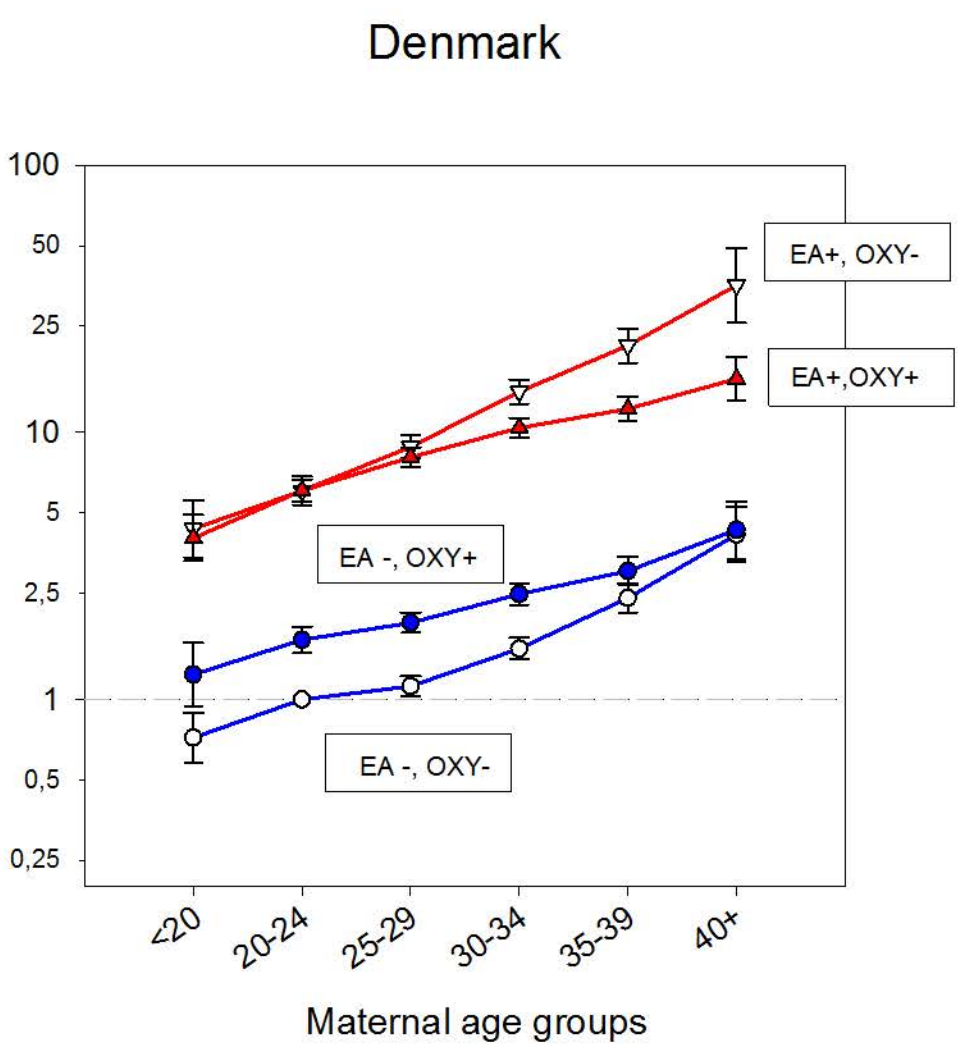
EA -, OXY-
EA -, OXY+
<20
20-24
25-29
30-34
35-39
40+
Maternal age groups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EA+,OXY+
EA -, OXY+
EA -, OXY-
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20-24
25-29
30-34
35-39
40+
Maternal age groups