Assessing the risk of oxytocin augmentation on obstetric anal sphincter injury in nulliparous women

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ASSESSING THE RISK OF OXYTOCIN AUGMENTATION ON OBSTETRIC ANAL SPHINCTER INJURY IN NULLIPAROUS WOMEN

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Oxytocin augmentation and anal sphincter injury

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ABSTRACT

Objective: To assess the effect of oxytocin augmentation on obstetric anal sphincter injury among nulliparous women.

Design: Cross-sectional, population-based study.

Setting: Primary and secondary teaching hospital serving a Norwegian region.

Population: 15 493 nulliparous women with spontaneous start of labour, single cephalic presentation, and gestation ≥37 weeks delivering vaginally between 1999 and 2012.

Methods: Based on the presence or absence of oxytocin augmentation, episiotomy, operative vaginal delivery, and birth weight (<4000 g vs. ≥4000 g), we did stratified analysis of all 16 combinations to assess the risk of anal sphincter injury. Within a modified model, we tested for possible confounding, and interactions between maternal age, ethnicity, occiput posterior position, and epidural analgesia.

Main outcome measure: Obstetric anal sphincter injury.

Results: Oxytocin augmentation was associated with an increased risk of obstetric anal sphincter injuries in women giving spontaneous birth to infants weighing <4000 g (OR 1.7; 95% CI: 1.4–2.1). Episiotomy did not influence the risk during spontaneous deliveries, but was protective in operative vaginal deliveries. Spontaneous delivery of infants weighing ≥4000 g was associated with a 3-fold increased risk of obstetric anal sphincter injuries, and epidural analgesia reduced the risk by 30%.

Conclusions: Oxytocin augmentation was associated with an increased risk of obstetric anal sphincter injuries during spontaneous deliveries of normal-sized infants. We observed a considerable effect modification between the most important risk factors involved in the active second stage of labour.

ARTICLE SUMMARY

Strengths and limitations of this study

- Stratifying by the main risk factors that are active during the expulsive phase of labour and testing for confounders is a strength of the study.
- We reveal how oxytocin augmentation interacts with other major risk factors active in the expulsive phase of labour.
- The study is based on prospectively collected data from a large unselected population, which make bias unlikely.
- The study design is a limitation, as we cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study, however a randomized, controlled study would not be feasible.

- There are possible risk modifiers that were unavailable in our database.

INTRODUCTION

Obstetric anal sphincter injuries occur in 0.5–5.0% of vaginal deliveries,[1] with a subsequently increased risk of fecal incontinence.[2-4] Primiparity,[1, 3, 5] high birth weight,[1, 3, 5, 6] operative vaginal delivery,[1, 3, 5] advanced maternal age,[1, 5, 6] ethnicity other than Caucasian,[1, 7] and prolonged second stage of labour[3, 7, 8] are consistently reported as risk factors for obstetric anal sphincter injuries , whereas the effect of epidural analgesia[9, 10] and episiotomy[1, 11-13] is debated. However, only a few authors have evaluated oxytocin augmentation as a possible risk factor for obstetric anal sphincter injuries.[5, 14, 15] The current literature dealing with risk factors for obstetric anal sphincter injuries has not sufficiently addressed their possible interactions. Studies usually present a summary of associations between risk factors and obstetric anal sphincter injuries adjusted for confounders without investigating effect modification, i.e. exploring whether the effects are uniform across various levels of the studied risk factors.

In many delivery units, oxytocin augmentation is used during more than half of births.[16, 17] Oxytocin augmentation has been shown to shorten the duration of labour, but not to decrease the need for operative deliveries.[18] We hypothesize that oxytocin augmentation may reduce control over contractions and impair perineal support by causing the delivery to progress too quickly, and thereby increase the risk of perineal injury. Thus, the widespread use of oxytocin in daily obstetric practice calls for an exploration of its possible harmful effects. The aim of our study was to explore the effect of oxytocin augmentation on the occurrence of obstetric anal sphincter injuries in a dynamic model of main risk factors in the active second stage of labour.

MATERIALS AND METHODS

The Department of Obstetrics and Gynaecology of Stavanger University Hospital serves as the only delivery unit for a population of 320 000 people, and approximately 4 500 deliveries occur there annually. From 1996 onward, all obstetric data have been consecutively recorded. The electronic database consists of clearly defined variables, and is continuously maintained using standardized procedures for data entry and quality control. During the study period (15 May 1999 to 15 May 2012), 56 517 women with a pregnancy duration of ≥23 weeks of gestation and infants with a birth weight of >300 grams delivered in the department. Estimated day of delivery was determined by second trimester ultrasound scan or from menstrual data when no ultrasound was performed. We restricted the study population to nulliparous women whose labour started spontaneously, with single cephalic presentation, pregnancies of ≥37 weeks of gestation (Group 1 in Robson's Ten Group Classification System; TGCS[19]), and who delivered vaginally. After excluding 52 women with no estimated day of delivery, this cross-sectional study comprised 15 493 women.

The main outcome measure was obstetric anal sphincter injuries as defined by the International Continence Society, i.e. partial or complete tears of the anal sphincter muscles, with or without disruption of the anal mucosa (grade 3–4 perineal tears).[20] When an obstetric anal sphincter injury was suspected, the obstetrician on call diagnosed the grade of the tear during surgical repair.

Oxytocin augmentation was defined as oxytocin used to stimulate contractions during established labour. An intravenous infusion of 5 international units (0.01mg) oxytocin in 500 ml saline was administered, starting with 30 ml per hour, and a dose increment of 15 ml per hour every 15 minutes to a maximum of 180 ml per hour, guided by the response. Normal births were taken care of by midwives, while doctors performed the operative deliveries. Throughout the study period, episiotomy was performed either medio-laterally or laterally.

According to our routines and national guidelines, operative vaginal delivery was indicated if delivery had not taken place after 60 minutes of bearing down. We used vacuum extraction with a Malmstrøm metal cup as the preferred procedure for operative vaginal delivery. Vacuum extraction was applied for mid-cavity and outlet release. A combination of low-dose ropivicaine/fentanyl was used for epidural analgesia. Ethnicity was classified as Caucasian or non-Caucasian.

We analysed our dataset using the Chi-squared test and forward stepwise logistic regression analyses with $p<0.05$ as significance level. We applied a stratified approach to investigate the impact of oxytocin augmentation on the outcome across the presence (+) or absence (–) during labour of episiotomy, operative vaginal delivery, and birth weight (<4000 g or ≥4000 g). We displayed all 16 possible combinations of the four variables, with absence of oxytocin augmentation, episiotomy, and operative vaginal delivery, and birth weight <4000 g set as the reference value. From these stratified analyses, we collapsed strata that were non-significant, taking the order of occurrence and the clinical impact of the risk factor into consideration. In this modified model, we tested for possible confounding effects and interactions from maternal age, ethnicity, occiput posterior position, and epidural analgesia in forward stepwise logistic regression analyses. Confounders were tested one by one and set to at least 10% change in any estimate of combinations of the modified target variables on obstetric anal sphincter injuries. Interaction terms were significant at $p<0.05$. Statistical analyses were performed with IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.

The Regional Committee for Medical and Health Research Ethics, Western Norway, approved the protocol as a quality assurance study in obstetric care, and fulfilling the requirements for data protection procedures (REK 2011-1247).

RESULTS

The study population comprised 15 493 (27%) of the 57 036 women giving birth during the study period, including 1014 (54%) of a total of 1894 women diagnosed with obstetric anal sphincter injuries.

The overall prevalence of obstetric anal sphincter injuries was 6.5%. The rate declined from 9.6% in 1999–2000 to 2.8% in 2010–2012. The characteristics of the study population and the prevalence of obstetric anal sphincter injuries are displayed in Table 1.

Table 1 Characteristics of the study population and the prevalence of obstetric anal sphincter injury

	Obstetric anal sphincter injury		In total	Prevalence	*p Value*
Factor	**No**	**Yes**			
	N=14 479	**N=1014**	**N=15 493**		
	%	**%**		**%**	
Time period					<0.001
1999–2000	11.1	16.9	1781	9.6	
2001–2003	19.7	30.6	3169	9.8	
2004–2006	22.9	29.6	3611	8.3	
2007–2009	25.5	14.3	3833	3.8	
2010–2012	20.8	8.6	3099	2.8	
Maternal factors					
Age (years)					<0.001
Younger than 25	26.6	19.3	4041	4.9	
25–29	33.5	37.6	5241	7.3	
30–34	17.8	20.9	2788	7.6	
35 and older	22.1	22.2	3423	6.6	
Origin					0.12
Caucasian	90.5	92.0	14 039	6.6	
Non-Caucasian	9.5	8,0	1454	5.6	
Obstetric factors					
Epidural analgesia					0.77
No	58.1	57.6	8997	6.5	
Yes	41.9	42.4	6496	6.6	
Oxytocin augmentation					<0.001
No	55.6	44.8	8507	5.3	
Yes	44.4	55.2	6986	8.0	
Active second stage of labour (min)					<0.001
0–14	11.4	7.1	1723	4.2	
15–29	26.8	18.4	4066	4.6	
30–59	40.1	37.8	6188	6.2	
>59	21.7	36.7	3516	10.6	
Episiotomy					0.24
No	67.1	65.3	10 376	6.4	
Yes	32.9	34.7	5117	6.9	
Operative vaginal delivery					<0.001

No	77.5	60.1	11 829	5.1	
Yes	22.5	39.9	3664	11.1	
Fetal factors					
Birth weight (g)					<0.001
<4000	88.3	74.8	13 543	5.6	
≥4000	11.7	25.2	1950	13.1	
Occiput posterior position					0.28
No	95.5	94.8	14 787	6.5	
Yes	4.5	5.2	706	7.5	

The prevalence was higher in women who received oxytocin augmentation (8.0% vs. 5.3%), those who were delivered instrumentally (11.1% vs. 5.1%), and in those who gave birth to an infant weighing ≥4000 g (13.1% vs. 5.6%). Furthermore, the prevalence increased with longer durations of the active part of the second stage of labour. In the subsequent analysis, missing data (Table 1) for birth weight (n=3), maternal age (n=2), fetal position at delivery (n=8), and duration of the second stage of labour (n=92) were re-coded into the reference category of each variable.

The results of the stratified analysis are presented in Table 2.

Table 2 Stratified analyses of the risk of obstetric anal sphincter injury by the presence (+) or absence (−) of risk factors: oxytocin augmentation, episiotomy, operative vaginal delivery, and birth weight (strata 1–16; risk group 1 as reference). Crude odds ratio (OR) and 95% confidence intervals (95%CI)

Risk group	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	95%CI
1	-	-	-	-	5353	201 (3.8)	1.0	
2	-	+	-	-	1444	60 (4.2)	1.11	0.8–1.5
3	+	-	-	-	2633	147 (5.6)	1.52	1.2–1.9
4	+	+	-	-	1055	60 (5.7)	1.55	1.2–2.1
5	-	+	+	-	539	44 (8.2)	2.3	1.6–3.2
6	+	+	+	-	1291	93 (7.2)	2.0	1.5–2.6
7	-	-	+	-	319	48 (15.0)	4.5	3.2–6.4
8	+	-	+	-	909	105 (11.6)	3.4	2.6–4.3
9	-	-	-	+	517	56 (10.8)	3.1	2.3–4.3
10	+	-	-	+	424	45 (10.6)	3.0	2.2–4.3
11	-	+	-	+	195	20 (10.3)	2.9	1.8–4.8
12	+	+	-	+	208	20 (9.6)	2.7	1.7–4.4
13	-	+	+	+	100	11 (11.0)	3.2	1.7–6.0
14	+	+	+	+	285	44 (15.4)	4.7	3.3–6.7
15	-	-	+	+	40	14 (35.0)	13.8	7.1–26.8

16	+	-	+	+	181	46 (25.4)	8.7	6.1–12.6

We found a strong effect modification between episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight on obstetric anal sphincter injuries. Oxytocin augmentation was associated with an increased risk of obstetric anal sphincter injuries during spontaneous deliveries of normal-sized infants, and was independent of episiotomy (risk groups 3 and 4). Episiotomy had no influence on anal sphincter injuries when the other risk factors were absent (risk groups 1 and 2). Oxytocin augmentation did not influence the risk of anal sphincter injury during instrumental deliveries of normal-sized infants without episiotomy (risk groups 7 and 8), which was similar to the risk associated with infants weighing ≥4000 g delivered spontaneously without episiotomy (risk groups 9 and 10). Furthermore, oxytocin use did not influence the risk of anal sphincter injuries in spontaneous (risk groups 11 and 12) or operative vaginal deliveries (risk groups 13 and 14) of infants weighing ≥4000 g when episiotomy was applied. Operative vaginal delivery of an infant weighing ≥4000 g without episiotomy represented the group with the highest risk of injury (risk groups 15 and 16) and was not influenced by oxytocin use. Episiotomy appeared to have a protective effect in operative vaginal deliveries regardless of the birth weight and the use of oxytocin (risk groups 5-8 and 13-16).

In the modified model (Table 3), we collapsed the groups shown in Table 2 that had similar risks of obstetric anal sphincter injury.

Table 3 Modified model displaying the collapsed non-significant strata (1–16) from Table 2 into new strata (A–G). Unadjusted Odds Ratios (OR), Adjusted (aOR), and 95% confidence intervals (95% CI) after adjusting for epidural analgesia

Risk group (Risk group from Table 2)	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women n	Obstetric anal sphincter injury n (%)	OR	aOR (95% CI)
A (1,2)	-	±	-	-	6797	261 (3.8)	1.0	1.0
B (3,4)	+	±	-	-	3368	207 (5.6)	1.5	1.7 (1.4–2.1)

C (5,6)	±	+	+	-	1830	137 (7.5)	2.0	2.3 (1.8–2.9)
D (7,8)	±	-	+	-	1228	153 (12.5)	3.6	4.1 (3.3–5.1)
E (9-12)	±	±	-	+	1344	141 (10.5)	2.9	3.2 (2.4–3.9)
F (13,14)	±	+	+	+	385	55 (14.3)	4.2	4.8 (3.5–6.5)
G (15,16)	±	-	+	+	221	60 (27.5)	9.3	10.7 (7.7–14.9)

Age, origin of the mother, and occiput posterior position did not change the estimates of obstetric anal sphincter injury across combinations of episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight (subgroups A to G in Table 3). The unadjusted odds ratio (OR) for the presence or absence of an epidural was 1.02; however, the adjusted OR for epidural analgesia was 0.7, i.e. an epidural reduced the risk of obstetric anal sphincter injury by 30%.

The use of oxytocin augmentation increased with the duration of the second stage of labour over all time periods (1999-2000, 2001-03, 2004-06, 2007-09, and 2010-12) from an average of 32% in <30 minutes, 46% in 30–59 minutes, and 66% (range 49–76%) in ≥60 minutes during the active second stage of labour. The prevalence of operative deliveries across all study periods was consistently between 45–48% when the active part of the second stage of labour lasted ≥60 minutes vs. 11–22% for durations of the second stage of labour of <60 minutes. We did not enter duration of second stage of labour into our modified model because of colinearity between oxytocin augmentation and duration of second stage, and colinearity between operative delivery and duration of second stage.

DISCUSSION

We found that oxytocin augmentation during active labour was associated with a 70% increased risk of obstetric anal sphincter injury in women in TGCS group 1 giving

spontaneous birth to an infant weighing <4000 g. We also found that an episiotomy did not influence the risk of tears during spontaneous deliveries, but was protective in all operative vaginal deliveries.

Oxytocin augmentation is widely used in delayed labour to prevent operative delivery. However, a Cochrane review concluded that a reduction of labour by two hours was the only proven effect, and there was no effect on operative deliveries.[18] Another recent review found the entire concept of active management of labour to be associated with a slightly reduced risk of caesarean delivery.[21] As in other studies, we found that approximately 50% of nulliparous women received oxytocin augmentation.[16, 17, 22] There is reason to believe that guidelines for the diagnosis and treatment of protracted labour are unclear or inconsistently applied in daily practice.[17] We hypothesize that stimulation with oxytocin may speed up the progress of the expulsive phase of labour, leading to rushed situations, impaired communication with the mother, and less focus on protecting the perineum and controlling delivery of the head. Recent studies from Norway indicate that focus on these elements are important to reduce the risk of perineal injuries.[23, 24]

Many authors have used logistic regression analysis to identify risk factors for obstetric anal sphincter injuries, but only a few have included oxytocin augmentation. Samuelsson et al.,[14] Prager et al.,[15] and Jander et al.[5] found that oxytocin augmentation was predictive of obstetric anal sphincter injuries in univariate analysis, but only Jander et al. confirmed this finding in multivariable analyses. Samuelsson et al. did not stratify by parity, which is a methodological weakness since the true effect of other factors is concealed by the strong impact of parity.[14] Prager et al. studied obstetric anal sphincter injuries in nulliparous women, entering oxytocin augmentation, duration of active second stage of labour, and instrumental delivery into the same model.[15]

Our study shows strong colinearity between a prolonged active second stage of labour and both oxytocin augmentation and instrumental delivery. We consider the duration of the active second stage of labour to be a "proxy" for oxytocin augmentation and instrumental delivery, and not a risk factor for obstetric anal sphincter injury in itself. Consequently, we omitted this factor from our analyses.

Jander et al. conducted a single institution, retrospective, case-control study of 214 cases to explore 44 possible risk factors, and found that oxytocin augmentation was a significant risk factor for obstetric anal sphincter injuries in multivariable analyses (OR 2.00; 95% CI 1.13–3.53).[5] However, these researchers did not stratify by parity or state whether or not interactions were tested for. Furthermore, three older studies on the risk of obstetric anal sphincter injury included oxytocin use without differentiating whether oxytocin was provided for induction or augmentation purposes.[25-27] Three large population-based studies on the risk of obstetric anal sphincter injuries did not include oxytocin augmentation in their analyses.[1, 7, 8]

The influence of epidural analgesia on anal sphincter injuries is unclear. Eskandar and Shet found a reduced risk, but did not stratify by parity.[9] Dahl and Kjølhede found epidural analgesia to be an independent protective factor in nulliparous women.[10] Poen et al. stratified by parity and found a significantly increased risk associated with epidural analgesia in nulliparous women.[28] In our study, epidural analgesia was associated with a significantly reduced risk of sphincter tears.

Our study takes into account four risk factors that exert their effect on the anal sphincter during the final minutes of delivery. As in previous studies,[1, 3, 5] we found both operative vaginal delivery and high birth weight to be strongly associated with obstetric anal sphincter injuries. We found episiotomy to be protective against sphincter tears in operative vaginal deliveries, but not in spontaneous births. This is consistent with a large national

registry study from Norway,[1] but differs from other studies.[8, 11, 13, 29, 30] In our study, neither oxytocin augmentation nor episiotomy influenced the risk of obstetric anal sphincter injuries during spontaneous delivery of infants weighing ≥4000 g.

Our methodological approach, stratifying by the main risk factors that are active during the expulsive phase of labour and testing for confounders, is a strength. This approach leads to a more detailed understanding of how oxytocin augmentation interacts with other major risk factors. Without testing for possible interactions, multivariable regression models, e.g. entering all variables simultaneously, would fail to reveal this information. This cross-sectional study is based on prospectively collected data from a large unselected population, and represents all deliveries meeting the inclusion criteria that occurred during the study period, which make bias unlikely. Our department has a high proportion of vaginal deliveries. The overall caesarean delivery rate in our institution was 12.5% over the study period. For women in TGCS group 1 the acute caesarean section rate increased from 5.0% in 1999 to 7.5% in 2012. Accordingly, the study population includes both high- and low-risk pregnancies, which adds to the external validity of our results.

However, some limitations apply. We cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study. On the other hand, for practical and ethical reasons this is not a research question that can be addressed in a randomized controlled trial. Furthermore, body mass index, maternal delivery positions, perineal support technique, and the birth attendant's experience level may be possible risk modifiers not registered in our database.

Our findings have some important implications. Birth attendants should be aware of oxytocin augmentation as an important risk factor for obstetric anal sphincter injuries in the large subgroup of nulliparous women giving spontaneous birth to a normal-sized infant. More restrictive use of oxytocin may help prevent obstetric anal sphincter injuries. Implementation

of evidence-based guidelines for using oxytocin augmentation should be encouraged, and use of a partogram with an action line defining failure to progress could be helpful.[31] Moreover, our study supports restricted use of episiotomy during normal births, and as a recommendation for operative vaginal deliveries. Birth weight is an important risk factor, but is not known prior to delivery. Fetal weight estimation by ultrasound may be considered when macrosomia is suspected.

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Contributorship

All four authors have contributed to the idea and design of the research project. ABR, TME managed the dataset and the statistical analyses were performed by FES. All four authors have contributed to the interpretation of the results and the writing of the manuscript.

Competing interests

None

Data Sharing

No additional data

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (R) In abstract; a cross sectional study, analyzed as case-control study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (R) Fulfilled
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (R) Recent studies have shown the importance of the perineal protection technique in preventing perineal tears. Oxytocin augmentation could impair the control of the perineum during the delivery by causing too fast progress in the last minutes of labour. Oxytocin augmentation is widely used (50% of births). Guidelines for its use are often deficient and the evidence for its positive effect is challenged. Therefore, oxytocin augmentation as a risk factor for obstetric anal sphincter injuries, and should be explored in a study taking other relevant risk factors into account.
Objectives	3	State specific objectives, including any prespecified hypotheses (R) To assess the effect of oxytocin augmentation on obstetric anal sphincter injury among nulliparous women.
Methods		
Study design	4	Present key elements of study design early in the paper (R) Present in Abstract and Methods.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (R) Setting: Tertiary teaching hospital. Location: Delivery department of Stavanger University Hospital, serving the total obstetric population of the region of South Rogaland. Dates 15 May 1999 – 15 May 2012. Data were collected consecutively.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. (R) Nulliparous women with spontaneous start of labour, single, cephalic pregnancy and ≥37 weeks gestation who delivered vaginally, where we had access to complete information on the main exposure and the explanatory variables. The source population was the entire obstetric population of the region.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect

		modifiers. Give diagnostic criteria, if applicable (R) Outcome: Obstetric anal sphincter injury; that is grade 3 and 4 perineal tears as defined by International Society of Incontinence. Exposure: Oxytocin augmentation in active labour, that is oxytocin intravenous infusion (5 international units (0.01mg) oxytocin in 500 ml saline) used in incremental doses during active labour. Predictors: NA Effect modifiers: Episiotomy, operative vaginal delivery, birth weight <4000 g vs ≥4000 g. Potential confounders: maternal age, ethnicity, occiput posterior position, duration of second stage of labour and epidural analgesia.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. (R) All variables are precisely defined in the obstetric databases of Stavanger University Hospital. The grade of perineal injury was assessed during operative repair and plotted directly into the database.
Bias	9	Describe any efforts to address potential sources of bias. (R) In this cross-sectional study all women giving births and who fulfil the inclusion criteria are included. There were very few cases with missing data. We may have missed some cases of perineal injury due to underreporting. The variables are hard variables with clear definitions: Use of oxotocin (yes/no), episiotomy (yes/no), mode of delivery (spontaneous/operative vaginal), birth weight categorized <4000/ ≥4000 g.
Study size	10	Explain how the study size was arrived at (R) The study size is given by the number of women fulfilling the eligibility criteria and who delivered at Stavanger University Hospital from 15 May 1999 to 15 May 2012.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. (R) Birth weight was categorized into < 4000/ ≥4000 g.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (R) Chi-square test and stepwise forward logistic regression using IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.
		(*b*) Describe any methods used to examine subgroups and interactions (R) We applied a stratified approach to control for interaction between the main variables (oxytocin augmentation, episiotomy, instrumental delivery and birth weight). Then we tested for confounding and interaction to a modified model by entering one variable at time.
		(*c*) Explain how missing data were addressed (R) Cases with missing data for estimated date of delivery were excluded. Cases with

		other missing data were recoded to the reference value in the logistic regression analyses. Very few cases with missing data (n=52).
		(*d*) If applicable, describe analytical methods taking account of sampling strategy (R) NA
		(*e*) Describe any sensitivity analyses (R) NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (R) Potentially eligible: 15 545 Confirmed eligible: 15 493 Included/analyzed: 15 493
		(b) Give reasons for non-participation at each stage (R) Cases with missing data for estimated date of delivery were excluded (n=52)
		(c) Consider use of a flow diagram (R) Not useful in this study.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (R) Given in Table 1. The study participants represent the total population of women fulfilling the inclusion criteria in a Norwegian region of 320 000 people. The study population is heterogeneous with regard to obstetric risk (overall caesarean section rate 12,5%), social status and ethnicity.
		(b) Indicate number of participants with missing data for each variable of interest (R) Cases with missing data for estimated date of delivery were excluded from the study population (n=52) Recoded to the reference category of the variable and included in the analyses: Birth weight 3 cases. Maternal age 2 cases. Lie at delivery 8 cases. Duration of second stage of labour 92 cases.
Outcome data	15*	Report numbers of outcome events or summary measures (R) Table 1. Outcome event, the dependant variable, anal sphincter injury: 1014 cases.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (R) Table 2 and 3. Confounders: paragraph 4 in Material and Methods.
		(*b*) Report category boundaries when continuous variables were categorized (R) Table 1

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (R) NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses R) NA
Discussion		
Key results	18	Summarise key results with reference to study objectives (R) Fulfilled.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (R) Bias regarding main outcome: We do not know the magnitude of underreporting of anal sphincter tear grade 3 and 4, however believe this to be low. Bias regarding main exposure: The quality system of the department relies on honest reporting by midwives and obstetricians, and has been a cornerstone in the systematic interdisciplinary work towards better clinical outcomes since 1996. We have reason to believe that ownership to the concept has resulted in good adherence to the reporting routines, and we believe the reporting of oxytocin augmentation to be a robust measure of what was actually practised. The midwives plotting the information were not aware of any research issue related to oxytocin augmentation. We consider the other main exposure variables to be robust: It is unlikely that reports of episiotomy, instrumental delivery and birth weight are skewed in any direction. The same applies to the possible confounders age, ethnicity, occiput posterior position and epidural analgesia. We believe that the reporting of these variables reflects the actual practice. Therefore we consider the estimates for risks related to anal sphincter tear grade 3 and 4 to be precise with little bias. Our stratified approach, modified model, takes care of the interaction problems between episiotomy, operative vaginal delivery, birth weight and oxytocin augmentation.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (R) Fulfilled.
Generalisability	21	Discuss the generalisability (external validity) of the study results. (R) The study participants represent the total population of women fulfilling the inclusion criteria in a Norwegian region of 320 000 people. The study population is heterogeneous with regard to obstetric risk (overall caesarean section rate 12,5%), social status and ethnicity. This adds value to the external validity of the study results. We encourage other study groups to make research on the effect of oxytocin augmentation on anal sphincter injury in other populations.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if

	applicable, for the original study on which the present article is based
	(R) No specific funding.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Assessing the association of oxytocin augmentation with obstetric anal sphincter injury in nulliparous women – a population-based, case-control study

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ASSESSING THE ASSOCIATION OF OXYTOCIN AUGMENTATION WITH OBSTETRIC ANAL SPHINCTER INJURY IN NULLIPAROUS WOMEN – A POPULATION-BASED, CASE CONTROL-STUDY

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Oxytocin augmentation and anal sphincter injury

Key words: anal sphincter injury, oxytocin, episiotomy, operative vaginal delivery, birth weight,
Word Count: 2619

ABSTRACT

Objective: To assess the association of oxytocin augmentation with obstetric anal sphincter injury among nulliparous women.

Design: A population-based, case-control study.

Setting: Primary and secondary teaching hospital serving a Norwegian region.

Population: 15 476 nulliparous women with spontaneous start of labour, single cephalic presentation, and gestation ≥37 weeks delivering vaginally between 1999 and 2012.

Methods: Based on the presence or absence of oxytocin augmentation, episiotomy, operative vaginal delivery, and birth weight (<4000 g vs. ≥4000 g), we did stratified analysis of all 16 combinations to assess the odds ratios (OR) of anal sphincter injury. Within a modified model, we tested for possible confounding, and interactions between maternal age, ethnicity, occiput posterior position, and epidural analgesia.

Main outcome measure: Obstetric anal sphincter injury.

Results: Oxytocin augmentation was associated with a higher OR of obstetric anal sphincter injuries in women giving spontaneous birth to infants weighing <4000 g (OR 1.8; 95% CI: 1.5–2.2). Episiotomy was not associated with sphincter injuries in spontaneous births, but with a lower OR in operative vaginal deliveries. Spontaneous delivery of infants weighing ≥ 4000 g was associated with a 3-fold higher OR, and epidural analgesia was associated with a 30% lower OR in comparison to no epidural analgesia.

Conclusions: Oxytocin augmentation was associated with a higher OR of obstetric anal sphincter injuries during spontaneous deliveries of normal-sized infants. We observed a

considerable effect modification between the most important factors involved in the active second stage of labour when anal sphincter injuries occur.

ARTICLE SUMMARY

Strengths and limitations of this study

- Stratifying by the main risk factors that are active during the expulsive phase of labour and testing for confounders are strengths of the study.
- We reveal how oxytocin augmentation interacts with the major factors active in the expulsive phase of labour.
- The study is based on prospectively collected data from a large, unselected population, which makes bias unlikely.
- The study design is a limitation, as we cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study.

INTRODUCTION

Obstetric anal sphincter injuries occur in 0.5–5.0% of vaginal deliveries,[1] with a subsequently increased risk of fecal incontinence.[2-4] Nulliparity,[1, 3, 5] high birth weight,[1, 3, 5, 6] operative vaginal delivery,[1, 3, 5] advanced maternal age,[1, 5, 6] Asian or African ethnicity,[1, 7] and prolonged second stage of labour[3, 7, 8] are consistently reported as risk factors for obstetric anal sphincter injuries , whereas the effect of epidural analgesia[9, 10] and episiotomy[1, 11-13] is debated. However, only a few authors have evaluated oxytocin augmentation as a possible risk factor for obstetric anal sphincter injuries.[5, 14, 15] Further, the current literature dealing with risk factors for obstetric anal sphincter injuries has not sufficiently addressed their possible interactions. Studies usually present a summary of associations between risk factors and obstetric anal sphincter injuries adjusted for confounders without investigating effect modification, i.e. exploring whether the effects are uniform across various levels of the studied risk factors.

In many delivery units, oxytocin augmentation is used during more than half of births.[16, 17] Oxytocin augmentation has been shown to shorten the duration of labour, but not to decrease the need for operative deliveries.[18] We hypothesize that oxytocin augmentation may reduce control over contractions and impair perineal support by causing the delivery to progress too quickly, and thereby increase the risk of perineal injury. Thus, the widespread use of oxytocin in daily obstetric practice calls for an exploration of its possible harmful effects. The aim of our study was to assess the association between oxytocin augmentation and obstetric anal sphincter injuries in a dynamic model related to the active second stage of labour.

MATERIALS AND METHODS

The Department of Obstetrics and Gynaecology of Stavanger University Hospital serves as the only delivery unit for a population of 320 000 people, and approximately 4500 deliveries occur there annually. From 1996 onward, all obstetric data have been consecutively recorded. The electronic database consists of clearly defined variables, and is continuously maintained using standardized procedures for data entry and quality control. During the study period 15 May 1999 to 15 May 2012, 56 517 women with a pregnancy duration of ≥23 weeks of gestation and infants with a birth weight of >300 grams delivered in the department. Estimated day of delivery was determined by second trimester ultrasound scan or from menstrual data when no ultrasound was performed. We restricted the study population to nulliparous women whose labour started spontaneously, with single cephalic presentation, pregnancies of ≥37 weeks of gestation (Group 1 in Robson's Ten Group Classification System; TGCS[19]), and who delivered vaginally. After excluding 69 women with missing data, (52 without an estimated day of delivery, 17 with missing information of fetal presentation at delivery), this case-control study comprised 15 476 women.

The main outcome measure was obstetric anal sphincter injuries as defined by the International Continence Society, i.e. partial or complete tears of the anal sphincter muscles, with or without disruption of the anal mucosa (grade 3–4 perineal tears).[20] When an obstetric anal sphincter injury was suspected, the obstetrician on call diagnosed the grade of the tear during surgical repair.

Oxytocin augmentation was defined as oxytocin used to stimulate contractions during established labour. An intravenous infusion of 5 international units (0.01mg) oxytocin in 500 ml saline was administered, starting with 30 ml per hour, and a dose increment of 15 ml per hour every 15 minutes to a maximum of 180 ml per hour, guided by the response. Normal births were taken care of by midwives, while doctors performed the operative deliveries.

Throughout the study period, episiotomy was performed either medio-laterally or laterally. According to our routines and national guidelines, operative vaginal delivery was indicated if delivery had not taken place after 60 minutes of bearing down. We used vacuum extraction with a Malmström metal cup as the preferred procedure for operative vaginal delivery. Vacuum extraction was applied for mid-cavity and outlet release. A combination of low-dose ropivicaine/fentanyl was used for epidural analgesia. Ethnicity was classified as Western i.e. originating from Europe or North America, or non-Western.

We analysed our dataset using the Chi-squared test and forward stepwise logistic regression analyses with $p<0.05$ as significance level. We applied a stratified approach to investigate the association of oxytocin augmentation and the outcome across the presence (+) or absence (–) during labour of episiotomy, operative vaginal delivery, and birth weight (<4000 g or ≥4000 g). We displayed all 16 possible combinations of the four variables, with absence of oxytocin augmentation, episiotomy, and operative vaginal delivery, and birth weight <4000 g set as the reference value. From these stratified analyses, we collapsed strata that were non-significant, taking the order of occurrence and the clinical impact of the variable into consideration. In this modified model, we tested for possible confounding effects and interactions from maternal age, ethnicity, occiput posterior position, and epidural analgesia in forward stepwise logistic regression analyses. Confounders were tested one by one and set to at least 10% change in any estimate of combinations of the modified target variables on obstetric anal sphincter injuries. Interaction terms were significant at $p<0.05$. Statistical analyses were performed with IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.

The Regional Committee for Medical and Health Research Ethics, Western Norway, approved the protocol as a quality assurance study in obstetric care, and fulfilling the requirements for data protection procedures (REK 2011-1247).

RESULTS

The study population comprised 15 476 (27%) of the 56 517 women giving birth during the study period, including 1013 (53%) of a total of 1894 women diagnosed with obstetric anal sphincter injuries.

The overall prevalence of obstetric anal sphincter injuries was 6.5%. The rate declined from 9.6% in 1999–2000 to 2.8% in 2010–2012. The characteristics of the study population and the prevalence of obstetric anal sphincter injuries are displayed in Table 1.

Table 1 Characteristics of the study population and the prevalence of obstetric anal sphincter injury. P-values from Chi-square tests.

Factor	Obstetric anal sphincter injury		In total	Prevalence	P
	No	Yes			
	N=14 463	N=1013	N=15 476		
	%	%		%	
Time period					<0.001
1999-2000	11.1	16.9	1781	9.6	
2001-2003	19.8	30.7	3169	9.8	
2004-2006	22.9	29.6	3611	8.3	
2007-2009	25.5	14.3	3826	3.8	
2010-2012	20.8	8.6	3089	2.8	
Maternal factors					
Age (years)					<0.001
<25	26.6	19.3	4040	4.9	
25-29	33.5	37.6	5233	7.3	
30-34	17.8	20.8	2785	7.6	
≥35	22.1	22.2	3418	6.6	
Origin					NS*
Western	90.5	92.0	14 025	6.6	
Non-Western	9.5	8.0	1451	5.6	
Obstetric factors					
Epidural analgesia					NS
No	58.1	57.7	8992	6.5	
Yes	41.9	42.3	6484	6.6	
Oxytocin augmentation					<0.001
No	55.6	44.7	8500	5.3	
Yes	44.4	55.3	6976	8.0	
Active 2nd stage of labour (min)					<0.001
Missing information	0.6	0.3	92	3.3	
0-14	10.8	6.8	1627	4.2	
15-29	26.8	18.5	4063	4.6	

30-59	40.1	37.8	6181	6.2	
≥60	21.7	36.6	3513	10.6	
Episiotomy					NS
No	67.1	65.4	10 372	6.4	
Yes	32.9	34.6	5104	6.9	
Operative vaginal delivery					<0.001
No	77.5	60.3	11 817	5.2	
Yes	22.5	39.7	3659	11.0	
Fetal factors					
Birth weight (g)					<0.001
<4000	87.8	74.2	13 454	5.6	
≥4000	12.2	25.8	2022	12.9	
Occiput posterior position					NS
No	95.4	94.8	14 771	6.5	
Yes	4.5	5.2	705	7.4	

* Non significant

The prevalence was higher in women who received oxytocin augmentation (8.0% vs. 5.3%), those who were delivered instrumentally (11.0% vs. 5.2%), and in those who gave birth to an infant weighing ≥4000 g (12.9% vs. 5.6%). Furthermore, the prevalence increased with longer durations of the active part of the second stage of labour.

The results of the stratified analysis are presented in Table 2.

Table 2 Stratified analyses of the prevalence of obstetric anal sphincter injury by the presence (+) or absence (−) of: oxytocin augmentation, episiotomy, operative vaginal delivery, and birth weight (strata 1–16; group 1 as reference). Crude odds ratio (OR) and 95% confidence intervals (95% CI)

Group	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	95% CI
1	-	-	-	-	5328	198 (3.7)	1.0	
2	-	+	-	-	1434	60 (4.2)	1.1	0.8-1.5
3	+	-	-	-	2621	148 (5.6)	1.5	1.3-1.9
4	+	+	-	-	1039	61 (5.9)	1.6	1.2-2.2
5	-	+	+	-	537	43 (8.0)	2.3	1.6-3.2
6	+	+	+	-	1283	92 (7.2)	2.0	1.6-2.6
7	-	-	+	-	316	47 (14.9)	4.5	3.2-6.4
8	+	-	+	-	896	103 (11.5)	3.4	2.6-4.3
9	-	-	-	+	539	59 (10.9)	3.2	2.4-4.3
10	+	-	-	+	438	45 (10.3)	3.0	2.1-4.2

11	-	+	-	+	203	20 (9.9)	2.8	1.7-4.6
12	+	+	-	+	215	20 (9.3)	2.7	1.6-4.3
13	-	+	+	+	101	11 (10.9)	3.2	1.7-6.0
14	+	+	+	+	292	44 (15.1)	4.6	3.2-6.5
15	-	-	+	+	42	15 (35.7)	14.4	7.5-27.5
16	+	-	+	+	192	47 (24.5)	8.4	5.9-12.0

We found a strong effect modification between episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight on obstetric anal sphincter injuries. Oxytocin augmentation was associated with an increased odds ratio of obstetric anal sphincter injuries during spontaneous deliveries of normal-sized infants, and was independent of episiotomy (groups 3 and 4). Episiotomy was not associated with anal sphincter injuries when the other factors were absent (groups 1 and 2). Oxytocin augmentation was not associated with anal sphincter injury during instrumental deliveries of normal-sized infants without episiotomy (groups 7 and 8), nor in spontaneous deliveries of infants weighing ≥4000 g without episiotomy (groups 9 and 10). Furthermore, oxytocin use was not associated with anal sphincter injuries in spontaneous (groups 11 and 12) or operative vaginal deliveries (groups 13 and 14) of infants weighing ≥4000 g when episiotomy was applied. Operative vaginal delivery of an infant weighing ≥4000 g without episiotomy represented the group with the highest prevalence of injury (groups 15 and 16) and was not associated with oxytocin use. Episiotomy appeared to be negatively associated with sphincter rupture in operative vaginal deliveries regardless of the birth weight and the use of oxytocin (groups 5-8 and 13-16).

In the modified model (Table 3), we collapsed the groups from Table 2 that had odds ratios of similar magnitude for obstetric anal sphincter injury.

Table 3 Modified model displaying the collapsed non-significant strata (1–16) from Table 2 into new strata (A–G). Unadjusted odds ratios (OR), adjusted (aOR), and 95% confidence intervals (95% CI) after adjusting for epidural analgesia

Group (Group in Table 2)	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	aOR (95% CI)
A (1,2)	-	+/-	-	-	6762	258 (3.8)	1.0	1.0
B (3,4)	+	+/-	-	-	3660	209 (5.7)	1.5	1.8 (1.5-2.2)
C (5,6)	+/-	+	+	-	1820	135 (7.4)	2.0	2.3 (1.8-2.8)
D (7,8)	+/-	-	+	-	1212	150 (12.4)	3.6	4.1 (3.3-5.1)
E (9-12)	+/-	+/-	-	+	1395	144 (10.3)	2.9	3.1 (2.4-3.9)
F (13,14)	+/-	+	+	+	393	55 (14.0)	4.1	4.7 (3.4-6.5)
G (15,16)	+/-	-	+	+	234	62 (26.5)	9.1	10.5 (7.6-14.4)

Age, origin of the mother, and occiput posterior position had no confounding effect on odds ratios for obstetric anal sphincter injury across combinations of episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight (groups A to G in Table 3). The use of oxytocin augmentation was restricted in the department from 2010 onwards, however, we observed a significant association between oxytocin augmentation and anal sphincter injuries through all time periods (1999-2003, 2004-2006, 2007-2009, 2010-2012). The unadjusted odds ratio (OR) for the presence or absence of epidural analgesia was 1.02; however, the adjusted OR for epidural analgesia was 0.73, (95% CI 0.63-0.84) i.e. epidural analgesia was associated with a 30% lower odds ratio of anal sphincter injury.

The use of oxytocin augmentation increased with the duration of the second stage of labour over all the time periods from an average of 32% in the <30 minutes group, 46% in the 30–59 minutes group, and 65% (range 49–76%) in the ≥60 minutes group during the active second stage of labour. The prevalence of operative deliveries across all study periods was consistently between 45–49% when the active part of the second stage of labour lasted ≥60

minutes vs. 12–21% for durations of the second stage of labour of <60 minutes. We found strong associations between oxytocin augmentation and the duration of second stage, and between operative delivery and the duration of second stage (collinearity), which means that the duration of second stage is measured through operative delivery and oxytocin augmentation.

DISCUSSION

We found that oxytocin augmentation during active labour was associated with a 70% increased odds ratio of obstetric anal sphincter injury in women in TGCS group 1 giving spontaneous birth to an infant weighing <4000 g. We did not find an association between episiotomy and tears during spontaneous deliveries, but a significantly reduced association in all operative vaginal deliveries.

Oxytocin augmentation is widely used in delayed labour to prevent operative delivery. However, a Cochrane review concluded that a reduction of labour by two hours was the only proven effect, and there was no effect on operative deliveries.[18] Another recent review found the entire concept of active management of labour to be associated with a slightly reduced risk of caesarean delivery.[21] As in other studies, we found that approximately 50% of nulliparous women received oxytocin augmentation.[16, 17, 22] There is reason to believe that guidelines for the diagnosis and treatment of protracted labour are unclear or inconsistently applied in daily practice.[17] We hypothesize that stimulation with oxytocin may speed up the progress of the expulsive phase of labour, leading to rushed situations, impaired communication with the mother, and less focus on protection of the perineum and a controlled delivery of the head. Recent studies from Norway indicate that focus on these elements is important in preventing perineal injuries.[23, 24]

Many authors have used logistic regression analysis to identify risk factors for obstetric anal sphincter injuries, but only a few have included oxytocin augmentation. Samuelsson et al.,[14] Prager et al.,[15] and Jander et al.[5] found oxytocin augmentation to be predictive of obstetric anal sphincter injuries in univariate analysis, but only Jander et al. confirmed this finding in multivariable analyses. Samuelsson et al. did not stratify by parity, which is a methodological weakness since the true effect of other factors is concealed by the strong impact of parity.[14] Prager et al. studied obstetric anal sphincter injuries in nulliparous women, entering oxytocin augmentation, duration of active second stage of labour, and instrumental delivery into the same model.[15]

Our study shows strong collinearity between a prolonged active second stage of labour and both oxytocin augmentation and instrumental delivery. We consider the duration of the active second stage of labour to be a "proxy" for oxytocin augmentation and instrumental delivery, and not a risk factor for obstetric anal sphincter injury in itself. Long duration of the second stage is a time related event before the expulsion of the head. During this latency the active forces do not inflict injury on the sphincter apparatus, the sphincter injury occurs during the expulsive phase. Consequently, we do not consider the duration of the active second stage as a risk factor for anal sphincter injuries.

Jander et al. conducted a single institution, retrospective, case-control study of 214 cases to explore 44 possible risk factors, and found that oxytocin augmentation was a significant risk factor for obstetric anal sphincter injuries in multivariable analyses (OR 2.00; 95% CI 1.13–3.53).[5] However, these researchers did not stratify by parity or state whether or not interactions were tested for. Furthermore, three older studies on the risk of obstetric anal sphincter injury included oxytocin use without differentiating whether oxytocin was provided for induction or augmentation purposes.[25-27] Three large population-based studies on the risk

of obstetric anal sphincter injuries did not include oxytocin augmentation in their analyses.[1, 7, 8]

The influence of epidural analgesia on anal sphincter injuries is unclear. Eskandar and Shet found a reduced risk, but did not stratify by parity.[9] Dahl and Kjølhede found epidural analgesia to be an independent protective factor in nulliparous women.[10] Poen et al. stratified by parity and found a significantly increased odds ratio associated with epidural analgesia in nulliparous women.[28] In our study, epidural analgesia was associated with a significantly reduced odds ratio for sphincter tears.

Our study takes into account four factors that exert their effect on the anal sphincter during the final minutes of delivery. As in previous studies,[1, 3, 5] we found both operative vaginal delivery and high birth weight to be strongly associated with obstetric anal sphincter injuries. We found episiotomy to be associated with a lower prevalence of sphincter tears in operative vaginal deliveries, but not in spontaneous births. This is consistent with a large national registry study from Norway,[1] but differs from other studies.[8, 11, 13, 29, 30] In our study, neither oxytocin augmentation nor episiotomy were associated with obstetric anal sphincter injury during spontaneous delivery of an infant weighing ≥4000 g.

Our methodological approach, stratifying by the factors that are active during the expulsive phase of labour and testing for confounders, is considered a strength of the study. This approach leads to a more detailed understanding of how oxytocin augmentation interacts with these major risk factors. Stepwise, forward multivariable regression analyses, without testing for possible interactions, would fail to reveal this information. This case-control study is based on prospectively collected data from a large unselected population, and represents all deliveries meeting the inclusion criteria that occurred during the study period, which make bias unlikely. Our department has a high proportion of vaginal deliveries. The overall caesarean delivery rate in our institution was 12.5% over the study period. For women in

TGCS group 1 the acute caesarean section rate increased from 5.0% in 1999 to 7.5% in 2012. Accordingly, the study population includes both high- and low-risk pregnancies, which adds to the external validity of our results.

However, some limitations apply. We cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study. Furthermore, socioeconomic status, smoking, body mass index, maternal delivery positions, perineal support technique, and the birth attendant's experience level may be possible risk modifiers not included in our database. Finally, single institution studies, also when based on unselected populations, should be interpreted with caution.

Our findings have some important implications. Birth attendants should be aware of the association between oxytocin augmentation and obstetric anal sphincter injuries in the large subgroup of nulliparous women giving spontaneous birth to a normal-sized infant. More restrictive use of oxytocin may help prevent obstetric anal sphincter injuries. Implementation of evidence-based guidelines for using oxytocin augmentation should be encouraged. The World Health Organization recommends the use of a partogram with an action line defining failure to progress. However, a recent Cochrane review could not confirm that such a partogram was beneficial in high resource settings.[31] Given the doubtful benefits from augmentation of labour, randomized controlled trials are strongly needed, and we propose anal sphincter injury as one of the most important endpoints.

Moreover, our study supports restricted use of episiotomy during normal births and as a recommendation for operative vaginal deliveries. Birth weight is an important, albeit unpredictable risk factor as weight estimation of a large fetus is unreliable.[32]

Acknowledgements

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Contributorship Statement

All four authors have contributed to the idea and design of the research project. ABR, TME managed the dataset and the statistical analyses were performed by FES. All four authors have contributed to the interpretation of the results and the writing of the manuscript.

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Competing interests

None

Data Sharing Statement

There is no additional data material to be shared.

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Assessing the association of oxytocin augmentation with obstetric anal sphincter injury in nulliparous women – a population-based, case-control study

Comment [ar1]: Title changed acc. to Editor and rev. comm.

ARTICLE SUMMARY

Strengths and limitations of this study

- Stratifying by the main risk factors that are active during the expulsive phase of labour and testing for confounders are strengths of the study.
- We reveal how oxytocin augmentation interacts with the major factors active in the expulsive phase of labour.
- The study is based on prospectively collected data from a large, unselected population, which makes bias unlikely.
- The study design is a limitation, as we cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study.

Comment [ar2]: Steer 1

INTRODUCTION

Obstetric anal sphincter injuries occur in 0.5–5.0% of vaginal deliveries,[1] with a subsequently increased risk of fecal incontinence.[2-4] Nulliparity,[1, 3, 5] high birth weight,[1, 3, 5, 6] operative vaginal delivery,[1, 3, 5] advanced maternal age,[1, 5, 6] Asian or African ethnicity,[1, 7] and prolonged second stage of labour[3, 7, 8] are consistently reported as risk factors for obstetric anal sphincter injuries , whereas the effect of epidural analgesia[9, 10] and episiotomy[1, 11-13] is debated. However, only a few authors have evaluated oxytocin augmentation as a possible risk factor for obstetric anal sphincter injuries.[5, 14, 15] Further, the current literature dealing with risk factors for obstetric anal sphincter injuries has not sufficiently addressed their possible interactions. Studies usually present a summary of associations between risk factors and obstetric anal sphincter injuries adjusted for confounders without investigating effect modification, i.e. exploring whether the effects are uniform across various levels of the studied risk factors.

In many delivery units, oxytocin augmentation is used during more than half of births.[16, 17] Oxytocin augmentation has been shown to shorten the duration of labour, but not to decrease the need for operative deliveries.[18] We hypothesize that oxytocin augmentation may reduce control over contractions and impair perineal support by causing the delivery to progress too quickly, and thereby increase the risk of perineal injury. Thus, the widespread use of oxytocin in daily obstetric practice calls for an exploration of its possible harmful effects. The aim of our study was to assess the association between oxytocin augmentation and obstetric anal sphincter injuries in a dynamic model related to the active second stage of labour.

Comment [ar3]: Steer, minor comment 1

Comment [ar4]: Steer 15 on origin, changed

Comment [ar5]: Steer 4

MATERIALS AND METHODS

The Department of Obstetrics and Gynaecology of Stavanger University Hospital serves as the only delivery unit for a population of 320 000 people, and approximately 4500 deliveries occur there annually. From 1996 onward, all obstetric data have been consecutively recorded. The electronic database consists of clearly defined variables, and is continuously maintained using standardized procedures for data entry and quality control. During the study period 15 May 1999 to 15 May 2012, 56 517 women with a pregnancy duration of ≥23 weeks of gestation and infants with a birth weight of >300 grams delivered in the department. Estimated day of delivery was determined by second trimester ultrasound scan or from menstrual data when no ultrasound was performed. We restricted the study population to nulliparous women whose labour started spontaneously, with single cephalic presentation, pregnancies of ≥37 weeks of gestation (Group 1 in Robson's Ten Group Classification System; TGCS[19]), and who delivered vaginally. After excluding 69 women with missing data, (52 without an estimated day of delivery, 17 with missing information of fetal presentation at delivery), this case-control study comprised 15 476 women.

Comment [ar6]: Gissler 1 on missing cases

The main outcome measure was obstetric anal sphincter injuries as defined by the International Continence Society, i.e. partial or complete tears of the anal sphincter muscles, with or without disruption of the anal mucosa (grade 3–4 perineal tears).[20] When an obstetric anal sphincter injury was suspected, the obstetrician on call diagnosed the grade of the tear during surgical repair.

Oxytocin augmentation was defined as oxytocin used to stimulate contractions during established labour. An intravenous infusion of 5 international units (0.01mg) oxytocin in 500 ml saline was administered, starting with 30 ml per hour, and a dose increment of 15 ml per hour every 15 minutes to a maximum of 180 ml per hour, guided by the response. Normal births were taken care of by midwives, while doctors performed the operative deliveries.

Throughout the study period, episiotomy was performed either medio-laterally or laterally. According to our routines and national guidelines, operative vaginal delivery was indicated if delivery had not taken place after 60 minutes of bearing down. We used vacuum extraction with a Malmstrøm metal cup as the preferred procedure for operative vaginal delivery. Vacuum extraction was applied for mid-cavity and outlet release. A combination of low-dose ropivicaine/fentanyl was used for epidural analgesia. Ethnicity was classified as Western i.e. originating from Europe or North America, or not.

We analysed our dataset using the Chi-squared test and forward stepwise logistic regression analyses with $p<0.05$ as significance level. We applied a stratified approach to investigate the association of oxytocin augmentation and the outcome across the presence (+) or absence (–) during labour of episiotomy, operative vaginal delivery, and birth weight (<4000 g or ≥4000 g). We displayed all 16 possible combinations of the four variables, with absence of oxytocin augmentation, episiotomy, and operative vaginal delivery, and birth weight <4000 g set as the reference value. From these stratified analyses, we collapsed strata that were non-significant, taking the order of occurrence and the clinical impact of the variable into consideration. In this modified model, we tested for possible confounding effects and interactions from maternal age, ethnicity, occiput posterior position, and epidural analgesia in forward stepwise logistic regression analyses. Confounders were tested one by one and set to at least 10% change in any estimate of combinations of the modified target variables on obstetric anal sphincter injuries. Interaction terms were significant at $p<0.05$. Statistical analyses were performed with IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.

The Regional Committee for Medical and Health Research Ethics, Western Norway, approved the protocol as a quality assurance study in obstetric care, and fulfilling the requirements for data protection procedures (REK 2011-1247).

Comment [ar7]: Steer minor comm. 2, Gissler minor comm. 1

Comment [ar8]: Steer 3, birth weight as dichotomous variable was needed for the stratified model

RESULTS

The study population comprised 15 476 (27%) of the 56 517 women giving birth during the study period, including 1013 (53%) of a total of 1894 women diagnosed with obstetric anal sphincter injuries.

The overall prevalence of obstetric anal sphincter injuries was 6.5%. The rate declined from 9.6% in 1999–2000 to 2.8% in 2010–2012. The characteristics of the study population and the prevalence of obstetric anal sphincter injuries are displayed in Table 1.

Table 1 Characteristics of the study population and the prevalence of obstetric anal sphincter injury

Factor	Obstetric anal sphincter injury		In total	Prevalence	P
	No N=14 463 %	Yes N=1013 %	N=15 476	%	
Time period					<0.001
1999-2000	11.1	16.9	1781	9.6	
2001-2003	19.8	30.7	3169	9.8	
2004-2006	22.9	29.6	3611	8.3	
2007-2009	25.5	14.3	3826	3.8	
2010-2012	20.8	8.6	3089	2.8	
Maternal factors					
Age (years)					<0.001
<25	26.6	19.3	4040	4.9	
25-29	33.5	37.6	5233	7.3	
30-34	17.8	20.8	2785	7.6	
≥35	22.1	22.2	3418	6.6	
Origin					NS*
Western	90.5	92.0	14 025	6.6	
Not Western	9.5	8.0	1451	5.6	
Obstetric factors					
Epidural analgesia					NS
No	58.1	57.7	8992	6.5	
Yes	41.9	42.3	6484	6.6	
Oxytocin augmentation					<0.001
No	55.6	44.7	8500	5.3	
Yes	44.4	55.3	6976	8.0	
Active 2nd stage of labour (min)					<0.001
Missing information	0.6	0.3	92	3.3	
0-14	10.8	6.8	1627	4.2	
15-29	26.8	18.5	4063	4.6	

Comment [ar9]: Throughout Results we have replaced terminology indicating causality, complying with Steers remark 4.

Comment [ar10]: 27% is still correct

Comment [ar11]: Now corrected to 53%

Comment [ar12]: New analyses

30-59	40.1	37.8	6181	6.2	
≥60	21.7	36.6	3513	10.6	
Episiotomy					NS
No	67.1	65.4	10 372	6.4	
Yes	32.9	34.6	5104	6.9	
Operative vaginal delivery					<0.001
No	77.5	60.3	11 817	5.2	
Yes	22.5	39.7	3659	11.0	
Fetal factors					
Birth weight (g)					<0.001
<4000	87.8	74.2	13 454	5.6	
≥4000	12.2	25.8	2022	12.9	
Occiput posterior position					NS
No	95.4	94.8	14 771	6.5	
Yes	4.5	5.2	705	7.4	

* Non significant

The prevalence was higher in women who received oxytocin augmentation (8.0% vs. 5.3%), those who were delivered instrumentally (11.0% vs. 5.2%), and in those who gave birth to an infant weighing ≥4000 g (12.9% vs. 5.6%). Furthermore, the prevalence increased with longer durations of the active part of the second stage of labour.

The results of the stratified analysis are presented in Table 2.

Table 2 Stratified analyses of the prevalence of obstetric anal sphincter injury by the presence (+) or absence (−) of: oxytocin augmentation, episiotomy, operative vaginal delivery, and birth weight (strata 1–16; group 1 as reference). Crude odds ratio (OR) and 95% confidence intervals (95% CI)

Comment [ar13]: new analysis

~~Risk~~ Group	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	95% CI
1	-	-	-	-	5328	198 (3.7)	1.0	
2	-	+	-	-	1434	60 (4.2)	1.13	0.8-1.5
3	+	-	-	-	2621	148 (5.6)	1.53	1.3-1.9
4	+	+	-	-	1039	61 (5.9)	1.62	1.2-2.2
5	-	+	+	-	537	43 (8.0)	2.3	1.6-3.2
6	+	+	+	-	1283	92 (7.2)	2.0	1.6-2.6
7	-	-	+	-	316	47 (14.9)	4.5	3.2-6.4
8	+	-	+	-	896	103 (11.5)	3.4	2.6-4.3
9	-	-	-	+	539	59 (10.9)	3.2	2.4-4.3
10	+	-	-	+	438	45 (10.3)	3.0	2.1-4.2

11	-	+	-	+	203	20 (9.9)	2.8	1.7-4.6
12	+	+	-	+	215	20 (9.3)	2.7	1.6-4.3
13	-	+	+	+	101	11 (10.9)	3.2	1.7-6.0
14	+	+	+	+	292	44 (15.1)	4.6	3.2-6.5
15	-	-	+	+	42	15 (35.7)	14.4	7.5-27.5
16	+	-	+	+	192	47 (24.5)	8.4	5.9-12.0

We found a strong effect modification between episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight on obstetric anal sphincter injuries. Oxytocin augmentation was associated with an increased odds ratio of obstetric anal sphincter injuries during spontaneous deliveries of normal-sized infants, and was independent of episiotomy (groups 3 and 4). Episiotomy was not associated with anal sphincter injuries when the other factors were absent (groups 1 and 2). Oxytocin augmentation was not associated with anal sphincter injury during instrumental deliveries of normal-sized infants without episiotomy (groups 7 and 8), nor in spontaneous deliveries of infants weighing ≥4000 g without episiotomy (groups 9 and 10). Furthermore, oxytocin use was not associated with anal sphincter injuries in spontaneous (groups 11 and 12) or operative vaginal deliveries (groups 13 and 14) of infants weighing ≥4000 g when episiotomy was applied. Operative vaginal delivery of an infant weighing ≥4000 g without episiotomy represented the group with the highest prevalence of injury (groups 15 and 16) and was not associated with oxytocin use. Episiotomy appeared to be negatively associated with sphincter rupture in operative vaginal deliveries regardless of the birth weight and the use of oxytocin (groups 5-8 and 13-16).

In the modified model (Table 3), we collapsed the groups from Table 2 that had odds ratios of similar magnitude for obstetric anal sphincter injury.

Table 3 Modified model displaying the collapsed non-significant strata (1–16) from Table 2 into new strata (A–G). Unadjusted odds ratios (OR), adjusted (aOR), and 95% confidence intervals (95% CI) after adjusting for epidural analgesia

Comment [ar14]: new analysis

Group (Group in Table 2)	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	aOR (95% CI)
A (1,2)	-	+/-	-	-	6762	258 (3.8)	1.0	1.0
B (3,4)	+	+/-	-	-	3660	209 (5.7)	1.5	1.8 (1.5-2.2)
C (5,6)	+/-	+	+	-	1820	135 (7.4)	2.0	2.3 (1.8-2.8)
D (7,8)	+/-	-	+	-	1212	150 (12.4)	3.6	4.1 (3.3-5.1)
E (9-12)	+/-	+/-	-	+	1395	144 (10.3)	2.9	3.1 (2.4-3.9)
F (13,14)	+/-	+	+	+	393	55 (14.0)	4.1	4.7 (3.4-6.5)
G (15,16)	+/-	-	+	+	234	62 (26.5)	9.1	10.5 (7.6-14.4)

Age, origin of the mother, and occiput posterior position had no confounding effect on odds ratios for obstetric anal sphincter injury across combinations of episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight (groups A to G in Table 3). The use of oxytocin augmentation was restricted in the department from 2010, however, we observed a significant association between oxytocin augmentation and anal sphincter injuries through all time periods (1999-2003, 2004-2006, 2007-2009, 2010-2012). The unadjusted odds ratio (OR) for the presence or absence of epidural analgesia was 1.02; however, the adjusted OR for epidural analgesia was 0.73, (95% CI 0.63-0.84) i.e. epidural analgesia was associated with a 30% lower odds ratio of anal sphincter injury.

Comment [ar15]: Comment Steer 2

Comment [ar16]: New analysis

The use of oxytocin augmentation increased with the duration of the second stage of labour over all the time periods from an average of 32% in the <30 minutes group, 46% in the 30–59 minutes group, and 65% (range 49–76%) in the ≥60 minutes group during the active second stage of labour. The prevalence of operative deliveries across all study periods was consistently between 45–49% when the active part of the second stage of labour lasted ≥60

minutes vs. 12–21% for durations of the second stage of labour of <60 minutes. We found strong associations between oxytocin augmentation and the duration of second stage, and between operative delivery and the duration of second stage (colinearity), which means that the duration of second stage is measured through operative delivery and oxytocin augmentation.

DISCUSSION

We found that oxytocin augmentation during active labour was associated with a 70% increased odds ratio of obstetric anal sphincter injury in women in TGCS group 1 giving spontaneous birth to an infant weighing <4000 g. We did not find an association between episiotomy and tears during spontaneous deliveries, but a significantly reduced association in all operative vaginal deliveries.

Comment [ar17]: Steer 4

Oxytocin augmentation is widely used in delayed labour to prevent operative delivery. However, a Cochrane review concluded that a reduction of labour by two hours was the only proven effect, and there was no effect on operative deliveries.[18] Another recent review found the entire concept of active management of labour to be associated with a slightly reduced risk of caesarean delivery.[21] As in other studies, we found that approximately 50% of nulliparous women received oxytocin augmentation.[16, 17, 22] There is reason to believe that guidelines for the diagnosis and treatment of protracted labour are unclear or inconsistently applied in daily practice.[17] We hypothesize that stimulation with oxytocin may speed up the progress of the expulsive phase of labour, leading to rushed situations, impaired communication with the mother, and less focus on protection of the perineum and a controlled delivery of the head. Recent studies from Norway indicate that focus on these elements is important in preventing perineal injuries.[23, 24]

Many authors have used logistic regression analysis to identify risk factors for obstetric anal sphincter injuries, but only a few have included oxytocin augmentation. Samuelsson et al.,[14] Prager et al.,[15] and Jander et al.[5] found oxytocin augmentation to be predictive of obstetric anal sphincter injuries in univariate analysis, but only Jander et al. confirmed this finding in multivariable analyses. Samuelsson et al. did not stratify by parity, which is a methodological weakness since the true effect of other factors is concealed by the strong impact of parity.[14] Prager et al. studied obstetric anal sphincter injuries in nulliparous women, entering oxytocin augmentation, duration of active second stage of labour, and instrumental delivery into the same model.[15]

Our study shows strong colinearity between a prolonged active second stage of labour and both oxytocin augmentation and instrumental delivery. We consider the duration of the active second stage of labour to be a "proxy" for oxytocin augmentation and instrumental delivery, and not a risk factor for obstetric anal sphincter injury in itself. Long duration of the second stage is a time related event before the expulsion of the head. During this latency the active forces do not inflict injury on the sphincter apparatus, the sphincter injury occurs during the expulsive phase. Consequently, we do not consider the duration of the active second stage as a risk factor for anal sphincter injuries.

Comment [ar18]: Gissler 3

Jander et al. conducted a single institution, retrospective, case-control study of 214 cases to explore 44 possible risk factors, and found that oxytocin augmentation was a significant risk factor for obstetric anal sphincter injuries in multivariable analyses (OR 2.00; 95% CI 1.13–3.53).[5] However, these researchers did not stratify by parity or state whether or not interactions were tested for. Furthermore, three older studies on the risk of obstetric anal sphincter injury included oxytocin use without differentiating whether oxytocin was provided for induction or augmentation purposes.[25-27] Three large population-based studies on the risk

of obstetric anal sphincter injuries did not include oxytocin augmentation in their analyses.[1, 7, 8]

The influence of epidural analgesia on anal sphincter injuries is unclear. Eskandar and Shet found a reduced risk, but did not stratify by parity.[9] Dahl and Kjølhede found epidural analgesia to be an independent protective factor in nulliparous women.[10] Poen et al. stratified by parity and found a significantly increased odds ratio associated with epidural analgesia in nulliparous women.[28] In our study, epidural analgesia was associated with a significantly reduced odds ratio for sphincter tears.

Our study takes into account four factors that exert their effect on the anal sphincter during the final minutes of delivery. As in previous studies,[1, 3, 5] we found both operative vaginal delivery and high birth weight to be strongly associated with obstetric anal sphincter injuries. We found episiotomy to be associated with a lower prevalence of sphincter tears in operative vaginal deliveries, but not in spontaneous births. This is consistent with a large national registry study from Norway,[1] but differs from other studies.[8, 11, 13, 29, 30] In our study, neither oxytocin augmentation nor episiotomy were associated with obstetric anal sphincter injury during spontaneous delivery of an infant weighing ≥4000 g.

Our methodological approach, stratifying by the factors that are active during the expulsive phase of labour and testing for confounders, is considered a strength of the study. This approach leads to a more detailed understanding of how oxytocin augmentation interacts with these major risk factors. Stepwise, forward multivariable regression analyses, without testing for possible interactions, would fail to reveal this information. This case-control study is based on prospectively collected data from a large unselected population, and represents all deliveries meeting the inclusion criteria that occurred during the study period, which make bias unlikely. Our department has a high proportion of vaginal deliveries. The overall caesarean delivery rate in our institution was 12.5% over the study period. For women in

Comment [ar19]: Steer 3

TGCS group 1 the acute caesarean section rate increased from 5.0% in 1999 to 7.5% in 2012. Accordingly, the study population includes both high- and low-risk pregnancies, which adds to the external validity of our results.

However, some limitations apply. We cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study. Furthermore, socioeconomic status, smoking, body mass index, maternal delivery positions, perineal support technique, and the birth attendant's experience level may be possible risk modifiers not included in our database. Finally, single institution studies, also when based on unselected populations, should be interpreted with caution.

Our findings have some important implications. Birth attendants should be aware of the association between oxytocin augmentation and obstetric anal sphincter injuries in the large subgroup of nulliparous women giving spontaneous birth to a normal-sized infant. More restrictive use of oxytocin may help prevent obstetric anal sphincter injuries. Implementation of evidence-based guidelines for using oxytocin augmentation should be encouraged. The World Health Organisation recommends the use of a partogram with an action line defining failure to progress. However, a recent Cochrane review could not confirm that such a partogram was beneficial in high resource settings.[31] Given the doubtful benefits from augmentation of labour, randomized controlled trials are strongly needed, and we propose anal sphincter injury as one of the most important endpoints.

Moreover, our study supports restricted use of episiotomy during normal births and as a recommendation for operative vaginal deliveries. Birth weight is an important, albeit unpredictable risk factor as weight estimation of a large fetus is unreliable.[32]

Comment [ar20]: Gissler, Steer 1

Comment [ar21]: Gissler 4

Comment [ar22]: Gissler 4

Comment [ar23]: Gissler 1 and Steer 4: Risk replaced by association

Comment [ar24]: On Steer 7, WHO vs Cochrane

Comment [ar25]: Steer 1, we agree.

Comment [ar26]: Steer 8, we have added a reference to emphasis this

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Competing interests

None

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No specific

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Comment [ar27]: New ref. (32), Steer 8

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (R) In abstract; a cross sectional study, analyzed as case-control study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (R) Fulfilled
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (R) Recent studies have shown the importance of the perineal protection technique in preventing perineal tears. Oxytocin augmentation could impair the control of the perineum during the delivery by causing too fast progress in the last minutes of labour. Oxytocin augmentation is widely used (50% of births). Guidelines for its use are often deficient and the evidence for its positive effect is challenged. Therefore, oxytocin augmentation as a risk factor for obstetric anal sphincter injuries, and should be explored in a study taking other relevant risk factors into account.
Objectives	3	State specific objectives, including any prespecified hypotheses (R) To assess the effect of oxytocin augmentation on obstetric anal sphincter injury among nulliparous women.
Methods		
Study design	4	Present key elements of study design early in the paper (R) Present in Abstract and Methods.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (R) Setting: Tertiary teaching hospital. Location: Delivery department of Stavanger University Hospital, serving the total obstetric population of the region of South Rogaland. Dates 15 May 1999 – 15 May 2012. Data were collected consecutively.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. (R) Nulliparous women with spontaneous start of labour, single, cephalic pregnancy and ≥37 weeks gestation who delivered vaginally, where we had access to complete information on the main exposure and the explanatory variables. The source population was the entire obstetric population of the region.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect

		modifiers. Give diagnostic criteria, if applicable (R) Outcome: Obstetric anal sphincter injury; that is grade 3 and 4 perineal tears as defined by International Society of Incontinence. Exposure: Oxytocin augmentation in active labour, that is oxytocin intravenous infusion (5 international units (0.01mg) oxytocin in 500 ml saline) used in incremental doses during active labour. Predictors: NA Effect modifiers: Episiotomy, operative vaginal delivery, birth weight <4000 g vs ≥4000 g. Potential confounders: maternal age, ethnicity, occiput posterior position, duration of second stage of labour and epidural analgesia.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. (R) All variables are precisely defined in the obstetric databases of Stavanger University Hospital. The grade of perineal injury was assessed during operative repair and plotted directly into the database.
Bias	9	Describe any efforts to address potential sources of bias. (R) In this cross-sectional study all women giving births and who fulfil the inclusion criteria are included. There were very few cases with missing data. We may have missed some cases of perineal injury due to underreporting. The variables are hard variables with clear definitions: Use of oxotocin (yes/no), episiotomy (yes/no), mode of delivery (spontaneous/operative vaginal), birth weight categorized <4000/ ≥4000 g.
Study size	10	Explain how the study size was arrived at (R) The study size is given by the number of women fulfilling the eligibility criteria and who delivered at Stavanger University Hospital from 15 May 1999 to 15 May 2012.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. (R) Birth weight was categorized into < 4000/ ≥4000 g.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (R) Chi-square test and stepwise forward logistic regression using IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.
		(*b*) Describe any methods used to examine subgroups and interactions (R) We applied a stratified approach to control for interaction between the main variables (oxytocin augmentation, episiotomy, instrumental delivery and birth weight). Then we tested for confounding and interaction to a modified model by entering one variable at time.
		(*c*) Explain how missing data were addressed (R) Cases with missing data for estimated date of delivery were excluded. Cases with

		other missing data were recoded to the reference value in the logistic regression analyses. Very few cases with missing data (n=52).
		(*d*) If applicable, describe analytical methods taking account of sampling strategy (R) NA
		(*e*) Describe any sensitivity analyses (R) NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (R) Potentially eligible: 15 545 Confirmed eligible: 15 493 Included/analyzed: 15 493
		(b) Give reasons for non-participation at each stage (R) Cases with missing data for estimated date of delivery were excluded (n=52)
		(c) Consider use of a flow diagram (R) Not useful in this study.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (R) Given in Table 1. The study participants represent the total population of women fulfilling the inclusion criteria in a Norwegian region of 320 000 people. The study population is heterogeneous with regard to obstetric risk (overall caesarean section rate 12,5%), social status and ethnicity.
		(b) Indicate number of participants with missing data for each variable of interest (R) Cases with missing data for estimated date of delivery were excluded from the study population (n=52) Recoded to the reference category of the variable and included in the analyses: Birth weight 3 cases. Maternal age 2 cases. Lie at delivery 8 cases. Duration of second stage of labour 92 cases.
Outcome data	15*	Report numbers of outcome events or summary measures (R) Table 1. Outcome event, the dependant variable, anal sphincter injury: 1014 cases.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (R) Table 2 and 3. Confounders: paragraph 4 in Material and Methods.
		(*b*) Report category boundaries when continuous variables were categorized (R) Table 1

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (R) NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses R) NA
Discussion		
Key results	18	Summarise key results with reference to study objectives (R) Fulfilled.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (R) Bias regarding main outcome: We do not know the magnitude of underreporting of anal sphincter tear grade 3 and 4, however believe this to be low. Bias regarding main exposure: The quality system of the department relies on honest reporting by midwives and obstetricians, and has been a cornerstone in the systematic interdisciplinary work towards better clinical outcomes since 1996. We have reason to believe that ownership to the concept has resulted in good adherence to the reporting routines, and we believe the reporting of oxytocin augmentation to be a robust measure of what was actually practised. The midwives plotting the information were not aware of any research issue related to oxytocin augmentation. We consider the other main exposure variables to be robust: It is unlikely that reports of episiotomy, instrumental delivery and birth weight are skewed in any direction. The same applies to the possible confounders age, ethnicity, occiput posterior position and epidural analgesia. We believe that the reporting of these variables reflects the actual practice. Therefore we consider the estimates for risks related to anal sphincter tear grade 3 and 4 to be precise with little bias. Our stratified approach, modified model, takes care of the interaction problems between episiotomy, operative vaginal delivery, birth weight and oxytocin augmentation.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (R) Fulfilled.
Generalisability	21	Discuss the generalisability (external validity) of the study results. (R) The study participants represent the total population of women fulfilling the inclusion criteria in a Norwegian region of 320 000 people. The study population is heterogeneous with regard to obstetric risk (overall caesarean section rate 12,5%), social status and ethnicity. This adds value to the external validity of the study results. We encourage other study groups to make research on the effect of oxytocin augmentation on anal sphincter injury in other populations.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if

	applicable, for the original study on which the present article is based
	(R) No specific funding.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Assessing the association of oxytocin augmentation with obstetric anal sphincter injury in nulliparous women – a population-based, case-control study

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Keywords:	Maternal medicine < OBSTETRICS, EPIDEMIOLOGY, Colorectal surgery < SURGERY

ASSESSING THE ASSOCIATION OF OXYTOCIN AUGMENTATION WITH OBSTETRIC ANAL SPHINCTER INJURY IN NULLIPAROUS WOMEN – A POPULATION-BASED, CASE CONTROL-STUDY

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Oxytocin augmentation and anal sphincter injury

Key words: anal sphincter injury, oxytocin, episiotomy, operative vaginal delivery, birth weight,
Word Count: 2619

ABSTRACT

Objective: To assess the association of oxytocin augmentation with obstetric anal sphincter injury among nulliparous women.

Design: A population-based, case-control study.

Setting: Primary and secondary teaching hospital serving a Norwegian region.

Population: 15 476 nulliparous women with spontaneous start of labour, single cephalic presentation, and gestation ≥37 weeks delivering vaginally between 1999 and 2012.

Methods: Based on the presence or absence of oxytocin augmentation, episiotomy, operative vaginal delivery, and birth weight (<4000 g vs. ≥4000 g), we did stratified analysis of all 16 combinations to assess the odds ratios (OR) of anal sphincter injury. Within a modified model, we tested for possible confounding, and interactions between maternal age, ethnicity, occiput posterior position, and epidural analgesia.

Main outcome measure: Obstetric anal sphincter injury.

Results: Oxytocin augmentation was associated with a higher OR of obstetric anal sphincter injuries in women giving spontaneous birth to infants weighing <4000 g (OR 1.8; 95% CI: 1.5–2.2). Episiotomy was not associated with sphincter injuries in spontaneous births, but with a lower OR in operative vaginal deliveries. Spontaneous delivery of infants weighing ≥ 4000 g was associated with a 3-fold higher OR, and epidural analgesia was associated with a 30% lower OR in comparison to no epidural analgesia.

Conclusions: Oxytocin augmentation was associated with a higher OR of obstetric anal sphincter injuries during spontaneous deliveries of normal-sized infants. We observed a

considerable effect modification between the most important factors involved in the active second stage of labour when anal sphincter injuries occur.

ARTICLE SUMMARY

Strengths and limitations of this study

- Stratifying by the main risk factors that are active during the expulsive phase of labour and testing for confounders are strengths of the study.
- We reveal how oxytocin augmentation interacts with the major factors active in the expulsive phase of labour.
- The study is based on prospectively collected data from a large, unselected population, which makes bias unlikely.
- The study design is a limitation, as we cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study.

INTRODUCTION

Obstetric anal sphincter injuries occur in 0.5–5.0% of vaginal deliveries,[1] with a subsequently increased risk of fecal incontinence.[2-4] Nulliparity,[1, 3, 5] high birth weight,[1, 3, 5, 6] operative vaginal delivery,[1, 3, 5] advanced maternal age,[1, 5, 6] Asian or African ethnicity,[1, 7] and prolonged second stage of labour[3, 7, 8] are consistently reported as risk factors for obstetric anal sphincter injuries , whereas the effect of epidural analgesia[9, 10] and episiotomy[1, 11-13] is debated. However, only a few authors have evaluated oxytocin augmentation as a possible risk factor for obstetric anal sphincter injuries.[5, 14, 15] Further, the current literature dealing with risk factors for obstetric anal sphincter injuries has not sufficiently addressed their possible interactions. Studies usually present a summary of associations between risk factors and obstetric anal sphincter injuries adjusted for confounders without investigating effect modification, i.e. exploring whether the effects are uniform across various levels of the studied risk factors.

In many delivery units, oxytocin augmentation is used during more than half of births.[16, 17] Oxytocin augmentation has been shown to shorten the duration of labour, but not to decrease the need for operative deliveries.[18] We hypothesize that oxytocin augmentation may reduce control over contractions and impair perineal support by causing the delivery to progress too quickly, and thereby increase the risk of perineal injury. Thus, the widespread use of oxytocin in daily obstetric practice calls for an exploration of its possible harmful effects. The aim of our study was to assess the association between oxytocin augmentation and obstetric anal sphincter injuries in a dynamic model related to the active second stage of labour.

MATERIALS AND METHODS

The Department of Obstetrics and Gynaecology of Stavanger University Hospital serves as the only delivery unit for a population of 320 000 people, and approximately 4500 deliveries occur there annually. From 1996 onward, all obstetric data have been consecutively recorded. The electronic database consists of clearly defined variables, and is continuously maintained using standardized procedures for data entry and quality control. During the study period 15 May 1999 to 15 May 2012, 56 517 women with a pregnancy duration of ≥23 weeks of gestation and infants with a birth weight of >300 grams delivered in the department. Estimated day of delivery was determined by second trimester ultrasound scan or from menstrual data when no ultrasound was performed. We restricted the study population to nulliparous women whose labour started spontaneously, with single cephalic presentation, pregnancies of ≥37 weeks of gestation (Group 1 in Robson's Ten Group Classification System; TGCS[19]), and who delivered vaginally. After excluding 69 women with missing data, (52 without an estimated day of delivery, 17 with missing information of fetal presentation at delivery), this case-control study comprised 15 476 women.

The main outcome measure was obstetric anal sphincter injuries as defined by the International Continence Society, i.e. partial or complete tears of the anal sphincter muscles, with or without disruption of the anal mucosa (grade 3–4 perineal tears).[20] When an obstetric anal sphincter injury was suspected, the obstetrician on call diagnosed the grade of the tear during surgical repair.

Oxytocin augmentation was defined as oxytocin used to stimulate contractions during established labour. An intravenous infusion of 5 international units (0.01mg) oxytocin in 500 ml saline was administered, starting with 30 ml per hour, and a dose increment of 15 ml per hour every 15 minutes to a maximum of 180 ml per hour, guided by the response. Normal births were taken care of by midwives, while doctors performed the operative deliveries.

Throughout the study period, episiotomy was performed either medio-laterally or laterally. According to our routines and national guidelines, operative vaginal delivery was indicated if delivery had not taken place after 60 minutes of bearing down. We used vacuum extraction with a Malmström metal cup as the preferred procedure for operative vaginal delivery. Vacuum extraction was applied for mid-cavity and outlet release. A combination of low-dose ropivicaine/fentanyl was used for epidural analgesia. Ethnicity was classified as Western i.e. originating from Europe or North America, or non-Western.

We analysed our dataset using the Chi-squared test and forward stepwise logistic regression analyses with $p<0.05$ as significance level. We applied a stratified approach to investigate the association of oxytocin augmentation and the outcome across the presence (+) or absence (–) during labour of episiotomy, operative vaginal delivery, and birth weight (<4000 g or ≥4000 g). We displayed all 16 possible combinations of the four variables, with absence of oxytocin augmentation, episiotomy, and operative vaginal delivery, and birth weight <4000 g set as the reference value. From these stratified analyses, we collapsed strata that were non-significant, taking the order of occurrence and the clinical impact of the variable into consideration. In this modified model, we tested for possible confounding effects and interactions from maternal age, ethnicity, occiput posterior position, and epidural analgesia in forward stepwise logistic regression analyses. Confounders were tested one by one and set to at least 10% change in any estimate of combinations of the modified target variables on obstetric anal sphincter injuries. Interaction terms were significant at $p<0.05$. Statistical analyses were performed with IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.

The Regional Committee for Medical and Health Research Ethics, Western Norway, approved the protocol as a quality assurance study in obstetric care, and fulfilling the requirements for data protection procedures (REK 2011-1247).

RESULTS

The study population comprised 15 476 (27%) of the 56 517 women giving birth during the study period, including 1013 (53%) of a total of 1894 women diagnosed with obstetric anal sphincter injuries.

The overall prevalence of obstetric anal sphincter injuries was 6.5%. The rate declined from 9.6% in 1999–2000 to 2.8% in 2010–2012. The characteristics of the study population and the prevalence of obstetric anal sphincter injuries are displayed in Table 1.

Table 1 Characteristics of the study population and the prevalence of obstetric anal sphincter injury. P-values from Chi-square tests.

Factor	Obstetric anal sphincter injury		In total	Prevalence	P
	No	Yes			
	N=14 463	N=1013	N=15 476		
	%	%		%	
Time period					<0.001
1999-2000	11.1	16.9	1781	9.6	
2001-2003	19.8	30.7	3169	9.8	
2004-2006	22.9	29.6	3611	8.3	
2007-2009	25.5	14.3	3826	3.8	
2010-2012	20.8	8.6	3089	2.8	
Maternal factors					
Age (years)					<0.001
<25	26.6	19.3	4040	4.9	
25-29	33.5	37.6	5233	7.3	
30-34	17.8	20.8	2785	7.6	
≥35	22.1	22.2	3418	6.6	
Origin					NS*
Western	90.5	92.0	14 025	6.6	
Non-Western	9.5	8.0	1451	5.6	
Obstetric factors					
Epidural analgesia					NS
No	58.1	57.7	8992	6.5	
Yes	41.9	42.3	6484	6.6	
Oxytocin augmentation					<0.001
No	55.6	44.7	8500	5.3	
Yes	44.4	55.3	6976	8.0	
Active 2nd stage of labour (min)					<0.001
Missing information	0.6	0.3	92	3.3	
0-14	10.8	6.8	1627	4.2	
15-29	26.8	18.5	4063	4.6	

30-59	40.1	37.8	6181	6.2	
≥60	21.7	36.6	3513	10.6	
Episiotomy					NS
No	67.1	65.4	10 372	6.4	
Yes	32.9	34.6	5104	6.9	
Operative vaginal delivery					<0.001
No	77.5	60.3	11 817	5.2	
Yes	22.5	39.7	3659	11.0	
Fetal factors					
Birth weight (g)					<0.001
<4000	87.8	74.2	13 454	5.6	
≥4000	12.2	25.8	2022	12.9	
Occiput posterior position					NS
No	95.4	94.8	14 771	6.5	
Yes	4.5	5.2	705	7.4	

* Non significant

The prevalence was higher in women who received oxytocin augmentation (8.0% vs. 5.3%), those who were delivered instrumentally (11.0% vs. 5.2%), and in those who gave birth to an infant weighing ≥4000 g (12.9% vs. 5.6%). Furthermore, the prevalence increased with longer durations of the active part of the second stage of labour.

The results of the stratified analysis are presented in Table 2.

Table 2 Stratified analyses of the prevalence of obstetric anal sphincter injury by the presence (+) or absence (−) of: oxytocin augmentation, episiotomy, operative vaginal delivery, and birth weight (strata 1–16; group 1 as reference). Crude odds ratio (OR) and 95% confidence intervals (95% CI)

Group	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	95% CI
1	-	-	-	-	5328	198 (3.7)	1.0	
2	-	+	-	-	1434	60 (4.2)	1.1	0.8-1.5
3	+	-	-	-	2621	148 (5.6)	1.5	1.3-1.9
4	+	+	-	-	1039	61 (5.9)	1.6	1.2-2.2
5	-	+	+	-	537	43 (8.0)	2.3	1.6-3.2
6	+	+	+	-	1283	92 (7.2)	2.0	1.6-2.6
7	-	-	+	-	316	47 (14.9)	4.5	3.2-6.4
8	+	-	+	-	896	103 (11.5)	3.4	2.6-4.3
9	-	-	-	+	539	59 (10.9)	3.2	2.4-4.3
10	+	-	-	+	438	45 (10.3)	3.0	2.1-4.2

11	-	+	-	+	203	20 (9.9)	2.8	1.7-4.6
12	+	+	-	+	215	20 (9.3)	2.7	1.6-4.3
13	-	+	+	+	101	11 (10.9)	3.2	1.7-6.0
14	+	+	+	+	292	44 (15.1)	4.6	3.2-6.5
15	-	-	+	+	42	15 (35.7)	14.4	7.5-27.5
16	+	-	+	+	192	47 (24.5)	8.4	5.9-12.0

We found a strong effect modification between episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight on obstetric anal sphincter injuries. Oxytocin augmentation was associated with an increased odds ratio of obstetric anal sphincter injuries during spontaneous deliveries of normal-sized infants, and was independent of episiotomy (groups 3 and 4). Episiotomy was not associated with anal sphincter injuries when the other factors were absent (groups 1 and 2). Oxytocin augmentation was not associated with anal sphincter injury during instrumental deliveries of normal-sized infants without episiotomy (groups 7 and 8), nor in spontaneous deliveries of infants weighing ≥4000 g without episiotomy (groups 9 and 10). Furthermore, oxytocin use was not associated with anal sphincter injuries in spontaneous (groups 11 and 12) or operative vaginal deliveries (groups 13 and 14) of infants weighing ≥4000 g when episiotomy was applied. Operative vaginal delivery of an infant weighing ≥4000 g without episiotomy represented the group with the highest prevalence of injury (groups 15 and 16) and was not associated with oxytocin use. Episiotomy appeared to be negatively associated with sphincter rupture in operative vaginal deliveries regardless of the birth weight and the use of oxytocin (groups 5-8 and 13-16).

In the modified model (Table 3), we collapsed the groups from Table 2 that had odds ratios of similar magnitude for obstetric anal sphincter injury.

Table 3 Modified model displaying the collapsed non-significant strata (1–16) from Table 2 into new strata (A–G). Unadjusted odds ratios (OR), adjusted (aOR), and 95% confidence intervals (95% CI) after adjusting for epidural analgesia

Group (Group in Table 2)	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	aOR (95% CI)
A (1,2)	-	+/-	-	-	6762	258 (3.8)	1.0	1.0
B (3,4)	+	+/-	-	-	3660	209 (5.7)	1.5	1.8 (1.5-2.2)
C (5,6)	+/-	+	+	-	1820	135 (7.4)	2.0	2.3 (1.8-2.8)
D (7,8)	+/-	-	+	-	1212	150 (12.4)	3.6	4.1 (3.3-5.1)
E (9-12)	+/-	+/-	-	+	1395	144 (10.3)	2.9	3.1 (2.4-3.9)
F (13,14)	+/-	+	+	+	393	55 (14.0)	4.1	4.7 (3.4-6.5)
G (15,16)	+/-	-	+	+	234	62 (26.5)	9.1	10.5 (7.6-14.4)

Age, origin of the mother, and occiput posterior position had no confounding effect on odds ratios for obstetric anal sphincter injury across combinations of episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight (groups A to G in Table 3). The use of oxytocin augmentation was restricted in the department from 2010 onwards, however, we observed a significant association between oxytocin augmentation and anal sphincter injuries through all time periods (1999-2003, 2004-2006, 2007-2009, 2010-2012). The unadjusted odds ratio (OR) for the presence or absence of epidural analgesia was 1.02; however, the adjusted OR for epidural analgesia was 0.73, (95% CI 0.63-0.84) i.e. epidural analgesia was associated with a 30% lower odds ratio of anal sphincter injury.

The use of oxytocin augmentation increased with the duration of the second stage of labour over all the time periods from an average of 32% in the <30 minutes group, 46% in the 30–59 minutes group, and 65% (range 49–76%) in the ≥60 minutes group during the active second stage of labour. The prevalence of operative deliveries across all study periods was consistently between 45–49% when the active part of the second stage of labour lasted ≥60

minutes vs. 12–21% for durations of the second stage of labour of <60 minutes. We found strong associations between oxytocin augmentation and the duration of second stage, and between operative delivery and the duration of second stage (collinearity), which means that the duration of second stage is measured through operative delivery and oxytocin augmentation.

DISCUSSION

We found that oxytocin augmentation during active labour was associated with a 70% increased odds ratio of obstetric anal sphincter injury in women in TGCS group 1 giving spontaneous birth to an infant weighing <4000 g. We did not find an association between episiotomy and tears during spontaneous deliveries, but a significantly reduced association in all operative vaginal deliveries.

Oxytocin augmentation is widely used in delayed labour to prevent operative delivery. However, a Cochrane review concluded that a reduction of labour by two hours was the only proven effect, and there was no effect on operative deliveries.[18] Another recent review found the entire concept of active management of labour to be associated with a slightly reduced risk of caesarean delivery.[21] As in other studies, we found that approximately 50% of nulliparous women received oxytocin augmentation.[16, 17, 22] There is reason to believe that guidelines for the diagnosis and treatment of protracted labour are unclear or inconsistently applied in daily practice.[17] We hypothesize that stimulation with oxytocin may speed up the progress of the expulsive phase of labour, leading to rushed situations, impaired communication with the mother, and less focus on protection of the perineum and a controlled delivery of the head. Recent studies from Norway indicate that focus on these elements is important in preventing perineal injuries.[23, 24]

Many authors have used logistic regression analysis to identify risk factors for obstetric anal sphincter injuries, but only a few have included oxytocin augmentation. Samuelsson et al.,[14] Prager et al.,[15] and Jander et al.[5] found oxytocin augmentation to be predictive of obstetric anal sphincter injuries in univariate analysis, but only Jander et al. confirmed this finding in multivariable analyses. Samuelsson et al. did not stratify by parity, which is a methodological weakness since the true effect of other factors is concealed by the strong impact of parity.[14] Prager et al. studied obstetric anal sphincter injuries in nulliparous women, entering oxytocin augmentation, duration of active second stage of labour, and instrumental delivery into the same model.[15]

Our study shows strong collinearity between a prolonged active second stage of labour and both oxytocin augmentation and instrumental delivery. We consider the duration of the active second stage of labour to be a "proxy" for oxytocin augmentation and instrumental delivery, and not a risk factor for obstetric anal sphincter injury in itself. Long duration of the second stage is a time related event before the expulsion of the head. During this latency the active forces do not inflict injury on the sphincter apparatus, the sphincter injury occurs during the expulsive phase. Consequently, we do not consider the duration of the active second stage as a risk factor for anal sphincter injuries.

Jander et al. conducted a single institution, retrospective, case-control study of 214 cases to explore 44 possible risk factors, and found that oxytocin augmentation was a significant risk factor for obstetric anal sphincter injuries in multivariable analyses (OR 2.00; 95% CI 1.13–3.53).[5] However, these researchers did not stratify by parity or state whether or not interactions were tested for. Furthermore, three older studies on the risk of obstetric anal sphincter injury included oxytocin use without differentiating whether oxytocin was provided for induction or augmentation purposes.[25-27] Three large population-based studies on the risk

of obstetric anal sphincter injuries did not include oxytocin augmentation in their analyses.[1, 7, 8]

The influence of epidural analgesia on anal sphincter injuries is unclear. Eskandar and Shet found a reduced risk, but did not stratify by parity.[9] Dahl and Kjølhede found epidural analgesia to be an independent protective factor in nulliparous women.[10] Poen et al. stratified by parity and found a significantly increased odds ratio associated with epidural analgesia in nulliparous women.[28] In our study, epidural analgesia was associated with a significantly reduced odds ratio for sphincter tears.

Our study takes into account four factors that exert their effect on the anal sphincter during the final minutes of delivery. As in previous studies,[1, 3, 5] we found both operative vaginal delivery and high birth weight to be strongly associated with obstetric anal sphincter injuries. We found episiotomy to be associated with a lower prevalence of sphincter tears in operative vaginal deliveries, but not in spontaneous births. This is consistent with a large national registry study from Norway,[1] but differs from other studies.[8, 11, 13, 29, 30] In our study, neither oxytocin augmentation nor episiotomy were associated with obstetric anal sphincter injury during spontaneous delivery of an infant weighing ≥4000 g.

Our methodological approach, stratifying by the factors that are active during the expulsive phase of labour and testing for confounders, is considered a strength of the study. This approach leads to a more detailed understanding of how oxytocin augmentation interacts with these major risk factors. Stepwise, forward multivariable regression analyses, without testing for possible interactions, would fail to reveal this information. This case-control study is based on prospectively collected data from a large unselected population, and represents all deliveries meeting the inclusion criteria that occurred during the study period, which make bias unlikely. Our department has a high proportion of vaginal deliveries. The overall caesarean delivery rate in our institution was 12.5% over the study period. For women in

TGCS group 1 the acute caesarean section rate increased from 5.0% in 1999 to 7.5% in 2012. Accordingly, the study population includes both high- and low-risk pregnancies, which adds to the external validity of our results.

However, some limitations apply. We cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study. Furthermore, socioeconomic status, smoking, body mass index, maternal delivery positions, perineal support technique, and the birth attendant's experience level may be possible risk modifiers not included in our database. Finally, single institution studies, also when based on unselected populations, should be interpreted with caution.

Our findings have some important implications. Birth attendants should be aware of the association between oxytocin augmentation and obstetric anal sphincter injuries in the large subgroup of nulliparous women giving spontaneous birth to a normal-sized infant. More restrictive use of oxytocin may help prevent obstetric anal sphincter injuries. Implementation of evidence-based guidelines for using oxytocin augmentation should be encouraged. The World Health Organization recommends the use of a partogram with an action line defining failure to progress. However, a recent Cochrane review could not confirm that such a partogram was beneficial in high resource settings.[31] Given the doubtful benefits from augmentation of labour, randomized controlled trials are strongly needed, and we propose anal sphincter injury as one of the most important endpoints.

Moreover, our study supports restricted use of episiotomy during normal births and as a recommendation for operative vaginal deliveries. Birth weight is an important, albeit unpredictable risk factor as weight estimation of a large fetus is unreliable.[32]

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Contributorship Statement

All four authors have contributed to the idea and design of the research project. ABR, TME managed the dataset and the statistical analyses were performed by FES. All four authors have contributed to the interpretation of the results and the writing of the manuscript.

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Competing interests

None

Data Sharing Statement

There is no additional data material to be shared.

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Assessing the association of oxytocin augmentation with obstetric anal sphincter injury in nulliparous women – a population-based, case-control study

ARTICLE SUMMARY

Strengths and limitations of this study

- Stratifying by the main risk factors that are active during the expulsive phase of labour and testing for confounders are strengths of the study.
- We reveal how oxytocin augmentation interacts with the major factors active in the expulsive phase of labour.
- The study is based on prospectively collected data from a large, unselected population, which makes bias unlikely.
- The study design is a limitation, as we cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study.

INTRODUCTION

Obstetric anal sphincter injuries occur in 0.5–5.0% of vaginal deliveries,[1] with a subsequently increased risk of fecal incontinence.[2-4] Nulliparity,[1, 3, 5] high birth weight,[1, 3, 5, 6] operative vaginal delivery,[1, 3, 5] advanced maternal age,[1, 5, 6] Asian or African ethnicity,[1, 7] and prolonged second stage of labour[3, 7, 8] are consistently reported as risk factors for obstetric anal sphincter injuries , whereas the effect of epidural analgesia[9, 10] and episiotomy[1, 11-13] is debated. However, only a few authors have evaluated oxytocin augmentation as a possible risk factor for obstetric anal sphincter injuries.[5, 14, 15] Further, the current literature dealing with risk factors for obstetric anal sphincter injuries has not sufficiently addressed their possible interactions. Studies usually present a summary of associations between risk factors and obstetric anal sphincter injuries adjusted for confounders without investigating effect modification, i.e. exploring whether the effects are uniform across various levels of the studied risk factors.

In many delivery units, oxytocin augmentation is used during more than half of births.[16, 17] Oxytocin augmentation has been shown to shorten the duration of labour, but not to decrease the need for operative deliveries.[18] We hypothesize that oxytocin augmentation may reduce control over contractions and impair perineal support by causing the delivery to progress too quickly, and thereby increase the risk of perineal injury. Thus, the widespread use of oxytocin in daily obstetric practice calls for an exploration of its possible harmful effects. The aim of our study was to assess the association between oxytocin augmentation and obstetric anal sphincter injuries in a dynamic model related to the active second stage of labour.

MATERIALS AND METHODS

The Department of Obstetrics and Gynaecology of Stavanger University Hospital serves as the only delivery unit for a population of 320 000 people, and approximately 4500 deliveries occur there annually. From 1996 onward, all obstetric data have been consecutively recorded. The electronic database consists of clearly defined variables, and is continuously maintained using standardized procedures for data entry and quality control. During the study period 15 May 1999 to 15 May 2012, 56 517 women with a pregnancy duration of ≥23 weeks of gestation and infants with a birth weight of >300 grams delivered in the department. Estimated day of delivery was determined by second trimester ultrasound scan or from menstrual data when no ultrasound was performed. We restricted the study population to nulliparous women whose labour started spontaneously, with single cephalic presentation, pregnancies of ≥37 weeks of gestation (Group 1 in Robson's Ten Group Classification System; TGCS[19]), and who delivered vaginally. After excluding 69 women with missing data, (52 without an estimated day of delivery, 17 with missing information of fetal presentation at delivery), this case-control study comprised 15 476 women.

The main outcome measure was obstetric anal sphincter injuries as defined by the International Continence Society, i.e. partial or complete tears of the anal sphincter muscles, with or without disruption of the anal mucosa (grade 3–4 perineal tears).[20] When an obstetric anal sphincter injury was suspected, the obstetrician on call diagnosed the grade of the tear during surgical repair.

Oxytocin augmentation was defined as oxytocin used to stimulate contractions during established labour. An intravenous infusion of 5 international units (0.01mg) oxytocin in 500 ml saline was administered, starting with 30 ml per hour, and a dose increment of 15 ml per hour every 15 minutes to a maximum of 180 ml per hour, guided by the response. Normal births were taken care of by midwives, while doctors performed the operative deliveries.

Throughout the study period, episiotomy was performed either medio-laterally or laterally. According to our routines and national guidelines, operative vaginal delivery was indicated if delivery had not taken place after 60 minutes of bearing down. We used vacuum extraction with a Malmström metal cup as the preferred procedure for operative vaginal delivery. Vacuum extraction was applied for mid-cavity and outlet release. A combination of low-dose ropivicaine/fentanyl was used for epidural analgesia. Ethnicity was classified as Western i.e. originating from Europe or North America, or non-Western.

We analysed our dataset using the Chi-squared test and forward stepwise logistic regression analyses with $p<0.05$ as significance level. We applied a stratified approach to investigate the association of oxytocin augmentation and the outcome across the presence (+) or absence (–) during labour of episiotomy, operative vaginal delivery, and birth weight (<4000 g or ≥4000 g). We displayed all 16 possible combinations of the four variables, with absence of oxytocin augmentation, episiotomy, and operative vaginal delivery, and birth weight <4000 g set as the reference value. From these stratified analyses, we collapsed strata that were non-significant, taking the order of occurrence and the clinical impact of the variable into consideration. In this modified model, we tested for possible confounding effects and interactions from maternal age, ethnicity, occiput posterior position, and epidural analgesia in forward stepwise logistic regression analyses. Confounders were tested one by one and set to at least 10% change in any estimate of combinations of the modified target variables on obstetric anal sphincter injuries. Interaction terms were significant at $p<0.05$. Statistical analyses were performed with IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.

The Regional Committee for Medical and Health Research Ethics, Western Norway, approved the protocol as a quality assurance study in obstetric care, and fulfilling the requirements for data protection procedures (REK 2011-1247).

RESULTS

The study population comprised 15 476 (27%) of the 56 517 women giving birth during the study period, including 1013 (53%) of a total of 1894 women diagnosed with obstetric anal sphincter injuries.

The overall prevalence of obstetric anal sphincter injuries was 6.5%. The rate declined from 9.6% in 1999–2000 to 2.8% in 2010–2012. The characteristics of the study population and the prevalence of obstetric anal sphincter injuries are displayed in Table 1.

Table 1 Characteristics of the study population and the prevalence of obstetric anal sphincter injury. P-values from Chi-square tests.

Factor	Obstetric anal sphincter injury No N=14 463 %	Obstetric anal sphincter injury Yes N=1013 %	In total N=15 476	Prevalence %	P
Time period					<0.001
1999-2000	11.1	16.9	1781	9.6	
2001-2003	19.8	30.7	3169	9.8	
2004-2006	22.9	29.6	3611	8.3	
2007-2009	25.5	14.3	3826	3.8	
2010-2012	20.8	8.6	3089	2.8	
Maternal factors					
Age (years)					<0.001
<25	26.6	19.3	4040	4.9	
25-29	33.5	37.6	5233	7.3	
30-34	17.8	20.8	2785	7.6	
≥35	22.1	22.2	3418	6.6	
Origin					NS*
Western	90.5	92.0	14 025	6.6	
Non-Western	9.5	8.0	1451	5.6	
Obstetric factors					
Epidural analgesia					NS
No	58.1	57.7	8992	6.5	
Yes	41.9	42.3	6484	6.6	
Oxytocin augmentation					<0.001
No	55.6	44.7	8500	5.3	
Yes	44.4	55.3	6976	8.0	
Active 2nd stage of labour (min)					<0.001
Missing information	0.6	0.3	92	3.3	
0-14	10.8	6.8	1627	4.2	
15-29	26.8	18.5	4063	4.6	

Comment [ar1]: Remark byWatson

Comment [ar2]: Changed to non-Western (Gissler)

30-59	40.1	37.8	6181	6.2	
≥60	21.7	36.6	3513	10.6	
Episiotomy					NS
No	67.1	65.4	10 372	6.4	
Yes	32.9	34.6	5104	6.9	
Operative vaginal delivery					<0.001
No	77.5	60.3	11 817	5.2	
Yes	22.5	39.7	3659	11.0	
Fetal factors					
Birth weight (g)					<0.001
<4000	87.8	74.2	13 454	5.6	
≥4000	12.2	25.8	2022	12.9	
Occiput posterior position					NS
No	95.4	94.8	14 771	6.5	
Yes	4.5	5.2	705	7.4	

* Non significant

The prevalence was higher in women who received oxytocin augmentation (8.0% vs. 5.3%), those who were delivered instrumentally (11.0% vs. 5.2%), and in those who gave birth to an infant weighing ≥4000 g (12.9% vs. 5.6%). Furthermore, the prevalence increased with longer durations of the active part of the second stage of labour.

The results of the stratified analysis are presented in Table 2.

Table 2 Stratified analyses of the prevalence of obstetric anal sphincter injury by the presence (+) or absence (−) of: oxytocin augmentation, episiotomy, operative vaginal delivery, and birth weight (strata 1–16; group 1 as reference). Crude odds ratio (OR) and 95% confidence intervals (95% CI)

Group	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	95% CI
1	-	-	-	-	5328	198 (3.7)	1.0	
2	-	+	-	-	1434	60 (4.2)	1.1	0.8-1.5
3	+	-	-	-	2621	148 (5.6)	1.5	1.3-1.9
4	+	+	-	-	1039	61 (5.9)	1.6	1.2-2.2
5	-	+	+	-	537	43 (8.0)	2.3	1.6-3.2
6	+	+	+	-	1283	92 (7.2)	2.0	1.6-2.6
7	-	-	+	-	316	47 (14.9)	4.5	3.2-6.4
8	+	-	+	-	896	103 (11.5)	3.4	2.6-4.3
9	-	-	-	+	539	59 (10.9)	3.2	2.4-4.3
10	+	-	-	+	438	45 (10.3)	3.0	2.1-4.2

11	-	+	-	+	203	20 (9.9)	2.8	1.7-4.6
12	+	+	-	+	215	20 (9.3)	2.7	1.6-4.3
13	-	+	+	+	101	11 (10.9)	3.2	1.7-6.0
14	+	+	+	+	292	44 (15.1)	4.6	3.2-6.5
15	-	-	+	+	42	15 (35.7)	14.4	7.5-27.5
16	+	-	+	+	192	47 (24.5)	8.4	5.9-12.0

We found a strong effect modification between episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight on obstetric anal sphincter injuries. Oxytocin augmentation was associated with an increased odds ratio of obstetric anal sphincter injuries during spontaneous deliveries of normal-sized infants, and was independent of episiotomy (groups 3 and 4). Episiotomy was not associated with anal sphincter injuries when the other factors were absent (groups 1 and 2). Oxytocin augmentation was not associated with anal sphincter injury during instrumental deliveries of normal-sized infants without episiotomy (groups 7 and 8), nor in spontaneous deliveries of infants weighing ≥4000 g without episiotomy (groups 9 and 10). Furthermore, oxytocin use was not associated with anal sphincter injuries in spontaneous (groups 11 and 12) or operative vaginal deliveries (groups 13 and 14) of infants weighing ≥4000 g when episiotomy was applied. Operative vaginal delivery of an infant weighing ≥4000 g without episiotomy represented the group with the highest prevalence of injury (groups 15 and 16) and was not associated with oxytocin use. Episiotomy appeared to be negatively associated with sphincter rupture in operative vaginal deliveries regardless of the birth weight and the use of oxytocin (groups 5-8 and 13-16).

In the modified model (Table 3), we collapsed the groups from Table 2 that had odds ratios of similar magnitude for obstetric anal sphincter injury.

Table 3 Modified model displaying the collapsed non-significant strata (1–16) from Table 2 into new strata (A–G). Unadjusted odds ratios (OR), adjusted (aOR), and 95% confidence intervals (95% CI) after adjusting for epidural analgesia

Group (Group in Table 2)	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	aOR (95% CI)
A (1,2)	-	+/-	-	-	6762	258 (3.8)	1.0	1.0
B (3,4)	+	+/-	-	-	3660	209 (5.7)	1.5	1.8 (1.5-2.2)
C (5,6)	+/-	+	+	-	1820	135 (7.4)	2.0	2.3 (1.8-2.8)
D (7,8)	+/-	-	+	-	1212	150 (12.4)	3.6	4.1 (3.3-5.1)
E (9-12)	+/-	+/-	-	+	1395	144 (10.3)	2.9	3.1 (2.4-3.9)
F (13,14)	+/-	+	+	+	393	55 (14.0)	4.1	4.7 (3.4-6.5)
G (15,16)	+/-	-	+	+	234	62 (26.5)	9.1	10.5 (7.6-14.4)

Age, origin of the mother, and occiput posterior position had no confounding effect on odds ratios for obstetric anal sphincter injury across combinations of episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight (groups A to G in Table 3). The use of oxytocin augmentation was restricted in the department from 2010 onwards, however, we observed a significant association between oxytocin augmentation and anal sphincter injuries through all time periods (1999-2003, 2004-2006, 2007-2009, 2010-2012). The unadjusted odds ratio (OR) for the presence or absence of epidural analgesia was 1.02; however, the adjusted OR for epidural analgesia was 0.73, (95% CI 0.63-0.84) i.e. epidural analgesia was associated with a 30% lower odds ratio of anal sphincter injury.

Comment [ar3]: Gissler

The use of oxytocin augmentation increased with the duration of the second stage of labour over all the time periods from an average of 32% in the <30 minutes group, 46% in the 30–59 minutes group, and 65% (range 49–76%) in the ≥60 minutes group during the active second stage of labour. The prevalence of operative deliveries across all study periods was consistently between 45–49% when the active part of the second stage of labour lasted ≥60

minutes vs. 12–21% for durations of the second stage of labour of <60 minutes. We found strong associations between oxytocin augmentation and the duration of second stage, and between operative delivery and the duration of second stage (collinearity), which means that the duration of second stage is measured through operative delivery and oxytocin augmentation.

Comment [ar4]: Gissler

DISCUSSION

We found that oxytocin augmentation during active labour was associated with a 70% increased odds ratio of obstetric anal sphincter injury in women in TGCS group 1 giving spontaneous birth to an infant weighing <4000 g. We did not find an association between episiotomy and tears during spontaneous deliveries, but a significantly reduced association in all operative vaginal deliveries.

Oxytocin augmentation is widely used in delayed labour to prevent operative delivery. However, a Cochrane review concluded that a reduction of labour by two hours was the only proven effect, and there was no effect on operative deliveries.[18] Another recent review found the entire concept of active management of labour to be associated with a slightly reduced risk of caesarean delivery.[21] As in other studies, we found that approximately 50% of nulliparous women received oxytocin augmentation.[16, 17, 22] There is reason to believe that guidelines for the diagnosis and treatment of protracted labour are unclear or inconsistently applied in daily practice.[17] We hypothesize that stimulation with oxytocin may speed up the progress of the expulsive phase of labour, leading to rushed situations, impaired communication with the mother, and less focus on protection of the perineum and a controlled delivery of the head. Recent studies from Norway indicate that focus on these elements is important in preventing perineal injuries.[23, 24]

Many authors have used logistic regression analysis to identify risk factors for obstetric anal sphincter injuries, but only a few have included oxytocin augmentation. Samuelsson et al.,[14] Prager et al.,[15] and Jander et al.[5] found oxytocin augmentation to be predictive of obstetric anal sphincter injuries in univariate analysis, but only Jander et al. confirmed this finding in multivariable analyses. Samuelsson et al. did not stratify by parity, which is a methodological weakness since the true effect of other factors is concealed by the strong impact of parity.[14] Prager et al. studied obstetric anal sphincter injuries in nulliparous women, entering oxytocin augmentation, duration of active second stage of labour, and instrumental delivery into the same model.[15]

Our study shows strong collinearity between a prolonged active second stage of labour and both oxytocin augmentation and instrumental delivery. We consider the duration of the active second stage of labour to be a "proxy" for oxytocin augmentation and instrumental delivery, and not a risk factor for obstetric anal sphincter injury in itself. Long duration of the second stage is a time related event before the expulsion of the head. During this latency the active forces do not inflict injury on the sphincter apparatus, the sphincter injury occurs during the expulsive phase. Consequently, we do not consider the duration of the active second stage as a risk factor for anal sphincter injuries.

Jander et al. conducted a single institution, retrospective, case-control study of 214 cases to explore 44 possible risk factors, and found that oxytocin augmentation was a significant risk factor for obstetric anal sphincter injuries in multivariable analyses (OR 2.00; 95% CI 1.13–3.53).[5] However, these researchers did not stratify by parity or state whether or not interactions were tested for. Furthermore, three older studies on the risk of obstetric anal sphincter injury included oxytocin use without differentiating whether oxytocin was provided for induction or augmentation purposes.[25-27] Three large population-based studies on the risk

Comment [ar5]: Gissler

of obstetric anal sphincter injuries did not include oxytocin augmentation in their analyses.[1, 7, 8]

The influence of epidural analgesia on anal sphincter injuries is unclear. Eskandar and Shet found a reduced risk, but did not stratify by parity.[9] Dahl and Kjølhede found epidural analgesia to be an independent protective factor in nulliparous women.[10] Poen et al. stratified by parity and found a significantly increased odds ratio associated with epidural analgesia in nulliparous women.[28] In our study, epidural analgesia was associated with a significantly reduced odds ratio for sphincter tears.

Our study takes into account four factors that exert their effect on the anal sphincter during the final minutes of delivery. As in previous studies,[1, 3, 5] we found both operative vaginal delivery and high birth weight to be strongly associated with obstetric anal sphincter injuries. We found episiotomy to be associated with a lower prevalence of sphincter tears in operative vaginal deliveries, but not in spontaneous births. This is consistent with a large national registry study from Norway,[1] but differs from other studies.[8, 11, 13, 29, 30] In our study, neither oxytocin augmentation nor episiotomy were associated with obstetric anal sphincter injury during spontaneous delivery of an infant weighing ≥4000 g.

Our methodological approach, stratifying by the factors that are active during the expulsive phase of labour and testing for confounders, is considered a strength of the study. This approach leads to a more detailed understanding of how oxytocin augmentation interacts with these major risk factors. Stepwise, forward multivariable regression analyses, without testing for possible interactions, would fail to reveal this information. This case-control study is based on prospectively collected data from a large unselected population, and represents all deliveries meeting the inclusion criteria that occurred during the study period, which make bias unlikely. Our department has a high proportion of vaginal deliveries. The overall caesarean delivery rate in our institution was 12.5% over the study period. For women in

TGCS group 1 the acute caesarean section rate increased from 5.0% in 1999 to 7.5% in 2012. Accordingly, the study population includes both high- and low-risk pregnancies, which adds to the external validity of our results.

However, some limitations apply. We cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study. Furthermore, socioeconomic status, smoking, body mass index, maternal delivery positions, perineal support technique, and the birth attendant's experience level may be possible risk modifiers not included in our database. Finally, single institution studies, also when based on unselected populations, should be interpreted with caution.

Our findings have some important implications. Birth attendants should be aware of the association between oxytocin augmentation and obstetric anal sphincter injuries in the large subgroup of nulliparous women giving spontaneous birth to a normal-sized infant. More restrictive use of oxytocin may help prevent obstetric anal sphincter injuries. Implementation of evidence-based guidelines for using oxytocin augmentation should be encouraged. The World Health Organi~~z~~sation recommends the use of a partogram with an action line defining failure to progress. However, a recent Cochrane review could not confirm that such a partogram was beneficial in high resource settings.[31] Given the doubtful benefits from augmentation of labour, randomized controlled trials are strongly needed, and we propose anal sphincter injury as one of the most important endpoints.

Comment [ar6]: Gissler

Moreover, our study supports restricted use of episiotomy during normal births and as a recommendation for operative vaginal deliveries. Birth weight is an important, albeit unpredictable risk factor as weight estimation of a large fetus is unreliable.[32]

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Competing interests

None

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No specific

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (R) In abstract; a cross sectional study, analyzed as case-control study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (R) Fulfilled
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (R) Recent studies have shown the importance of the perineal protection technique in preventing perineal tears. Oxytocin augmentation could impair the control of the perineum during the delivery by causing too fast progress in the last minutes of labour. Oxytocin augmentation is widely used (50% of births). Guidelines for its use are often deficient and the evidence for its positive effect is challenged. Therefore, oxytocin augmentation as a risk factor for obstetric anal sphincter injuries, and should be explored in a study taking other relevant risk factors into account.
Objectives	3	State specific objectives, including any prespecified hypotheses (R) To assess the effect of oxytocin augmentation on obstetric anal sphincter injury among nulliparous women.
Methods		
Study design	4	Present key elements of study design early in the paper (R) Present in Abstract and Methods.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (R) Setting: Tertiary teaching hospital. Location: Delivery department of Stavanger University Hospital, serving the total obstetric population of the region of South Rogaland. Dates 15 May 1999 – 15 May 2012. Data were collected consecutively.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. (R) Nulliparous women with spontaneous start of labour, single, cephalic pregnancy and ≥37 weeks gestation who delivered vaginally, where we had access to complete information on the main exposure and the explanatory variables. The source population was the entire obstetric population of the region.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect

		modifiers. Give diagnostic criteria, if applicable (R) Outcome: Obstetric anal sphincter injury; that is grade 3 and 4 perineal tears as defined by International Society of Incontinence. Exposure: Oxytocin augmentation in active labour, that is oxytocin intravenous infusion (5 international units (0.01mg) oxytocin in 500 ml saline) used in incremental doses during active labour. Predictors: NA Effect modifiers: Episiotomy, operative vaginal delivery, birth weight <4000 g vs ≥4000 g. Potential confounders: maternal age, ethnicity, occiput posterior position, duration of second stage of labour and epidural analgesia.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. (R) All variables are precisely defined in the obstetric databases of Stavanger University Hospital. The grade of perineal injury was assessed during operative repair and plotted directly into the database.
Bias	9	Describe any efforts to address potential sources of bias. (R) In this cross-sectional study all women giving births and who fulfil the inclusion criteria are included. There were very few cases with missing data. We may have missed some cases of perineal injury due to underreporting. The variables are hard variables with clear definitions: Use of oxotocin (yes/no), episiotomy (yes/no), mode of delivery (spontaneous/operative vaginal), birth weight categorized <4000/ ≥4000 g.
Study size	10	Explain how the study size was arrived at (R) The study size is given by the number of women fulfilling the eligibility criteria and who delivered at Stavanger University Hospital from 15 May 1999 to 15 May 2012.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. (R) Birth weight was categorized into < 4000/ ≥4000 g.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (R) Chi-square test and stepwise forward logistic regression using IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.
		(*b*) Describe any methods used to examine subgroups and interactions (R) We applied a stratified approach to control for interaction between the main variables (oxytocin augmentation, episiotomy, instrumental delivery and birth weight). Then we tested for confounding and interaction to a modified model by entering one variable at time.
		(*c*) Explain how missing data were addressed (R) Cases with missing data for estimated date of delivery were excluded. Cases with

		other missing data were recoded to the reference value in the logistic regression analyses. Very few cases with missing data (n=52).
		(*d*) If applicable, describe analytical methods taking account of sampling strategy (R) NA
		(*e*) Describe any sensitivity analyses (R) NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (R) Potentially eligible: 15 545 Confirmed eligible: 15 493 Included/analyzed: 15 493
		(b) Give reasons for non-participation at each stage (R) Cases with missing data for estimated date of delivery were excluded (n=52)
		(c) Consider use of a flow diagram (R) Not useful in this study.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (R) Given in Table 1. The study participants represent the total population of women fulfilling the inclusion criteria in a Norwegian region of 320 000 people. The study population is heterogeneous with regard to obstetric risk (overall caesarean section rate 12,5%), social status and ethnicity.
		(b) Indicate number of participants with missing data for each variable of interest (R) Cases with missing data for estimated date of delivery were excluded from the study population (n=52) Recoded to the reference category of the variable and included in the analyses: Birth weight 3 cases. Maternal age 2 cases. Lie at delivery 8 cases. Duration of second stage of labour 92 cases.
Outcome data	15*	Report numbers of outcome events or summary measures (R) Table 1. Outcome event, the dependant variable, anal sphincter injury: 1014 cases.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (R) Table 2 and 3. Confounders: paragraph 4 in Material and Methods.
		(*b*) Report category boundaries when continuous variables were categorized (R) Table 1

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (R) NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses R) NA
Discussion		
Key results	18	Summarise key results with reference to study objectives (R) Fulfilled.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (R) Bias regarding main outcome: We do not know the magnitude of underreporting of anal sphincter tear grade 3 and 4, however believe this to be low. Bias regarding main exposure: The quality system of the department relies on honest reporting by midwives and obstetricians, and has been a cornerstone in the systematic interdisciplinary work towards better clinical outcomes since 1996. We have reason to believe that ownership to the concept has resulted in good adherence to the reporting routines, and we believe the reporting of oxytocin augmentation to be a robust measure of what was actually practised. The midwives plotting the information were not aware of any research issue related to oxytocin augmentation. We consider the other main exposure variables to be robust: It is unlikely that reports of episiotomy, instrumental delivery and birth weight are skewed in any direction. The same applies to the possible confounders age, ethnicity, occiput posterior position and epidural analgesia. We believe that the reporting of these variables reflects the actual practice. Therefore we consider the estimates for risks related to anal sphincter tear grade 3 and 4 to be precise with little bias. Our stratified approach, modified model, takes care of the interaction problems between episiotomy, operative vaginal delivery, birth weight and oxytocin augmentation.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (R) Fulfilled.
Generalisability	21	Discuss the generalisability (external validity) of the study results. (R) The study participants represent the total population of women fulfilling the inclusion criteria in a Norwegian region of 320 000 people. The study population is heterogeneous with regard to obstetric risk (overall caesarean section rate 12,5%), social status and ethnicity. This adds value to the external validity of the study results. We encourage other study groups to make research on the effect of oxytocin augmentation on anal sphincter injury in other populations.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if

	applicable, for the original study on which the present article is based
	(R) No specific funding.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Assessing the association of oxytocin augmentation with obstetric anal sphincter injury in nulliparous women – a population-based, case-control study

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ASSESSING THE ASSOCIATION OF OXYTOCIN AUGMENTATION WITH OBSTETRIC ANAL SPHINCTER INJURY IN NULLIPAROUS WOMEN – A POPULATION-BASED, CASE CONTROL-STUDY

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Oxytocin augmentation and anal sphincter injury

Key words: anal sphincter injury, oxytocin, episiotomy, operative vaginal delivery, birth weight,
Word Count: 2815

ABSTRACT

Objective: To assess the association of oxytocin augmentation with obstetric anal sphincter injury among nulliparous women.

Design: A population-based, case-control study.

Setting: Primary and secondary teaching hospital serving a Norwegian region.

Population: 15 476 nulliparous women with spontaneous start of labour, single cephalic presentation, and gestation ≥37 weeks delivering vaginally between 1999 and 2012.

Methods: Based on the presence or absence of oxytocin augmentation, episiotomy, operative vaginal delivery, and birth weight (<4000 g vs. ≥4000 g), we modelled in logistic regression the best fit for prediction of anal sphincter injury. Within the modified model of main exposures, we tested for possible confounding, and interactions between maternal age, ethnicity, occiput posterior position, and epidural analgesia.

Comment [ar1]: New modeling

Main outcome measure: Obstetric anal sphincter injury.

Results: Oxytocin augmentation was associated with a higher OR of obstetric anal sphincter injuries in women giving spontaneous birth to infants weighing <4000 g (OR 1.8; 95% CI: 1.5–2.2). Episiotomy was not associated with sphincter injuries in spontaneous births, but with a lower OR in operative vaginal deliveries. Spontaneous delivery of infants weighing ≥ 4000 g was associated with a 3-fold higher OR, and epidural analgesia was associated with a 30% lower OR in comparison to no epidural analgesia.

Conclusions: Oxytocin augmentation was associated with a higher OR of obstetric anal sphincter injuries during spontaneous deliveries of normal-sized infants. We observed a considerable effect modification between the most important factors predicting anal sphincter injuries in the active second stage of labour.

ARTICLE SUMMARY

Strengths and limitations of this study

- Stratifying by the main risk factors that are active during the expulsive phase of labour and testing for confounders are strengths of the study.
- We reveal how oxytocin augmentation interacts with the major factors active in the expulsive phase of labour.
- The study is based on prospectively collected data from a large, unselected population, which makes bias unlikely.
- The study design is a limitation, as we cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study.

INTRODUCTION

Obstetric anal sphincter injuries occur in 0.5–5.0% of vaginal deliveries,[1] with a subsequently increased risk of fecal incontinence.[2-4] Nulliparity,[1, 3, 5] high birth weight,[1, 3, 5, 6] operative vaginal delivery,[1, 3, 5] advanced maternal age,[1, 5, 6] Asian or African ethnicity,[1, 7] and prolonged second stage of labour[3, 7, 8] are consistently reported as risk factors for obstetric anal sphincter injuries , whereas the effect of epidural analgesia[9, 10] and episiotomy[1, 11-13] is debated. However, only a few authors have evaluated oxytocin augmentation as a possible risk factor for obstetric anal sphincter injuries.[5, 14, 15] Further, the current literature dealing with risk factors for obstetric anal sphincter injuries has not sufficiently addressed their possible interactions. Studies usually present a summary of associations between risk factors and obstetric anal sphincter injuries adjusted for confounders without investigating effect modification, i.e. exploring whether the effects are uniform across various levels of the studied risk factors.

In many delivery units, oxytocin augmentation is used during more than half of births.[16, 17] Oxytocin augmentation has been shown to shorten the duration of labour, but not to decrease the need for operative deliveries.[18] We hypothesize that oxytocin augmentation may reduce control over contractions and impair perineal support by causing the delivery to progress too quickly, and thereby increase the risk of perineal injury. Thus, the widespread use of oxytocin in daily obstetric practice calls for an exploration of its possible harmful effects. The aim of our study was to assess the association between oxytocin augmentation and obstetric anal sphincter injuries in a dynamic model related to the active second stage of labour.

MATERIALS AND METHODS

The Department of Obstetrics and Gynaecology of Stavanger University Hospital serves as the only delivery unit for a population of 320 000 people, and approximately 4500 deliveries occur there annually. From 1996 onward, all obstetric data have been consecutively recorded. The electronic database consists of clearly defined variables, and is continuously maintained using standardized procedures for data entry and quality control. During the study period 15 May 1999 to 15 May 2012, 56 517 women with a pregnancy duration of ≥23 weeks of gestation and infants with a birth weight of >300 grams delivered in the department. Estimated day of delivery was determined by second trimester ultrasound scan or from menstrual data when no ultrasound examination was performed. We restricted the study population to nulliparous women whose labour started spontaneously, with single cephalic presentation, pregnancies of ≥37 weeks of gestation (Group 1 in Robson's Ten Group Classification System; TGCS[19]), and who delivered vaginally. After excluding 69 women with missing data, (52 without an estimated day of delivery, 17 with missing information of fetal presentation at delivery), this case-control study comprised 15 476 women.

The main outcome measure was obstetric anal sphincter injuries as defined by the International Continence Society, i.e. partial or complete tears of the anal sphincter muscles, with or without disruption of the anal mucosa (grade 3–4 perineal tears).[20] When an obstetric anal sphincter injury was suspected, the obstetrician on call diagnosed the grade of the tear during surgical repair.

Oxytocin augmentation was defined as oxytocin used to stimulate contractions during established labour. An intravenous infusion of 5 international units (0.01mg) oxytocin in 500 ml saline was administered, starting with 30 ml per hour, and a dose increment of 15 ml per hour every 15 minutes to a maximum of 180 ml per hour, guided by the response. Normal births were taken care of by midwives, while doctors performed the operative deliveries.

Throughout the study period, episiotomy was performed either medio-laterally or laterally. According to our routines and national guidelines, operative vaginal delivery was indicated if delivery had not taken place after 60 minutes of bearing down. We used vacuum extraction with a Malmström metal cup as the preferred procedure for operative vaginal delivery. Vacuum extraction was applied for mid-cavity and outlet release. A combination of low-dose ropivicaine/fentanyl was used for epidural analgesia. Ethnicity was classified as Western i.e. originating from Europe or North America, or non-Western.

The intention of this study was to explore the effect of three obstetric practices (oxytocin augmentation (O), episiotomy (E) and vacuum/forceps (VF)) and birth weight (BW) on obstetric anal sphincter injuries before other risk factors were considered. These main risk factors correlate as episiotomy is often used for instrumental deliveries and when large babies are expected. Furthermore, oxytocin augmentation is provided for failure to progress because of dystocia. Women with dystocia are more often delivered instrumentally than women without dystocia. This basic understanding of the birth dynamics of the first and second stage of labour indicates that the main risk factors may have a direct or indirect effect on obstetric anal sphincter injuries, and that the effects of categories across different explanatory variables are not constant on the outcome.

We analysed our dataset using the Chi-squared test and backward manual stepwise logistic regression analyses with $p<0.05$ as significance level. We built and checked the fit of our regression model as proposed by Agresti [21]. At step one we compared a model of the highest order interaction term (four-way product term; E*O*VF*BW) and the main risk factors (E+O+VF+BW) with a model comprising only the main risk factors. If the highest order product term is not significant, Agresti propose to continue with second highest order terms by removing the term with the highest p-value until the model of best fit is reached.

Confounders, possible risk factors in addition to the main factors of interest, were tested one by one and set to at least 10% change in any estimate in the model of best fit. Interaction terms were significant at $p<0.05$. Statistical analyses were performed with IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.

The Regional Committee for Medical and Health Research Ethics, Western Norway, approved the protocol as a quality assurance study in obstetric care, and fulfilling the requirements for data protection procedures (REK 2011-1247).

RESULTS

The study population comprised 15 476 (27%) of the 56 517 women giving birth during the study period, including 1013 (53%) of a total of 1894 women diagnosed with obstetric anal sphincter injuries.

The overall prevalence of obstetric anal sphincter injuries was 6.5%. The rate declined from 9.6% in 1999–2000 to 2.8% in 2010–2012. The characteristics of the study population and the prevalence of obstetric anal sphincter injuries are displayed in Table 1.

Table 1 Characteristics of the study population and the prevalence of obstetric anal sphincter injury. P-values from Chi-square tests.

Factor	Obstetric anal sphincter injury No N=14 463 %	Yes N=1013 %	In total N=15 476	Prevalence %	P
Time period					<0.001
1999-2000	11.1	16.9	1781	9.6	
2001-2003	19.8	30.7	3169	9.8	
2004-2006	22.9	29.6	3611	8.3	
2007-2009	25.5	14.3	3826	3.8	
2010-2012	20.8	8.6	3089	2.8	
Maternal factors					
Age (years)					<0.001
<25	26.6	19.3	4040	4.9	
25-29	33.5	37.6	5233	7.3	

30-34	17.8	20.8	2785	7.6	
≥35	22.1	22.2	3418	6.6	
Origin					NS*
Western	90.5	92.0	14 025	6.6	
Non-Western	9.5	8.0	1451	5.6	
Obstetric factors					
Epidural analgesia					NS
No	58.1	57.7	8992	6.5	
Yes	41.9	42.3	6484	6.6	
Oxytocin augmentation					<0.001
No	55.6	44.7	8500	5.3	
Yes	44.4	55.3	6976	8.0	
Active 2nd stage of labour (min)					<0.001
Missing information	0.6	0.3	92	3.3	
0-14	10.8	6.8	1627	4.2	
15-29	26.8	18.5	4063	4.6	
30-59	40.1	37.8	6181	6.2	
≥60	21.7	36.6	3513	10.6	
Episiotomy					NS
No	67.1	65.4	10 372	6.4	
Yes	32.9	34.6	5104	6.9	
Operative vaginal delivery					<0.001
No	77.5	60.3	11 817	5.2	
Yes	22.5	39.7	3659	11.0	
Fetal factors					
Birth weight (g)					<0.001
<4000	87.8	74.2	13 454	5.6	
≥4000	12.2	25.8	2022	12.9	
Occiput posterior position					NS
No	95.4	94.8	14 771	6.5	
Yes	4.5	5.2	705	7.4	

* Non significant

The prevalence was higher in women who received oxytocin augmentation (8.0% vs. 5.3%), those who were delivered instrumentally (11.0% vs. 5.2%), and in those who gave birth to an infant weighing ≥4000 g (12.9% vs. 5.6%). Furthermore, the prevalence increased with longer durations of the active part of the second stage of labour.

The log likelihood-ratio score from the highest order model (O*E*VF*FW+O+E+VF+BW; -2 LR: 7213.8) did not differ from the model comprising the main effects (O+E+VF+BW, -2 LR: 7215.9). After removing insignificant three-way interaction product terms, and playing with the remaining two-ways interaction terms, the model that gave the best fit comprised the interaction of oxytocin augmentation, episiotomy and instrumental delivery (O*E*VF), in addition to episiotomy/birth weight (E*BW) and instrumental delivery/birth weight (VF*BW) (-2 LR: 7371.2) (Model A). We could resolve

interaction terms into stratified analysis of 8 strata of combinations of oxytocin augmentation, episiotomy and instrumental delivery for birth weights <4000 g, and 4 strata of combinations of episiotomy, instrumental delivery and birth weight ≥4000 g, independent of oxytocin augmentation. The results are displayed in Table 2.

Table 2 Model A. Stratified analyses of 8 strata of combinations of oxytocin augmentation, episiotomy, instrumental delivery and birth weights <4000 g, and 4 strata of episiotomy, instrumental delivery and birth weights ≥4000 g, independent of oxytocin augmentation. Crude odds ratio (OR) and 95% confidence intervals (95% CI)

Group	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	95% CI
1	-	-	-	-	5328	198 (3.7)	1.0	
2	-	+	-	-	1434	60 (4.2)	1.1	0.8-1.5
3	-	+	+	-	537	43 (8.0)	2.3	1.6-3.2
4	-	-	+	-	316	47 (14.9)	4.5	3.2-6.4
5	+	+	+	-	1283	92 (7.2)	2.0	1.6-2.6
6	+	-	+	-	896	103 (11.5)	3.4	2.6-4.3
7	+	-	-	-	2621	148 (5.6)	1.6	1.3-1.9
8	+	+	-	-	1039	61 (5.9)	1.6	1.2-2.2
9	+/-	+	-	+	418	40 (9.6)	2.7	1.9-3.9
10	+/-	-	-	+	977	104 (10.6)	3.1	2.4-4.0
11	+/-	+	+	+	393	55 (14.0)	4.2	3.1-5.8
12	+/-	-	+	+	234	62 (26.5)	9.3	6.8-12.9

From a clinical perspective we can simplify model A into model B by collapsing groups that comprise similar risks for sphincter injury by obstetric interventions despite overlapping confidence intervals. Spontaneous delivery of an infant weighing <4000 g without oxytocin augmentation and episiotomy was chosen as the reference group (group 1). We collapsed group 1 and 2 as the odds for sphincter injury was similar with and without episiotomy in unstimulated, spontaneous births of normal-sized infants. Group 3 to 6 display the odds for sphincter injury in instrumental deliveries of normal-sized infants with and without oxytocin

augmentation and episiotomy. A marked difference in the odds for sphincter injury was observed between women delivered instrumentally with (group 3 and 5) and without (group 4 and 6) episiotomy, despite the fact that those stimulated with oxytocin had a non-significant lower odds for sphincter injury. It was therefore reasonable to collapse group 3 and 5, and group 4 and 6. Furthermore, we collapsed group 7 and 8 as the odds for sphincter injury was similar with and without episiotomy during spontaneous deliveries of infants <4000 g, regardless of oxytocin augmentation. Finally, the use of episiotomy appeared to be strongly associated with lower odds for sphincter injury in instrumental deliveries of infants ≥4000 g (group 11 and 12). The modified model B (Table 3) comprises a clinically relevant risk estimation of anal sphincter injury among the main modified risk factors for sphincter injury.

Table 3 Modified model displaying the collapsed non-significant strata (1–12) from Table 2 into new strata (A–G). Unadjusted odds ratios (OR), adjusted (aOR), and 95% confidence intervals (95% CI) after adjusting for epidural analgesia

Group (Group in Table 2)	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	aOR (95% CI)
A (1,2)	-	+/-	-	-	6762	258 (3.8)	1.0	1.0
B (7,8)	+	+/-	-	-	3660	209 (5.7)	1.5	1.8 (1.5-2.2)
C (3,5)	+/-	+	+	-	1820	135 (7.4)	2.0	2.3 (1.8-2.8)
D (4,6)	+/-	-	+	-	1212	150 (12.4)	3.6	4.1 (3.3-5.1)
E (9-10)	+/-	+/-	-	+	1395	144 (10.3)	2.9	3.1 (2.5-3.9)
F (11)	+/-	+	+	+	393	55 (14.0)	4.1	4.7 (3.4-6.5)
G (12)	+/-	-	+	+	234	62 (26.5)	9.1	10.5 (7.6-14.4)

Age, origin of the mother, and occiput posterior position had no confounding effect on odds ratios for obstetric anal sphincter injury across combinations of episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight (groups A to G in Table 3).

The unadjusted odds ratio (OR) for the presence or absence of epidural analgesia was 1.02; however, the adjusted OR for epidural analgesia was 0.73, (95% CI 0.63-0.84) i.e. epidural analgesia was associated with a 30% lower odds ratio of anal sphincter injury.

The use of oxytocin augmentation increased with the duration of the second stage of labour over all the time periods from an average of 32% in the <30 minutes group, 46% in the 30–59 minutes group, and 65% (range 49–76%) in the ≥60 minutes group during the active second stage of labour. The prevalence of operative deliveries across all study periods was consistently between 45–49% when the active part of the second stage of labour lasted ≥60 minutes vs. 12–21% for durations of the second stage of labour of <60 minutes. We found strong associations between oxytocin augmentation and the duration of second stage, and between operative delivery and the duration of second stage (collinearity), which means that the duration of second stage is measured through operative delivery and oxytocin augmentation.

DISCUSSION

We found that oxytocin augmentation during active labour was associated with a 80% increased odds ratio of obstetric anal sphincter injury in women in TGCS group 1 giving spontaneous birth to an infant weighing <4000 g. We did not find an association between episiotomy and tears during spontaneous deliveries, but a significantly reduced association in all operative vaginal deliveries.

Oxytocin augmentation is widely used in delayed labour to prevent operative delivery. However, a Cochrane review concluded that a reduction of labour by two hours was the only

proven effect, and there was no effect on operative deliveries.[18] Another recent review found the entire concept of active management of labour to be associated with a slightly reduced risk of caesarean delivery.[22] As in other studies, we found that approximately 50% of nulliparous women received oxytocin augmentation.[16, 17, 23] There is reason to believe that guidelines for the diagnosis and treatment of protracted labour are unclear or inconsistently applied in daily practice.[17] We hypothesize that stimulation with oxytocin may speed up the progress of the expulsive phase of labour, leading to rushed situations, impaired communication with the mother, and less focus on protection of the perineum and a controlled delivery of the head. Recent studies from Norway indicate that focus on these elements is important in preventing perineal injuries.[24, 25]

Many authors have used logistic regression analysis to identify risk factors for obstetric anal sphincter injuries, but only a few have included oxytocin augmentation. Samuelsson et al.,[14] Prager et al.,[15] and Jander et al.[5] found oxytocin augmentation to be predictive of obstetric anal sphincter injuries in univariate analysis, but only Jander et al. confirmed this finding in multivariable analyses. Samuelsson et al. did not stratify by parity, which is a methodological weakness since the true effect of other factors is concealed by the strong impact of parity.[14] Prager et al. studied obstetric anal sphincter injuries in nulliparous women, entering oxytocin augmentation, duration of active second stage of labour, and instrumental delivery into the same model.[15]

Our study shows strong collinearity between a prolonged active second stage of labour and both oxytocin augmentation and instrumental delivery. We consider the duration of the active second stage of labour to be a "proxy" for oxytocin augmentation and instrumental delivery, and not a risk factor for obstetric anal sphincter injury in itself. Long duration of the second stage is a time related event before the expulsion of the head. During this latency the active forces do not inflict injury on the sphincter apparatus, the sphincter injury occurs

during the expulsive phase. Consequently, we do not consider the duration of the active second stage as a risk factor for anal sphincter injuries.

Jander et al. conducted a single institution, retrospective, case-control study of 214 cases to explore 44 possible risk factors, and found that oxytocin augmentation was a significant risk factor for obstetric anal sphincter injuries in multivariable analyses (OR 2.00; 95% CI 1.13–3.53).[5] However, these researchers did not stratify by parity or state whether or not interactions were tested for. Furthermore, three older studies on the risk of obstetric anal sphincter injury included oxytocin use without differentiating whether oxytocin was provided for induction or augmentation purposes.[26-28] Three large population-based studies on the risk of obstetric anal sphincter injuries did not include oxytocin augmentation in their analyses.[1, 7, 8]

The influence of epidural analgesia on anal sphincter injuries is unclear. Eskandar and Shet found a reduced risk, but did not stratify by parity.[9] Dahl and Kjølhede found epidural analgesia to be an independent protective factor in nulliparous women.[10] Poen et al. stratified by parity and found a significantly increased odds ratio associated with epidural analgesia in nulliparous women.[29] In our study, epidural analgesia was associated with a significantly reduced odds ratio for sphincter tears.

Our study takes into account four factors that exert their effect on the anal sphincter during the final minutes of delivery. As in previous studies,[1, 3, 5] we found both operative vaginal delivery and high birth weight to be strongly associated with obstetric anal sphincter injuries. We found episiotomy to be associated with a lower prevalence of sphincter tears in operative vaginal deliveries, but not in spontaneous births. This is consistent with a large national registry study from Norway,[1] but differs from other studies.[8, 11, 13, 30, 31] In our study, neither oxytocin augmentation nor episiotomy were associated with obstetric anal sphincter injury during spontaneous delivery of an infant weighing ≥4000 g.

Our methodological approach, stratifying by the factors that are active during the expulsive phase of labour and testing for confounders, is considered a strength of the study. This approach leads to a more detailed understanding of how oxytocin augmentation interacts with these major risk factors. Logistic regression analyses, without testing for possible interactions, would fail to reveal this information. This case-control study is based on prospectively collected data from a large unselected population, and represents all deliveries meeting the inclusion criteria that occurred during the study period, which make bias unlikely. Our department has a high proportion of vaginal deliveries. The overall caesarean delivery rate in our institution was 12.5% over the study period. For women in TGCS group 1 the acute caesarean section rate increased from 5.0% in 1999 to 7.5% in 2012. Accordingly, the study population includes both high- and low-risk pregnancies, which adds to the external validity of our results.

However, some limitations apply. We cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study. Furthermore, socioeconomic status, smoking, body mass index, maternal delivery positions, perineal support technique, and the birth attendant's experience level may be possible risk modifiers not included in our database. Finally, single institution studies, also when based on unselected populations, should be interpreted with caution.

Our findings have some important implications. Birth attendants should be aware of the association between oxytocin augmentation and obstetric anal sphincter injuries in the large subgroup of nulliparous women giving spontaneous birth to a normal-sized infant. More restrictive use of oxytocin may help prevent obstetric anal sphincter injuries. Implementation of evidence-based guidelines for using oxytocin augmentation should be encouraged. The World Health Organization recommends the use of a partogram with an action line defining failure to progress. However, a recent Cochrane review could not confirm that such a

partogram was beneficial in high resource settings.[32] Given the doubtful benefits from augmentation of labour, randomized controlled trials are strongly needed, and we propose anal sphincter injury as one of the most important endpoints.

Moreover, our study supports restricted use of episiotomy during normal births and as a recommendation for operative vaginal deliveries. Birth weight is an important, albeit unpredictable risk factor as weight estimation of a large fetus is unreliable.[33]

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Competing interests

None

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Contributorship Statement

All four authors have contributed to the idea and design of the research project. ABR, TME managed the dataset and the statistical analyses were performed by FES. All four authors have contributed to the interpretation of the results and the writing of the manuscript.

Data Sharing Statement

No additional data available

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Assessing the association of oxytocin augmentation with obstetric anal sphincter injury in nulliparous women – a population-based, case-control study

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- The study design is a limitation, as we cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study.

INTRODUCTION

Obstetric anal sphincter injuries occur in 0.5–5.0% of vaginal deliveries,[1] with a subsequently increased risk of fecal incontinence.[2-4] Nulliparity,[1, 3, 5] high birth weight,[1, 3, 5, 6] operative vaginal delivery,[1, 3, 5] advanced maternal age,[1, 5, 6] Asian or African ethnicity,[1, 7] and prolonged second stage of labour[3, 7, 8] are consistently reported as risk factors for obstetric anal sphincter injuries , whereas the effect of epidural analgesia[9, 10] and episiotomy[1, 11-13] is debated. However, only a few authors have evaluated oxytocin augmentation as a possible risk factor for obstetric anal sphincter injuries.[5, 14, 15] Further, the current literature dealing with risk factors for obstetric anal sphincter injuries has not sufficiently addressed their possible interactions. Studies usually present a summary of associations between risk factors and obstetric anal sphincter injuries adjusted for confounders without investigating effect modification, i.e. exploring whether the effects are uniform across various levels of the studied risk factors.

In many delivery units, oxytocin augmentation is used during more than half of births.[16, 17] Oxytocin augmentation has been shown to shorten the duration of labour, but not to decrease the need for operative deliveries.[18] We hypothesize that oxytocin augmentation may reduce control over contractions and impair perineal support by causing the delivery to progress too quickly, and thereby increase the risk of perineal injury. Thus, the widespread use of oxytocin in daily obstetric practice calls for an exploration of its possible harmful effects. The aim of our study was to assess the association between oxytocin augmentation and obstetric anal sphincter injuries in a dynamic model related to the active second stage of labour.

MATERIALS AND METHODS

The Department of Obstetrics and Gynaecology of Stavanger University Hospital serves as the only delivery unit for a population of 320 000 people, and approximately 4500 deliveries occur there annually. From 1996 onward, all obstetric data have been consecutively recorded. The electronic database consists of clearly defined variables, and is continuously maintained using standardized procedures for data entry and quality control. During the study period 15 May 1999 to 15 May 2012, 56 517 women with a pregnancy duration of ≥23 weeks of gestation and infants with a birth weight of >300 grams delivered in the department. Estimated day of delivery was determined by second trimester ultrasound scan or from menstrual data when no ultrasound examination was performed. We restricted the study population to nulliparous women whose labour started spontaneously, with single cephalic presentation, pregnancies of ≥37 weeks of gestation (Group 1 in Robson's Ten Group Classification System; TGCS[19]), and who delivered vaginally. After excluding 69 women with missing data, (52 without an estimated day of delivery, 17 with missing information of fetal presentation at delivery), this case-control study comprised 15 476 women.

The main outcome measure was obstetric anal sphincter injuries as defined by the International Continence Society, i.e. partial or complete tears of the anal sphincter muscles, with or without disruption of the anal mucosa (grade 3–4 perineal tears).[20] When an obstetric anal sphincter injury was suspected, the obstetrician on call diagnosed the grade of the tear during surgical repair.

Oxytocin augmentation was defined as oxytocin used to stimulate contractions during established labour. An intravenous infusion of 5 international units (0.01mg) oxytocin in 500 ml saline was administered, starting with 30 ml per hour, and a dose increment of 15 ml per hour every 15 minutes to a maximum of 180 ml per hour, guided by the response. Normal births were taken care of by midwives, while doctors performed the operative deliveries.

Throughout the study period, episiotomy was performed either medio-laterally or laterally. According to our routines and national guidelines, operative vaginal delivery was indicated if delivery had not taken place after 60 minutes of bearing down. We used vacuum extraction with a Malmström metal cup as the preferred procedure for operative vaginal delivery. Vacuum extraction was applied for mid-cavity and outlet release. A combination of low-dose ropivicaine/fentanyl was used for epidural analgesia. Ethnicity was classified as Western i.e. originating from Europe or North America, or non-Western.

The intention of this study was to explore the effect of three obstetric practices (oxytocin augmentation (O), episiotomy (E) and vacuum/forceps (VF)) and birth weight (BW) on obstetric anal sphincter injuries before other risk factors were considered. These main risk factors correlate as episiotomy is often used for instrumental deliveries and when large babies are expected. Furthermore, oxytocin augmentation is provided for failure to progress because of dystocia. Women with dystocia are more often delivered instrumentally than women without dystocia. This basic understanding of the birth dynamics of the first and second stage of labour indicates that the main risk factors may have a direct or indirect effect on obstetric anal sphincter injuries, and that the effects of categories across different explanatory variables are not constant on the outcome.

We analysed our dataset using the Chi-squared test and backward manual stepwise logistic regression analyses with $p<0.05$ as significance level. We built and checked the fit of our regression model as proposed by Agresti [21]. At step one we compared a model of the highest order interaction term (four-way product term; E*O*VF*BW) and the main risk factors (E+O+VF+BW) with a model comprising only the main risk factors. If the highest order product term is not significant, Agresti propose to continue with second highest order terms by removing the term with the highest p-value until the model of best fit is reached.

Confounders, possible risk factors in addition to the main factors of interest, were tested one by one and set to at least 10% change in any estimate in the model of best fit. Interaction terms were significant at $p<0.05$. Statistical analyses were performed with IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.

The Regional Committee for Medical and Health Research Ethics, Western Norway, approved the protocol as a quality assurance study in obstetric care, and fulfilling the requirements for data protection procedures (REK 2011-1247).

RESULTS

The study population comprised 15 476 (27%) of the 56 517 women giving birth during the study period, including 1013 (53%) of a total of 1894 women diagnosed with obstetric anal sphincter injuries.

The overall prevalence of obstetric anal sphincter injuries was 6.5%. The rate declined from 9.6% in 1999–2000 to 2.8% in 2010–2012. The characteristics of the study population and the prevalence of obstetric anal sphincter injuries are displayed in Table 1.

Table 1 Characteristics of the study population and the prevalence of obstetric anal sphincter injury. P-values from Chi-square tests.

Factor	Obstetric anal sphincter injury		In total	Prevalence	P
	No	Yes			
	N=14 463	N=1013	N=15 476		
	%	%		%	
Time period					<0.001
1999-2000	11.1	16.9	1781	9.6	
2001-2003	19.8	30.7	3169	9.8	
2004-2006	22.9	29.6	3611	8.3	
2007-2009	25.5	14.3	3826	3.8	
2010-2012	20.8	8.6	3089	2.8	
Maternal factors					
Age (years)					<0.001
<25	26.6	19.3	4040	4.9	
25-29	33.5	37.6	5233	7.3	

30-34	17.8	20.8	2785	7.6	
≥35	22.1	22.2	3418	6.6	
Origin					NS*
Western	90.5	92.0	14 025	6.6	
Non-Western	9.5	8.0	1451	5.6	
Obstetric factors					
Epidural analgesia					NS
No	58.1	57.7	8992	6.5	
Yes	41.9	42.3	6484	6.6	
Oxytocin augmentation					<0.001
No	55.6	44.7	8500	5.3	
Yes	44.4	55.3	6976	8.0	
Active 2nd stage of labour (min)					<0.001
Missing information	0.6	0.3	92	3.3	
0-14	10.8	6.8	1627	4.2	
15-29	26.8	18.5	4063	4.6	
30-59	40.1	37.8	6181	6.2	
≥60	21.7	36.6	3513	10.6	
Episiotomy					NS
No	67.1	65.4	10 372	6.4	
Yes	32.9	34.6	5104	6.9	
Operative vaginal delivery					<0.001
No	77.5	60.3	11 817	5.2	
Yes	22.5	39.7	3659	11.0	
Fetal factors					
Birth weight (g)					<0.001
<4000	87.8	74.2	13 454	5.6	
≥4000	12.2	25.8	2022	12.9	
Occiput posterior position					NS
No	95.4	94.8	14 771	6.5	
Yes	4.5	5.2	705	7.4	

* Non significant

The prevalence was higher in women who received oxytocin augmentation (8.0% vs. 5.3%), those who were delivered instrumentally (11.0% vs. 5.2%), and in those who gave birth to an infant weighing ≥4000 g (12.9% vs. 5.6%). Furthermore, the prevalence increased with longer durations of the active part of the second stage of labour.

The log likelihood-ratio score from the highest order model (O*E*VF*FW+O+E+VF+BW; -2 LR: 7213.8) did not differ from the model comprising the main effects (O+E+VF+BW, -2 LR: 7215.9). After removing insignificant three-way interaction product terms, and playing with the remaining two-ways interaction terms, the model that gave the best fit comprised the interaction of oxytocin augmentation, episiotomy and instrumental delivery (O*E*VF), in addition to episiotomy/birth weight (E*BW) and instrumental delivery/birth weight (VF*BW) (-2 LR: 7371.2) (Model A). We could resolve

interaction terms into stratified analysis of 8 strata of combinations of oxytocin augmentation, episiotomy and instrumental delivery for birth weights <4000 g, and 4 strata of combinations of episiotomy, instrumental delivery and birth weight ≥4000 g, independent of oxytocin augmentation. The results are displayed in Table 2.

Table 2 Model A. Stratified analyses of 8 strata of combinations of oxytocin augmentation, episiotomy, instrumental delivery and birth weights <4000 g, and 4 strata of episiotomy, instrumental delivery and birth weights ≥4000 g, independent of oxytocin augmentation. Crude odds ratio (OR) and 95% confidence intervals (95% CI)

Group	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	95% CI
1	-	-	-	-	5328	198 (3.7)	1.0	
2	-	+	-	-	1434	60 (4.2)	1.1	0.8-1.5
3	-	+	+	-	537	43 (8.0)	2.3	1.6-3.2
4	-	-	+	-	316	47 (14.9)	4.5	3.2-6.4
5	+	+	+	-	1283	92 (7.2)	2.0	1.6-2.6
6	+	-	+	-	896	103 (11.5)	3.4	2.6-4.3
7	+	-	-	-	2621	148 (5.6)	1.6	1.3-1.9
8	+	+	-	-	1039	61 (5.9)	1.6	1.2-2.2
9	+/-	+	-	+	418	40 (9.6)	2.7	1.9-3.9
10	+/-	-	-	+	977	104 (10.6)	3.1	2.4-4.0
11	+/-	+	+	+	393	55 (14.0)	4.2	3.1-5.8
12	+/-	-	+	+	234	62 (26.5)	9.3	6.8-12.9

From a clinical perspective we can simplify model A into model B by collapsing groups that comprise similar risks for sphincter injury by obstetric interventions despite overlapping confidence intervals. Spontaneous delivery of an infant weighing <4000 g without oxytocin augmentation and episiotomy was chosen as the reference group (group 1). We collapsed group 1 and 2 as the odds for sphincter injury was similar with and without episiotomy in unstimulated, spontaneous births of normal-sized infants. Group 3 to 6 display the odds for sphincter injury in instrumental deliveries of normal-sized infants with and without oxytocin

augmentation and episiotomy. A marked difference in the odds for sphincter injury was observed between women delivered instrumentally with (group 3 and 5) and without (group 4 and 6) episiotomy, despite the fact that those stimulated with oxytocin had a non-significant lower odds for sphincter injury. It was therefore reasonable to collapse group 3 and 5, and group 4 and 6. Furthermore, we collapsed group 7 and 8 as the odds for sphincter injury was similar with and without episiotomy during spontaneous deliveries of infants <4000 g, regardless of oxytocin augmentation. Finally, the use of episiotomy appeared to be strongly associated with lower odds for sphincter injury in instrumental deliveries of infants ≥4000 g (group 11 and 12). The modified model B (Table 3) comprises a clinically relevant risk estimation of anal sphincter injury among the main modified risk factors for sphincter injury.

Table 3 Modified model displaying the collapsed non-significant strata (1–12) from Table 2 into new strata (A–G). Unadjusted odds ratios (OR), adjusted (aOR), and 95% confidence intervals (95% CI) after adjusting for epidural analgesia

Group (Group in Table 2)	Oxytocin augmentation	Episiotomy	Operative vaginal delivery	Birth weight ≥4000 g	Women N	Obstetric anal sphincter injury N (%)	OR	aOR (95% CI)
A (1,2)	-	+/-	-	-	6762	258 (3.8)	1.0	1.0
B (7,8)	+	+/-	-	-	3660	209 (5.7)	1.5	1.8 (1.5-2.2)
C (3,5)	+/-	+	+	-	1820	135 (7.4)	2.0	2.3 (1.8-2.8)
D (4,6)	+/-	-	+	-	1212	150 (12.4)	3.6	4.1 (3.3-5.1)
E (9-10)	+/-	+/-	-	+	1395	144 (10.3)	2.9	3.1 (2.5-3.9)
F (11)	+/-	+	+	+	393	55 (14.0)	4.1	4.7 (3.4-6.5)
G (12)	+/-	-	+	+	234	62 (26.5)	9.1	10.5 (7.6-14.4)

Age, origin of the mother, and occiput posterior position had no confounding effect on odds ratios for obstetric anal sphincter injury across combinations of episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight (groups A to G in Table 3).

The unadjusted odds ratio (OR) for the presence or absence of epidural analgesia was 1.02; however, the adjusted OR for epidural analgesia was 0.73, (95% CI 0.63-0.84) i.e. epidural analgesia was associated with a 30% lower odds ratio of anal sphincter injury.

The use of oxytocin augmentation increased with the duration of the second stage of labour over all the time periods from an average of 32% in the <30 minutes group, 46% in the 30–59 minutes group, and 65% (range 49–76%) in the ≥60 minutes group during the active second stage of labour. The prevalence of operative deliveries across all study periods was consistently between 45–49% when the active part of the second stage of labour lasted ≥60 minutes vs. 12–21% for durations of the second stage of labour of <60 minutes. We found strong associations between oxytocin augmentation and the duration of second stage, and between operative delivery and the duration of second stage (collinearity), which means that the duration of second stage is measured through operative delivery and oxytocin augmentation.

DISCUSSION

We found that oxytocin augmentation during active labour was associated with a 80% increased odds ratio of obstetric anal sphincter injury in women in TGCS group 1 giving spontaneous birth to an infant weighing <4000 g. We did not find an association between episiotomy and tears during spontaneous deliveries, but a significantly reduced association in all operative vaginal deliveries.

Oxytocin augmentation is widely used in delayed labour to prevent operative delivery. However, a Cochrane review concluded that a reduction of labour by two hours was the only

proven effect, and there was no effect on operative deliveries.[18] Another recent review found the entire concept of active management of labour to be associated with a slightly reduced risk of caesarean delivery.[22] As in other studies, we found that approximately 50% of nulliparous women received oxytocin augmentation.[16, 17, 23] There is reason to believe that guidelines for the diagnosis and treatment of protracted labour are unclear or inconsistently applied in daily practice.[17] We hypothesize that stimulation with oxytocin may speed up the progress of the expulsive phase of labour, leading to rushed situations, impaired communication with the mother, and less focus on protection of the perineum and a controlled delivery of the head. Recent studies from Norway indicate that focus on these elements is important in preventing perineal injuries.[24, 25]

Many authors have used logistic regression analysis to identify risk factors for obstetric anal sphincter injuries, but only a few have included oxytocin augmentation. Samuelsson et al.,[14] Prager et al.,[15] and Jander et al.[5] found oxytocin augmentation to be predictive of obstetric anal sphincter injuries in univariate analysis, but only Jander et al. confirmed this finding in multivariable analyses. Samuelsson et al. did not stratify by parity, which is a methodological weakness since the true effect of other factors is concealed by the strong impact of parity.[14] Prager et al. studied obstetric anal sphincter injuries in nulliparous women, entering oxytocin augmentation, duration of active second stage of labour, and instrumental delivery into the same model.[15]

Our study shows strong collinearity between a prolonged active second stage of labour and both oxytocin augmentation and instrumental delivery. We consider the duration of the active second stage of labour to be a "proxy" for oxytocin augmentation and instrumental delivery, and not a risk factor for obstetric anal sphincter injury in itself. Long duration of the second stage is a time related event before the expulsion of the head. During this latency the active forces do not inflict injury on the sphincter apparatus, the sphincter injury occurs

during the expulsive phase. Consequently, we do not consider the duration of the active second stage as a risk factor for anal sphincter injuries.

Jander et al. conducted a single institution, retrospective, case-control study of 214 cases to explore 44 possible risk factors, and found that oxytocin augmentation was a significant risk factor for obstetric anal sphincter injuries in multivariable analyses (OR 2.00; 95% CI 1.13–3.53).[5] However, these researchers did not stratify by parity or state whether or not interactions were tested for. Furthermore, three older studies on the risk of obstetric anal sphincter injury included oxytocin use without differentiating whether oxytocin was provided for induction or augmentation purposes.[26-28] Three large population-based studies on the risk of obstetric anal sphincter injuries did not include oxytocin augmentation in their analyses.[1, 7, 8]

The influence of epidural analgesia on anal sphincter injuries is unclear. Eskandar and Shet found a reduced risk, but did not stratify by parity.[9] Dahl and Kjølhede found epidural analgesia to be an independent protective factor in nulliparous women.[10] Poen et al. stratified by parity and found a significantly increased odds ratio associated with epidural analgesia in nulliparous women.[29] In our study, epidural analgesia was associated with a significantly reduced odds ratio for sphincter tears.

Our study takes into account four factors that exert their effect on the anal sphincter during the final minutes of delivery. As in previous studies,[1, 3, 5] we found both operative vaginal delivery and high birth weight to be strongly associated with obstetric anal sphincter injuries. We found episiotomy to be associated with a lower prevalence of sphincter tears in operative vaginal deliveries, but not in spontaneous births. This is consistent with a large national registry study from Norway,[1] but differs from other studies.[8, 11, 13, 30, 31] In our study, neither oxytocin augmentation nor episiotomy were associated with obstetric anal sphincter injury during spontaneous delivery of an infant weighing ≥4000 g.

Our methodological approach, stratifying by the factors that are active during the expulsive phase of labour and testing for confounders, is considered a strength of the study. This approach leads to a more detailed understanding of how oxytocin augmentation interacts with these major risk factors. Logistic regression analyses, without testing for possible interactions, would fail to reveal this information. This case-control study is based on prospectively collected data from a large unselected population, and represents all deliveries meeting the inclusion criteria that occurred during the study period, which make bias unlikely. Our department has a high proportion of vaginal deliveries. The overall caesarean delivery rate in our institution was 12.5% over the study period. For women in TGCS group 1 the acute caesarean section rate increased from 5.0% in 1999 to 7.5% in 2012. Accordingly, the study population includes both high- and low-risk pregnancies, which adds to the external validity of our results.

However, some limitations apply. We cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study. Furthermore, socioeconomic status, smoking, body mass index, maternal delivery positions, perineal support technique, and the birth attendant's experience level may be possible risk modifiers not included in our database. Finally, single institution studies, also when based on unselected populations, should be interpreted with caution.

Our findings have some important implications. Birth attendants should be aware of the association between oxytocin augmentation and obstetric anal sphincter injuries in the large subgroup of nulliparous women giving spontaneous birth to a normal-sized infant. More restrictive use of oxytocin may help prevent obstetric anal sphincter injuries. Implementation of evidence-based guidelines for using oxytocin augmentation should be encouraged. The World Health Organization recommends the use of a partogram with an action line defining failure to progress. However, a recent Cochrane review could not confirm that such a

partogram was beneficial in high resource settings.[32] Given the doubtful benefits from augmentation of labour, randomized controlled trials are strongly needed, and we propose anal sphincter injury as one of the most important endpoints.

Moreover, our study supports restricted use of episiotomy during normal births and as a recommendation for operative vaginal deliveries. Birth weight is an important, albeit unpredictable risk factor as weight estimation of a large fetus is unreliable.[33]

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Competing interests

None

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No specific

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Comment [ar1]: 21. Agresti new ref, statistical modeling

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (R) In abstract; a cross sectional study, analyzed as case-control study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (R) Fulfilled
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (R) Recent studies have shown the importance of the perineal protection technique in preventing perineal tears. Oxytocin augmentation could impair the control of the perineum during the delivery by causing too fast progress in the last minutes of labour. Oxytocin augmentation is widely used (50% of births). Guidelines for its use are often deficient and the evidence for its positive effect is challenged. Therefore, oxytocin augmentation as a risk factor for obstetric anal sphincter injuries, and should be explored in a study taking other relevant risk factors into account.
Objectives	3	State specific objectives, including any prespecified hypotheses (R) To assess the effect of oxytocin augmentation on obstetric anal sphincter injury among nulliparous women.
Methods		
Study design	4	Present key elements of study design early in the paper (R) Present in Abstract and Methods.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (R) Setting: Tertiary teaching hospital. Location: Delivery department of Stavanger University Hospital, serving the total obstetric population of the region of South Rogaland. Dates 15 May 1999 – 15 May 2012. Data were collected consecutively.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. (R) Nulliparous women with spontaneous start of labour, single, cephalic pregnancy and ≥37 weeks gestation who delivered vaginally, where we had access to complete information on the main exposure and the explanatory variables. The source population was the entire obstetric population of the region.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect

		modifiers. Give diagnostic criteria, if applicable (R) Outcome: Obstetric anal sphincter injury; that is grade 3 and 4 perineal tears as defined by International Society of Incontinence. Exposure: Oxytocin augmentation in active labour, that is oxytocin intravenous infusion (5 international units (0.01mg) oxytocin in 500 ml saline) used in incremental doses during active labour. Predictors: NA Effect modifiers: Episiotomy, operative vaginal delivery, birth weight <4000 g vs ≥4000 g. Potential confounders: maternal age, ethnicity, occiput posterior position, duration of second stage of labour and epidural analgesia.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. (R) All variables are precisely defined in the obstetric databases of Stavanger University Hospital. The grade of perineal injury was assessed during operative repair and plotted directly into the database.
Bias	9	Describe any efforts to address potential sources of bias. (R) In this cross-sectional study all women giving births and who fulfil the inclusion criteria are included. There were very few cases with missing data. We may have missed some cases of perineal injury due to underreporting. The variables are hard variables with clear definitions: Use of oxotocin (yes/no), episiotomy (yes/no), mode of delivery (spontaneous/operative vaginal), birth weight categorized <4000/ ≥4000 g.
Study size	10	Explain how the study size was arrived at (R) The study size is given by the number of women fulfilling the eligibility criteria and who delivered at Stavanger University Hospital from 15 May 1999 to 15 May 2012.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. (R) Birth weight was categorized into < 4000/ ≥4000 g.
Statistical methods	12	*(*a) Describe all statistical methods, including those used to control for confounding (R) Chi-square test and stepwise forward logistic regression using IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.
		(*b*) Describe any methods used to examine subgroups and interactions (R) We applied a stratified approach to control for interaction between the main variables (oxytocin augmentation, episiotomy, instrumental delivery and birth weight). Then we tested for confounding and interaction to a modified model by entering one variable at time.
		(*c*) Explain how missing data were addressed (R) Cases with missing data for estimated date of delivery were excluded. Cases with

		other missing data were recoded to the reference value in the logistic regression analyses. Very few cases with missing data (n=52).
		(*d*) If applicable, describe analytical methods taking account of sampling strategy (R) NA
		(*e*) Describe any sensitivity analyses (R) NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (R) Potentially eligible: 15 545 Confirmed eligible: 15 493 Included/analyzed: 15 493
		(b) Give reasons for non-participation at each stage (R) Cases with missing data for estimated date of delivery were excluded (n=52)
		(c) Consider use of a flow diagram (R) Not useful in this study.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (R) Given in Table 1. The study participants represent the total population of women fulfilling the inclusion criteria in a Norwegian region of 320 000 people. The study population is heterogeneous with regard to obstetric risk (overall caesarean section rate 12,5%), social status and ethnicity.
		(b) Indicate number of participants with missing data for each variable of interest (R) Cases with missing data for estimated date of delivery were excluded from the study population (n=52) Recoded to the reference category of the variable and included in the analyses: Birth weight 3 cases. Maternal age 2 cases. Lie at delivery 8 cases. Duration of second stage of labour 92 cases.
Outcome data	15*	Report numbers of outcome events or summary measures (R) Table 1. Outcome event, the dependant variable, anal sphincter injury: 1014 cases.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (R) Table 2 and 3. Confounders: paragraph 4 in Material and Methods.
		(*b*) Report category boundaries when continuous variables were categorized (R) Table 1

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (R) NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses R) NA
Discussion		
Key results	18	Summarise key results with reference to study objectives (R) Fulfilled.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (R) Bias regarding main outcome: We do not know the magnitude of underreporting of anal sphincter tear grade 3 and 4, however believe this to be low. Bias regarding main exposure: The quality system of the department relies on honest reporting by midwives and obstetricians, and has been a cornerstone in the systematic interdisciplinary work towards better clinical outcomes since 1996. We have reason to believe that ownership to the concept has resulted in good adherence to the reporting routines, and we believe the reporting of oxytocin augmentation to be a robust measure of what was actually practised. The midwives plotting the information were not aware of any research issue related to oxytocin augmentation. We consider the other main exposure variables to be robust: It is unlikely that reports of episiotomy, instrumental delivery and birth weight are skewed in any direction. The same applies to the possible confounders age, ethnicity, occiput posterior position and epidural analgesia. We believe that the reporting of these variables reflects the actual practice. Therefore we consider the estimates for risks related to anal sphincter tear grade 3 and 4 to be precise with little bias. Our stratified approach, modified model, takes care of the interaction problems between episiotomy, operative vaginal delivery, birth weight and oxytocin augmentation.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (R) Fulfilled.
Generalisability	21	Discuss the generalisability (external validity) of the study results. (R) The study participants represent the total population of women fulfilling the inclusion criteria in a Norwegian region of 320 000 people. The study population is heterogeneous with regard to obstetric risk (overall caesarean section rate 12,5%), social status and ethnicity. This adds value to the external validity of the study results. We encourage other study groups to make research on the effect of oxytocin augmentation on anal sphincter injury in other populations.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if

	applicable, for the original study on which the present article is based
	(R) No specific funding.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Assessing the association of oxytocin augmentation with obstetric anal sphincter injury in nulliparous women – a population-based, case-control study

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Oxytocin augmentation and anal sphincter injury

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Word Count: 2804

ABSTRACT

Objective: To assess the association of oxytocin augmentation with obstetric anal sphincter injury among nulliparous women.

Design: Population-based, case-control study.

Setting: Primary and secondary teaching hospital serving a Norwegian region.

Population: 15 476 nulliparous women with spontaneous start of labour, single cephalic presentation, and gestation ≥37 weeks delivering vaginally between 1999 and 2012.

Methods: Based on the presence or absence of oxytocin augmentation, episiotomy, operative vaginal delivery, and birth weight (<4000 g vs. ≥4000 g), we modelled in logistic regression the best fit for prediction of anal sphincter injury. Within the modified model of main exposures, we tested for possible confounding, and interactions between maternal age, ethnicity, occiput posterior position, and epidural analgesia.

Main outcome measure: Obstetric anal sphincter injury.

Results: Oxytocin augmentation was associated with a higher OR of obstetric anal sphincter injuries in women giving spontaneous birth to infants weighing <4000 g (OR 1.8; 95% CI: 1.5–2.2). Episiotomy was not associated with sphincter injuries in spontaneous births, but with a lower OR in operative vaginal deliveries. Spontaneous delivery of infants weighing ≥ 4000 g was associated with a 3-fold higher OR, and epidural analgesia was associated with a 30% lower OR in comparison to no epidural analgesia.

Conclusions: Oxytocin augmentation was associated with a higher OR of obstetric anal sphincter injuries during spontaneous deliveries of normal-sized infants. We observed a considerable effect modification between the most important factors predicting anal sphincter injuries in the active second stage of labour.

ARTICLE SUMMARY

Strengths and limitations of this study

- Stratifying by the main risk factors that are active during the expulsive phase of labour and testing for confounders are strengths of the study.
- We reveal how oxytocin augmentation interacts with the major factors active in the expulsive phase of labour.
- The study is based on prospectively collected data from a large, unselected population, which makes bias unlikely.
- The study design is a limitation, as we cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study.

INTRODUCTION

Obstetric anal sphincter injuries occur in 0.5–5.0% of vaginal deliveries,[1] with a subsequently increased risk of fecal incontinence.[2-4] Nulliparity,[1, 3, 5] high birth weight,[1, 3, 5, 6] operative vaginal delivery,[1, 3, 5] advanced maternal age,[1, 5, 6] Asian or African ethnicity,[1, 7] and prolonged second stage of labour[3, 7, 8] are consistently reported as risk factors for obstetric anal sphincter injuries , whereas the effect of epidural analgesia[9, 10] and episiotomy[1, 11-13] is debated. However, only a few authors have evaluated oxytocin augmentation as a possible risk factor for obstetric anal sphincter injuries.[5, 14, 15] Further, the current literature dealing with risk factors for obstetric anal sphincter injuries has not sufficiently addressed their possible interactions. Studies usually present a summary of associations between risk factors and obstetric anal sphincter injuries adjusted for confounders without investigating effect modification, i.e. exploring whether the effects are uniform across various levels of the studied risk factors.

In many delivery units, oxytocin augmentation is used during more than half of births.[16, 17] Oxytocin augmentation has been shown to shorten the duration of labour, but not to decrease the need for operative deliveries.[18] We hypothesize that oxytocin augmentation may reduce control over contractions and impair perineal support by causing the delivery to progress too quickly, and thereby increase the risk of perineal injury. Thus, the widespread use of oxytocin in daily obstetric practice calls for an exploration of its possible harmful effects. The aim of our study was to assess the association between oxytocin augmentation and obstetric anal sphincter injuries in a dynamic model related to the active second stage of labour.

MATERIALS AND METHODS

The Department of Obstetrics and Gynaecology of Stavanger University Hospital serves as the only delivery unit for a population of 320 000 people, and approximately 4500 deliveries occur there annually. From 1996 onward, all obstetric data have been consecutively recorded. The electronic database consists of clearly defined variables, and is continuously maintained using standardized procedures for data entry and quality control. During the study period 15 May 1999 to 15 May 2012, 56 517 women with a pregnancy duration of ≥23 weeks of gestation and infants with a birth weight of >300 grams delivered in the department. Estimated day of delivery was determined by second trimester ultrasound scan or from menstrual data when no ultrasound examination was performed. We restricted the study population to nulliparous women whose labour started spontaneously, with single cephalic presentation, pregnancies of ≥37 weeks of gestation (Group 1 in Robson's Ten Group Classification System; TGCS[19]), and who delivered vaginally. After excluding 69 women with missing data, (52 without an estimated day of delivery, 17 with missing information of fetal presentation at delivery), this case-control study comprised 15 476 women.

The main outcome measure was obstetric anal sphincter injuries as defined by the International Continence Society, i.e. partial or complete tears of the anal sphincter muscles, with or without disruption of the anal mucosa (grade 3–4 perineal tears).[20] When an obstetric anal sphincter injury was suspected, the obstetrician on call diagnosed the grade of the tear during surgical repair.

Oxytocin augmentation was defined as oxytocin used to stimulate contractions during established labour. An intravenous infusion of 5 international units (0.01mg) oxytocin in 500 ml saline was administered, starting with 30 ml per hour, and a dose increment of 15 ml per hour every 15 minutes to a maximum of 180 ml per hour, guided by the response. Normal births were taken care of by midwives, while doctors performed the operative deliveries.

Throughout the study period, episiotomy was performed either medio-laterally or laterally. According to our routines and national guidelines, operative vaginal delivery was indicated if delivery had not taken place after 60 minutes of bearing down. We used vacuum extraction with a Malmström metal cup as the preferred procedure for operative vaginal delivery. Vacuum extraction was applied for mid-cavity and outlet release. A combination of low-dose ropivicaine/fentanyl was used for epidural analgesia. Ethnicity was classified as Western i.e. originating from Europe or North America, or non-Western.

The intention of this study was to explore the effect of three obstetric practices (oxytocin augmentation (O), episiotomy (E) and vacuum/forceps (VF)) and birth weight (BW) on obstetric anal sphincter injuries before other risk factors were considered. These main risk factors correlate as episiotomy is often used for instrumental deliveries and when large babies are expected. Furthermore, oxytocin augmentation is provided for failure to progress because of dystocia. Women with dystocia are more often delivered instrumentally than women without dystocia. This basic understanding of the birth dynamics of the first and second stage of labour indicates that the main risk factors may have a direct or indirect effect on obstetric anal sphincter injuries, and that the effects of categories across different explanatory variables are not constant on the outcome.

We analysed our dataset using the Chi-squared test and backward manual stepwise logistic regression analyses with $p<0.05$ as significance level. We built and checked the fit of our regression model as proposed by Agresti [21]. Step one compares the model including the highest order four-way interaction with a model without the four-way interaction. If the highest order product is not significant, Agresti proposes continuing removing the highest order term with the highest non-significant p-value until all remaining terms have statistically significant p-values. Four main predictors (O=oxytocin augmentation, E=episiotomy, VF=Vacuum/forceps and BW=birth weight) are used to predict the

proportions of women with sphincter injuries. Confounders, possible risk factors in addition to the main factors of interest, were tested one by one and set to at least 10% change in any estimate in the model of best fit. Interaction terms were significant at $p<0.05$. Statistical analyses were performed with IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.

The Regional Committee for Medical and Health Research Ethics, Western Norway, approved the protocol as a quality assurance study in obstetric care, and fulfilling the requirements for data protection procedures (REK 2011-1247).

RESULTS

The study population comprised 15 476 (27%) of the 56 517 women giving birth during the study period, including 1013 (53%) of a total of 1894 women diagnosed with obstetric anal sphincter injuries.

The overall prevalence of obstetric anal sphincter injuries was 6.5%. The rate declined from 9.6% in 1999–2000 to 2.8% in 2010–2012. The characteristics of the study population and the prevalence of obstetric anal sphincter injuries are displayed in Table 1.

Table 1 Characteristics of the study population and the prevalence of obstetric anal sphincter injury. P-values from Chi-square tests.

Factor	Obstetric anal sphincter injury		In total	Prevalence	P
	No	Yes			
	N=14 463	N=1013	N=15 476		
	%	%		%	
Time period					<0.001
1999-2000	11.1	16.9	1781	9.6	
2001-2003	19.8	30.7	3169	9.8	
2004-2006	22.9	29.6	3611	8.3	
2007-2009	25.5	14.3	3826	3.8	
2010-2012	20.8	8.6	3089	2.8	
Maternal factors					

Age (years)					<0.001
<25	26.6	19.3	4040	4.9	
25-29	33.5	37.6	5233	7.3	
30-34	17.8	20.8	2785	7.6	
≥35	22.1	22.2	3418	6.6	
Origin					NS*
Western	90.5	92.0	14 025	6.6	
Non-Western	9.5	8.0	1451	5.6	
Obstetric factors					
Epidural analgesia					NS
No	58.1	57.7	8992	6.5	
Yes	41.9	42.3	6484	6.6	
Oxytocin augmentation					<0.001
No	55.6	44.7	8500	5.3	
Yes	44.4	55.3	6976	8.0	
Active 2nd stage of labour (min)					<0.001
Missing information	0.6	0.3	92	3.3	
0-14	10.8	6.8	1627	4.2	
15-29	26.8	18.5	4063	4.6	
30-59	40.1	37.8	6181	6.2	
≥60	21.7	36.6	3513	10.6	
Episiotomy					NS
No	67.1	65.4	10 372	6.4	
Yes	32.9	34.6	5104	6.9	
Operative vaginal delivery					<0.001
No	77.5	60.3	11 817	5.2	
Yes	22.5	39.7	3659	11.0	
Fetal factors					
Birth weight (g)					<0.001
<4000	87.8	74.2	13 454	5.6	
≥4000	12.2	25.8	2022	12.9	
Occiput posterior position					NS
No	95.4	94.8	14 771	6.5	
Yes	4.5	5.2	705	7.4	

* Non significant

The prevalence was higher in women who received oxytocin augmentation (8.0% vs. 5.3%), those who were delivered instrumentally (11.0% vs. 5.2%), and in those who gave birth to an infant weighing ≥4000 g (12.9% vs. 5.6%). Furthermore, the prevalence increased with longer durations of the active part of the second stage of labour.

After adopting the strategy of Agresti by deleting the highest statistically non-significant terms in the model until all remaining terms are statistically significant, we ended up with a best fitting model involving the three-way interaction of oxytocin augmentation, episiotomy and vacuum/forceps (O x E x VF) and the two two-way interactions episiotomy/ birth weight (E x BW) and vacuum/forceps (VF x BW). (Model A). We could resolve interaction terms into stratified analysis of 8 strata of combinations of oxytocin augmentation,

episiotomy and instrumental delivery for birth weights <4000 g, and 4 strata of combinations of episiotomy, instrumental delivery and birth weight ≥4000 g, independent of oxytocin augmentation. The results are displayed in Table 2.

Table 2 Model A. Stratified analyses of 8 strata of combinations of oxytocin augmentation, episiotomy, instrumental delivery and birth weights <4000 g, and 4 strata of episiotomy, instrumental delivery and birth weights ≥4000 g, independent of oxytocin augmentation. Crude odds ratio (OR) and 95% confidence intervals (95% CI)

Group	Oxytocin augmentation[a]	Episiotomy[a]	Operative vaginal delivery[a]	Birth Weight[b]	Women N	OASI[c] N (%)	OR	95% CI
1	-	-	-	-	5328	198 (3.7)	1.0	
2	-	+	-	-	1434	60 (4.2)	1.1	0.8-1.5
3	-	+	+	-	537	43 (8.0)	2.3	1.6-3.2
4	-	-	+	-	316	47 (14.9)	4.5	3.2-6.4
5	+	+	+	-	1283	92 (7.2)	2.0	1.6-2.6
6	+	-	+	-	896	103 (11.5)	3.4	2.6-4.3
7	+	-	-	-	2621	148 (5.6)	1.6	1.3-1.9
8	+	+	-	-	1039	61 (5.9)	1.6	1.2-2.2
9	+/-	+	-	+	418	40 (9.6)	2.7	1.9-3.9
10	+/-	-	-	+	977	104 (10.6)	3.1	2.4-4.0
11	+/-	+	+	+	393	55 (14.0)	4.2	3.1-5.8
12	+/-	-	+	+	234	62 (26.5)	9.3	6.8-12.9

[a]Used (+) / unused (-), [b]≥4000 g (+) / <4000 g (-), [c]Obstetric anal sphincter injury

From a clinical perspective we can simplify model A into model B by collapsing groups that comprise similar risks for sphincter injury by obstetric interventions despite overlapping confidence intervals. Spontaneous delivery of an infant weighing <4000 g without oxytocin augmentation and episiotomy was chosen as the reference group (group 1). We collapsed group 1 and 2 as the odds for sphincter injury was similar with and without episiotomy in unstimulated, spontaneous births of normal-sized infants. Group 3 to 6 display the odds for sphincter injury in instrumental deliveries of normal-sized infants with and without oxytocin

augmentation and episiotomy. A marked difference in the odds for sphincter injury was observed between women delivered instrumentally with (group 3 and 5) and without (group 4 and 6) episiotomy, despite the fact that those stimulated with oxytocin had a non-significant lower odds for sphincter injury. It was therefore reasonable to collapse group 3 and 5, and group 4 and 6. Furthermore, we collapsed group 7 and 8 as the odds for sphincter injury was similar with and without episiotomy during spontaneous deliveries of infants <4000 g, regardless of oxytocin augmentation. Finally, the use of episiotomy appeared to be strongly associated with lower odds for sphincter injury in instrumental deliveries of infants ≥4000 g (group 11 and 12). The modified model B (Table 3) comprises a clinically relevant risk estimation of anal sphincter injury among the main modified risk factors for sphincter injury.

Table 3 Modified model displaying the collapsed non-significant strata (1–12) from Table 2 into new strata (A–G). Unadjusted odds ratios (OR), adjusted (aOR), and 95% confidence intervals (95% CI) after adjusting for epidural analgesia

Group (Group in Table 2)	Oxytocin augmentation[a]	Episiotomy[a]	Operative vaginal delivery[a]	Birth weight[b]	Women N	OASI[c] N (%)	OR	aOR (95% CI)
A (1,2)	-	+/-	-	-	6762	258 (3.8)	1.0	1.0
B (7,8)	+	+/-	-	-	3660	209 (5.7)	1.5	1.8 (1.5-2.2)
C (3,5)	+/-	+	+	-	1820	135 (7.4)	2.0	2.3 (1.8-2.8)
D (4,6)	+/-	-	+	-	1212	150 (12.4)	3.6	4.1 (3.3-5.1)
E (9-10)	+/-	+/-	-	+	1395	144 (10.3)	2.9	3.1 (2.5-3.9)
F (11)	+/-	+	+	+	393	55 (14.0)	4.1	4.7 (3.4-6.5)
G (12)	+/-	-	+	+	234	62 (26.5)	9.1	10.5 (7.6-14.4)

[a]Used (+) / unused (-), [b]≥4000 g (+) / <4000 g (-), [c]Obstetric anal sphincter injury

Age, origin of the mother, and occiput posterior position had no confounding effect on odds ratios for obstetric anal sphincter injury across combinations of episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight (groups A to G in Table 3).

The unadjusted odds ratio (OR) for the presence or absence of epidural analgesia was 1.02; however, the adjusted OR for epidural analgesia was 0.73, (95% CI 0.63-0.84) i.e. epidural analgesia was associated with a 30% lower odds ratio of anal sphincter injury.

The use of oxytocin augmentation increased with the duration of the second stage of labour over all the time periods from an average of 32% in the <30 minutes group, 46% in the 30–59 minutes group, and 65% (range 49–76%) in the ≥60 minutes group during the active second stage of labour. The prevalence of operative deliveries across all study periods was consistently between 45–49% when the active part of the second stage of labour lasted ≥60 minutes vs. 12–21% for durations of the second stage of labour of <60 minutes. We found strong associations between oxytocin augmentation and the duration of second stage, and between operative delivery and the duration of second stage (collinearity), which means that the duration of second stage is measured through operative delivery and oxytocin augmentation.

DISCUSSION

We found that oxytocin augmentation during active labour was associated with a 80% increased odds ratio of obstetric anal sphincter injury in women in TGCS group 1 giving spontaneous birth to an infant weighing <4000 g. We did not find an association between episiotomy and tears during spontaneous deliveries, but a significantly reduced association in all operative vaginal deliveries.

Oxytocin augmentation is widely used in delayed labour to prevent operative delivery. However, a Cochrane review concluded that a reduction of labour by two hours was the only

proven effect, and there was no effect on operative deliveries.[18] Another recent review found the entire concept of active management of labour to be associated with a slightly reduced risk of caesarean delivery.[22] As in other studies, we found that approximately 50% of nulliparous women received oxytocin augmentation.[16, 17, 23] There is reason to believe that guidelines for the diagnosis and treatment of protracted labour are unclear or inconsistently applied in daily practice.[17] We hypothesize that stimulation with oxytocin may speed up the progress of the expulsive phase of labour, leading to rushed situations, impaired communication with the mother, and less focus on protection of the perineum and a controlled delivery of the head. Recent studies from Norway indicate that focus on these elements is important in preventing perineal injuries.[24, 25]

Many authors have used logistic regression analysis to identify risk factors for obstetric anal sphincter injuries, but only a few have included oxytocin augmentation. Samuelsson et al.,[14] Prager et al.,[15] and Jander et al.[5] found oxytocin augmentation to be predictive of obstetric anal sphincter injuries in univariate analysis, but only Jander et al. confirmed this finding in multivariable analyses. Samuelsson et al. did not stratify by parity, which is a methodological weakness since the true effect of other factors is concealed by the strong impact of parity.[14] Prager et al. studied obstetric anal sphincter injuries in nulliparous women, entering oxytocin augmentation, duration of active second stage of labour, and instrumental delivery into the same model.[15]

Our study shows strong collinearity between a prolonged active second stage of labour and both oxytocin augmentation and instrumental delivery. We consider the duration of the active second stage of labour to be a “proxy” for oxytocin augmentation and instrumental delivery, and not a risk factor for obstetric anal sphincter injury in itself. Long duration of the second stage is a time related event before the expulsion of the head. During this latency the active forces do not inflict injury on the sphincter apparatus, the sphincter injury occurs

during the expulsive phase. Consequently, we do not consider the duration of the active second stage as a risk factor for anal sphincter injuries.

Jander et al. conducted a single institution, retrospective, case-control study of 214 cases to explore 44 possible risk factors, and found that oxytocin augmentation was a significant risk factor for obstetric anal sphincter injuries in multivariable analyses (OR 2.00; 95% CI 1.13–3.53).[5] However, these researchers did not stratify by parity or state whether or not interactions were tested for. Furthermore, three older studies on the risk of obstetric anal sphincter injury included oxytocin use without differentiating whether oxytocin was provided for induction or augmentation purposes.[26-28] Three large population-based studies on the risk of obstetric anal sphincter injuries did not include oxytocin augmentation in their analyses.[1, 7, 8]

The influence of epidural analgesia on anal sphincter injuries is unclear. Eskandar and Shet found a reduced risk, but did not stratify by parity.[9] Dahl and Kjølhede found epidural analgesia to be an independent protective factor in nulliparous women.[10] Poen et al. stratified by parity and found a significantly increased odds ratio associated with epidural analgesia in nulliparous women.[29] In our study, epidural analgesia was associated with a significantly reduced odds ratio for sphincter tears.

Our study takes into account four factors that exert their effect on the anal sphincter during the final minutes of delivery. As in previous studies,[1, 3, 5] we found both operative vaginal delivery and high birth weight to be strongly associated with obstetric anal sphincter injuries. We found episiotomy to be associated with a lower prevalence of sphincter tears in operative vaginal deliveries, but not in spontaneous births. This is consistent with a large national registry study from Norway,[1] but differs from other studies.[8, 11, 13, 30, 31] In our study, neither oxytocin augmentation nor episiotomy were associated with obstetric anal sphincter injury during spontaneous delivery of an infant weighing ≥4000 g.

Our methodological approach, stratifying by the factors that are active during the expulsive phase of labour and testing for confounders, is considered a strength of the study. This approach leads to a more detailed understanding of how oxytocin augmentation interacts with these major risk factors. Logistic regression analyses, without testing for possible interactions, would fail to reveal this information. This case-control study is based on prospectively collected data from a large unselected population, and represents all deliveries meeting the inclusion criteria that occurred during the study period, which make bias unlikely. Our department has a high proportion of vaginal deliveries. The overall caesarean delivery rate in our institution was 12.5% over the study period. For women in TGCS group 1 the acute caesarean section rate increased from 5.0% in 1999 to 7.5% in 2012. Accordingly, the study population includes both high- and low-risk pregnancies, which adds to the external validity of our results.

However, some limitations apply. We cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study. Furthermore, socioeconomic status, smoking, body mass index, maternal delivery positions, perineal support technique, and the birth attendant's experience level may be possible risk modifiers not included in our database. Finally, single institution studies, also when based on unselected populations, should be interpreted with caution.

Our findings have some important implications. Birth attendants should be aware of the association between oxytocin augmentation and obstetric anal sphincter injuries in the large subgroup of nulliparous women giving spontaneous birth to a normal-sized infant. More restrictive use of oxytocin may help prevent obstetric anal sphincter injuries. Implementation of evidence-based guidelines for using oxytocin augmentation should be encouraged. The World Health Organization recommends the use of a partogram with an action line defining failure to progress. However, a recent Cochrane review could not confirm that such a

partogram was beneficial in high resource settings.[32] Given the doubtful benefits from augmentation of labour, randomized controlled trials are strongly needed, and we propose anal sphincter injury as one of the most important endpoints.

Moreover, our study supports restricted use of episiotomy during normal births and as a recommendation for operative vaginal deliveries. Birth weight is an important, albeit unpredictable risk factor as weight estimation of a large fetus is unreliable.[33]

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Contributorship Statement

All four authors have contributed to the idea and design of the research project. ABR, TME managed the dataset and the statistical analyses were performed by FES. All four authors have contributed to the interpretation of the results and the writing of the manuscript.

Competing interests

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Assessing the association of oxytocin augmentation with obstetric anal sphincter injury in nulliparous women – a population-based, case-control study

ARTICLE SUMMARY

Strengths and limitations of this study

- Stratifying by the main risk factors that are active during the expulsive phase of labour and testing for confounders are strengths of the study.
- We reveal how oxytocin augmentation interacts with the major factors active in the expulsive phase of labour.
- The study is based on prospectively collected data from a large, unselected population, which makes bias unlikely.
- The study design is a limitation, as we cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study.

INTRODUCTION

Obstetric anal sphincter injuries occur in 0.5–5.0% of vaginal deliveries,[1] with a subsequently increased risk of fecal incontinence.[2-4] Nulliparity,[1, 3, 5] high birth weight,[1, 3, 5, 6] operative vaginal delivery,[1, 3, 5] advanced maternal age,[1, 5, 6] Asian or African ethnicity,[1, 7] and prolonged second stage of labour[3, 7, 8] are consistently reported as risk factors for obstetric anal sphincter injuries , whereas the effect of epidural analgesia[9, 10] and episiotomy[1, 11-13] is debated. However, only a few authors have evaluated oxytocin augmentation as a possible risk factor for obstetric anal sphincter injuries.[5, 14, 15] Further, the current literature dealing with risk factors for obstetric anal sphincter injuries has not sufficiently addressed their possible interactions. Studies usually present a summary of associations between risk factors and obstetric anal sphincter injuries adjusted for confounders without investigating effect modification, i.e. exploring whether the effects are uniform across various levels of the studied risk factors.

In many delivery units, oxytocin augmentation is used during more than half of births.[16, 17] Oxytocin augmentation has been shown to shorten the duration of labour, but not to decrease the need for operative deliveries.[18] We hypothesize that oxytocin augmentation may reduce control over contractions and impair perineal support by causing the delivery to progress too quickly, and thereby increase the risk of perineal injury. Thus, the widespread use of oxytocin in daily obstetric practice calls for an exploration of its possible harmful effects. The aim of our study was to assess the association between oxytocin augmentation and obstetric anal sphincter injuries in a dynamic model related to the active second stage of labour.

MATERIALS AND METHODS

The Department of Obstetrics and Gynaecology of Stavanger University Hospital serves as the only delivery unit for a population of 320 000 people, and approximately 4500 deliveries occur there annually. From 1996 onward, all obstetric data have been consecutively recorded. The electronic database consists of clearly defined variables, and is continuously maintained using standardized procedures for data entry and quality control. During the study period 15 May 1999 to 15 May 2012, 56 517 women with a pregnancy duration of ≥23 weeks of gestation and infants with a birth weight of >300 grams delivered in the department. Estimated day of delivery was determined by second trimester ultrasound scan or from menstrual data when no ultrasound examination was performed. We restricted the study population to nulliparous women whose labour started spontaneously, with single cephalic presentation, pregnancies of ≥37 weeks of gestation (Group 1 in Robson's Ten Group Classification System; TGCS[19]), and who delivered vaginally. After excluding 69 women with missing data, (52 without an estimated day of delivery, 17 with missing information of fetal presentation at delivery), this case-control study comprised 15 476 women.

The main outcome measure was obstetric anal sphincter injuries as defined by the International Continence Society, i.e. partial or complete tears of the anal sphincter muscles, with or without disruption of the anal mucosa (grade 3–4 perineal tears).[20] When an obstetric anal sphincter injury was suspected, the obstetrician on call diagnosed the grade of the tear during surgical repair.

Oxytocin augmentation was defined as oxytocin used to stimulate contractions during established labour. An intravenous infusion of 5 international units (0.01mg) oxytocin in 500 ml saline was administered, starting with 30 ml per hour, and a dose increment of 15 ml per hour every 15 minutes to a maximum of 180 ml per hour, guided by the response. Normal births were taken care of by midwives, while doctors performed the operative deliveries.

Throughout the study period, episiotomy was performed either medio-laterally or laterally. According to our routines and national guidelines, operative vaginal delivery was indicated if delivery had not taken place after 60 minutes of bearing down. We used vacuum extraction with a Malmström metal cup as the preferred procedure for operative vaginal delivery. Vacuum extraction was applied for mid-cavity and outlet release. A combination of low-dose ropivicaine/fentanyl was used for epidural analgesia. Ethnicity was classified as Western i.e. originating from Europe or North America, or non-Western.

The intention of this study was to explore the effect of three obstetric practices (oxytocin augmentation (O), episiotomy (E) and vacuum/forceps (VF)) and birth weight (BW) on obstetric anal sphincter injuries before other risk factors were considered. These main risk factors correlate as episiotomy is often used for instrumental deliveries and when large babies are expected. Furthermore, oxytocin augmentation is provided for failure to progress because of dystocia. Women with dystocia are more often delivered instrumentally than women without dystocia. This basic understanding of the birth dynamics of the first and second stage of labour indicates that the main risk factors may have a direct or indirect effect on obstetric anal sphincter injuries, and that the effects of categories across different explanatory variables are not constant on the outcome.

We analysed our dataset using the Chi-squared test and backward manual stepwise logistic regression analyses with $p<0.05$ as significance level. We built and checked the fit of our regression model as proposed by Agresti [21]. Step one compares the model including the highest order four-way interaction with a model without the four-way interaction. If the highest order product is not significant, Agresti proposes continuing removing the highest order term with the highest non-significant p-value until all remaining terms have statistically significant p-values. Four main predictors (O=oxytocin augmentation, E=episiotomy, VF=Vacuum/forceps and BW=birth weight) are used to predict the

proportions of women with sphincter injuries. Confounders, possible risk factors in addition to the main factors of interest, were tested one by one and set to at least 10% change in any estimate in the model of best fit. Interaction terms were significant at $p<0.05$. Statistical analyses were performed with IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.

The Regional Committee for Medical and Health Research Ethics, Western Norway, approved the protocol as a quality assurance study in obstetric care, and fulfilling the requirements for data protection procedures (REK 2011-1247).

RESULTS

The study population comprised 15 476 (27%) of the 56 517 women giving birth during the study period, including 1013 (53%) of a total of 1894 women diagnosed with obstetric anal sphincter injuries.

The overall prevalence of obstetric anal sphincter injuries was 6.5%. The rate declined from 9.6% in 1999–2000 to 2.8% in 2010–2012. The characteristics of the study population and the prevalence of obstetric anal sphincter injuries are displayed in Table 1.

Table 1 Characteristics of the study population and the prevalence of obstetric anal sphincter injury. P-values from Chi-square tests.

Factor	Obstetric anal sphincter injury		In total	Prevalence	P
	No	Yes			
	N=14 463	N=1013	N=15 476		
	%	%		%	
Time period					<0.001
1999-2000	11.1	16.9	1781	9.6	
2001-2003	19.8	30.7	3169	9.8	
2004-2006	22.9	29.6	3611	8.3	
2007-2009	25.5	14.3	3826	3.8	
2010-2012	20.8	8.6	3089	2.8	
Maternal factors					

Age (years)					<0.001
<25	26.6	19.3	4040	4.9	
25-29	33.5	37.6	5233	7.3	
30-34	17.8	20.8	2785	7.6	
≥35	22.1	22.2	3418	6.6	
Origin					NS*
Western	90.5	92.0	14 025	6.6	
Non-Western	9.5	8.0	1451	5.6	
Obstetric factors					
Epidural analgesia					NS
No	58.1	57.7	8992	6.5	
Yes	41.9	42.3	6484	6.6	
Oxytocin augmentation					<0.001
No	55.6	44.7	8500	5.3	
Yes	44.4	55.3	6976	8.0	
Active 2nd stage of labour (min)					<0.001
Missing information	0.6	0.3	92	3.3	
0-14	10.8	6.8	1627	4.2	
15-29	26.8	18.5	4063	4.6	
30-59	40.1	37.8	6181	6.2	
≥60	21.7	36.6	3513	10.6	
Episiotomy					NS
No	67.1	65.4	10 372	6.4	
Yes	32.9	34.6	5104	6.9	
Operative vaginal delivery					<0.001
No	77.5	60.3	11 817	5.2	
Yes	22.5	39.7	3659	11.0	
Fetal factors					
Birth weight (g)					<0.001
<4000	87.8	74.2	13 454	5.6	
≥4000	12.2	25.8	2022	12.9	
Occiput posterior position					NS
No	95.4	94.8	14 771	6.5	
Yes	4.5	5.2	705	7.4	

* Non significant

The prevalence was higher in women who received oxytocin augmentation (8.0% vs. 5.3%), those who were delivered instrumentally (11.0% vs. 5.2%), and in those who gave birth to an infant weighing ≥4000 g (12.9% vs. 5.6%). Furthermore, the prevalence increased with longer durations of the active part of the second stage of labour.

After adopting the strategy of Agresti by deleting the highest statistically non-significant terms in the model until all remaining terms are statistically significant, we ended up with a best fitting model involving the three-way interaction of oxytocin augmentation, episiotomy and vacuum/forceps (O x E x VF) and the two two-way interactions episiotomy/ birth weight (E x BW) and vacuum/forceps (VF x BW). (Model A). We could resolve interaction terms into stratified analysis of 8 strata of combinations of oxytocin augmentation,

episiotomy and instrumental delivery for birth weights <4000 g, and 4 strata of combinations of episiotomy, instrumental delivery and birth weight ≥4000 g, independent of oxytocin augmentation. The results are displayed in Table 2.

Table 2 Model A. Stratified analyses of 8 strata of combinations of oxytocin augmentation, episiotomy, instrumental delivery and birth weights <4000 g, and 4 strata of episiotomy, instrumental delivery and birth weights ≥4000 g, independent of oxytocin augmentation. Crude odds ratio (OR) and 95% confidence intervals (95% CI)

Group	Oxytocin augmentation[a]	Episiotomy[a]	Operative vaginal delivery[a]	Birth Weight[b]	Women N	OASI[c] N (%)	OR	95% CI
1	-	-	-	-	5328	198 (3.7)	1.0	
2	-	+	-	-	1434	60 (4.2)	1.1	0.8-1.5
3	-	+	+	-	537	43 (8.0)	2.3	1.6-3.2
4	-	-	+	-	316	47 (14.9)	4.5	3.2-6.4
5	+	+	+	-	1283	92 (7.2)	2.0	1.6-2.6
6	+	-	+	-	896	103 (11.5)	3.4	2.6-4.3
7	+	-	-	-	2621	148 (5.6)	1.6	1.3-1.9
8	+	+	-	-	1039	61 (5.9)	1.6	1.2-2.2
9	+/-	+	-	+	418	40 (9.6)	2.7	1.9-3.9
10	+/-	-	-	+	977	104 (10.6)	3.1	2.4-4.0
11	+/-	+	+	+	393	55 (14.0)	4.2	3.1-5.8
12	+/-	-	+	+	234	62 (26.5)	9.3	6.8-12.9

[a]Used (+) / unused (-), [b]≥4000 g (+) / <4000 g (-), [c]Obstetric anal sphincter injury

From a clinical perspective we can simplify model A into model B by collapsing groups that comprise similar risks for sphincter injury by obstetric interventions despite overlapping confidence intervals. Spontaneous delivery of an infant weighing <4000 g without oxytocin augmentation and episiotomy was chosen as the reference group (group 1). We collapsed group 1 and 2 as the odds for sphincter injury was similar with and without episiotomy in unstimulated, spontaneous births of normal-sized infants. Group 3 to 6 display the odds for sphincter injury in instrumental deliveries of normal-sized infants with and without oxytocin

augmentation and episiotomy. A marked difference in the odds for sphincter injury was observed between women delivered instrumentally with (group 3 and 5) and without (group 4 and 6) episiotomy, despite the fact that those stimulated with oxytocin had a non-significant lower odds for sphincter injury. It was therefore reasonable to collapse group 3 and 5, and group 4 and 6. Furthermore, we collapsed group 7 and 8 as the odds for sphincter injury was similar with and without episiotomy during spontaneous deliveries of infants <4000 g, regardless of oxytocin augmentation. Finally, the use of episiotomy appeared to be strongly associated with lower odds for sphincter injury in instrumental deliveries of infants ≥4000 g (group 11 and 12). The modified model B (Table 3) comprises a clinically relevant risk estimation of anal sphincter injury among the main modified risk factors for sphincter injury.

Table 3 Modified model displaying the collapsed non-significant strata (1–12) from Table 2 into new strata (A–G). Unadjusted odds ratios (OR), adjusted (aOR), and 95% confidence intervals (95% CI) after adjusting for epidural analgesia

Group (Group in Table 2)	Oxytocin augmentation[a]	Episiotomy[a]	Operative vaginal delivery[a]	Birth weight[b]	Women N	OASI[c] N (%)	OR	aOR (95% CI)
A (1,2)	-	+/-	-	-	6762	258 (3.8)	1.0	1.0
B (7,8)	+	+/-	-	-	3660	209 (5.7)	1.5	1.8 (1.5-2.2)
C (3,5)	+/-	+	+	-	1820	135 (7.4)	2.0	2.3 (1.8-2.8)
D (4,6)	+/-	-	+	-	1212	150 (12.4)	3.6	4.1 (3.3-5.1)
E (9-10)	+/-	+/-	-	+	1395	144 (10.3)	2.9	3.1 (2.5-3.9)
F (11)	+/-	+	+	+	393	55 (14.0)	4.1	4.7 (3.4-6.5)
G (12)	+/-	-	+	+	234	62 (26.5)	9.1	10.5 (7.6-14.4)

[a]Used (+) / unused (-), [b]≥4000 g (+) / <4000 g (-), [c]Obstetric anal sphincter injury

Age, origin of the mother, and occiput posterior position had no confounding effect on odds ratios for obstetric anal sphincter injury across combinations of episiotomy, oxytocin augmentation, operative vaginal delivery, and birth weight (groups A to G in Table 3).

The unadjusted odds ratio (OR) for the presence or absence of epidural analgesia was 1.02; however, the adjusted OR for epidural analgesia was 0.73, (95% CI 0.63-0.84) i.e. epidural analgesia was associated with a 30% lower odds ratio of anal sphincter injury.

The use of oxytocin augmentation increased with the duration of the second stage of labour over all the time periods from an average of 32% in the <30 minutes group, 46% in the 30–59 minutes group, and 65% (range 49–76%) in the ≥60 minutes group during the active second stage of labour. The prevalence of operative deliveries across all study periods was consistently between 45–49% when the active part of the second stage of labour lasted ≥60 minutes vs. 12–21% for durations of the second stage of labour of <60 minutes. We found strong associations between oxytocin augmentation and the duration of second stage, and between operative delivery and the duration of second stage (collinearity), which means that the duration of second stage is measured through operative delivery and oxytocin augmentation.

DISCUSSION

We found that oxytocin augmentation during active labour was associated with a 80% increased odds ratio of obstetric anal sphincter injury in women in TGCS group 1 giving spontaneous birth to an infant weighing <4000 g. We did not find an association between episiotomy and tears during spontaneous deliveries, but a significantly reduced association in all operative vaginal deliveries.

Oxytocin augmentation is widely used in delayed labour to prevent operative delivery. However, a Cochrane review concluded that a reduction of labour by two hours was the only

proven effect, and there was no effect on operative deliveries.[18] Another recent review found the entire concept of active management of labour to be associated with a slightly reduced risk of caesarean delivery.[22] As in other studies, we found that approximately 50% of nulliparous women received oxytocin augmentation.[16, 17, 23] There is reason to believe that guidelines for the diagnosis and treatment of protracted labour are unclear or inconsistently applied in daily practice.[17] We hypothesize that stimulation with oxytocin may speed up the progress of the expulsive phase of labour, leading to rushed situations, impaired communication with the mother, and less focus on protection of the perineum and a controlled delivery of the head. Recent studies from Norway indicate that focus on these elements is important in preventing perineal injuries.[24, 25]

Many authors have used logistic regression analysis to identify risk factors for obstetric anal sphincter injuries, but only a few have included oxytocin augmentation. Samuelsson et al.,[14] Prager et al.,[15] and Jander et al.[5] found oxytocin augmentation to be predictive of obstetric anal sphincter injuries in univariate analysis, but only Jander et al. confirmed this finding in multivariable analyses. Samuelsson et al. did not stratify by parity, which is a methodological weakness since the true effect of other factors is concealed by the strong impact of parity.[14] Prager et al. studied obstetric anal sphincter injuries in nulliparous women, entering oxytocin augmentation, duration of active second stage of labour, and instrumental delivery into the same model.[15]

Our study shows strong collinearity between a prolonged active second stage of labour and both oxytocin augmentation and instrumental delivery. We consider the duration of the active second stage of labour to be a “proxy” for oxytocin augmentation and instrumental delivery, and not a risk factor for obstetric anal sphincter injury in itself. Long duration of the second stage is a time related event before the expulsion of the head. During this latency the active forces do not inflict injury on the sphincter apparatus, the sphincter injury occurs

during the expulsive phase. Consequently, we do not consider the duration of the active second stage as a risk factor for anal sphincter injuries.

Jander et al. conducted a single institution, retrospective, case-control study of 214 cases to explore 44 possible risk factors, and found that oxytocin augmentation was a significant risk factor for obstetric anal sphincter injuries in multivariable analyses (OR 2.00; 95% CI 1.13–3.53).[5] However, these researchers did not stratify by parity or state whether or not interactions were tested for. Furthermore, three older studies on the risk of obstetric anal sphincter injury included oxytocin use without differentiating whether oxytocin was provided for induction or augmentation purposes.[26-28] Three large population-based studies on the risk of obstetric anal sphincter injuries did not include oxytocin augmentation in their analyses.[1, 7, 8]

The influence of epidural analgesia on anal sphincter injuries is unclear. Eskandar and Shet found a reduced risk, but did not stratify by parity.[9] Dahl and Kjølhede found epidural analgesia to be an independent protective factor in nulliparous women.[10] Poen et al. stratified by parity and found a significantly increased odds ratio associated with epidural analgesia in nulliparous women.[29] In our study, epidural analgesia was associated with a significantly reduced odds ratio for sphincter tears.

Our study takes into account four factors that exert their effect on the anal sphincter during the final minutes of delivery. As in previous studies,[1, 3, 5] we found both operative vaginal delivery and high birth weight to be strongly associated with obstetric anal sphincter injuries. We found episiotomy to be associated with a lower prevalence of sphincter tears in operative vaginal deliveries, but not in spontaneous births. This is consistent with a large national registry study from Norway,[1] but differs from other studies.[8, 11, 13, 30, 31] In our study, neither oxytocin augmentation nor episiotomy were associated with obstetric anal sphincter injury during spontaneous delivery of an infant weighing ≥4000 g.

Our methodological approach, stratifying by the factors that are active during the expulsive phase of labour and testing for confounders, is considered a strength of the study. This approach leads to a more detailed understanding of how oxytocin augmentation interacts with these major risk factors. Logistic regression analyses, without testing for possible interactions, would fail to reveal this information. This case-control study is based on prospectively collected data from a large unselected population, and represents all deliveries meeting the inclusion criteria that occurred during the study period, which make bias unlikely. Our department has a high proportion of vaginal deliveries. The overall caesarean delivery rate in our institution was 12.5% over the study period. For women in TGCS group 1 the acute caesarean section rate increased from 5.0% in 1999 to 7.5% in 2012. Accordingly, the study population includes both high- and low-risk pregnancies, which adds to the external validity of our results.

However, some limitations apply. We cannot prove causality between oxytocin augmentation and obstetric anal sphincter injuries in an observational study. Furthermore, socioeconomic status, smoking, body mass index, maternal delivery positions, perineal support technique, and the birth attendant's experience level may be possible risk modifiers not included in our database. Finally, single institution studies, also when based on unselected populations, should be interpreted with caution.

Our findings have some important implications. Birth attendants should be aware of the association between oxytocin augmentation and obstetric anal sphincter injuries in the large subgroup of nulliparous women giving spontaneous birth to a normal-sized infant. More restrictive use of oxytocin may help prevent obstetric anal sphincter injuries. Implementation of evidence-based guidelines for using oxytocin augmentation should be encouraged. The World Health Organization recommends the use of a partogram with an action line defining failure to progress. However, a recent Cochrane review could not confirm that such a

partogram was beneficial in high resource settings.[32] Given the doubtful benefits from augmentation of labour, randomized controlled trials are strongly needed, and we propose anal sphincter injury as one of the most important endpoints.

Moreover, our study supports restricted use of episiotomy during normal births and as a recommendation for operative vaginal deliveries. Birth weight is an important, albeit unpredictable risk factor as weight estimation of a large fetus is unreliable.[33]

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Competing interests

None

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No specific

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (R) In abstract; a cross sectional study, analyzed as case-control study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (R) Fulfilled
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (R) Recent studies have shown the importance of the perineal protection technique in preventing perineal tears. Oxytocin augmentation could impair the control of the perineum during the delivery by causing too fast progress in the last minutes of labour. Oxytocin augmentation is widely used (50% of births). Guidelines for its use are often deficient and the evidence for its positive effect is challenged. Therefore, oxytocin augmentation as a risk factor for obstetric anal sphincter injuries, and should be explored in a study taking other relevant risk factors into account.
Objectives	3	State specific objectives, including any prespecified hypotheses (R) To assess the effect of oxytocin augmentation on obstetric anal sphincter injury among nulliparous women.
Methods		
Study design	4	Present key elements of study design early in the paper (R) Present in Abstract and Methods.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (R) Setting: Tertiary teaching hospital. Location: Delivery department of Stavanger University Hospital, serving the total obstetric population of the region of South Rogaland. Dates 15 May 1999 – 15 May 2012. Data were collected consecutively.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. (R) Nulliparous women with spontaneous start of labour, single, cephalic pregnancy and ≥37 weeks gestation who delivered vaginally, where we had access to complete information on the main exposure and the explanatory variables. The source population was the entire obstetric population of the region.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect

		modifiers. Give diagnostic criteria, if applicable (R) Outcome: Obstetric anal sphincter injury; that is grade 3 and 4 perineal tears as defined by International Society of Incontinence. Exposure: Oxytocin augmentation in active labour, that is oxytocin intravenous infusion (5 international units (0.01mg) oxytocin in 500 ml saline) used in incremental doses during active labour. Predictors: NA Effect modifiers: Episiotomy, operative vaginal delivery, birth weight <4000 g vs ≥4000 g. Potential confounders: maternal age, ethnicity, occiput posterior position, duration of second stage of labour and epidural analgesia.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. (R) All variables are precisely defined in the obstetric databases of Stavanger University Hospital. The grade of perineal injury was assessed during operative repair and plotted directly into the database.
Bias	9	Describe any efforts to address potential sources of bias. (R) In this cross-sectional study all women giving births and who fulfil the inclusion criteria are included. There were very few cases with missing data. We may have missed some cases of perineal injury due to underreporting. The variables are hard variables with clear definitions: Use of oxotocin (yes/no), episiotomy (yes/no), mode of delivery (spontaneous/operative vaginal), birth weight categorized <4000/ ≥4000 g.
Study size	10	Explain how the study size was arrived at (R) The study size is given by the number of women fulfilling the eligibility criteria and who delivered at Stavanger University Hospital from 15 May 1999 to 15 May 2012.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. (R) Birth weight was categorized into < 4000/ ≥4000 g.
Statistical methods	12	*(*a) Describe all statistical methods, including those used to control for confounding (R) Chi-square test and stepwise forward logistic regression using IBM SPSS Statistics for Windows, v. 19.0 Armonk, NY: IBM Corp.
		(*b*) Describe any methods used to examine subgroups and interactions (R) We applied a stratified approach to control for interaction between the main variables (oxytocin augmentation, episiotomy, instrumental delivery and birth weight). Then we tested for confounding and interaction to a modified model by entering one variable at time.
		(*c*) Explain how missing data were addressed (R) Cases with missing data for estimated date of delivery were excluded. Cases with

		other missing data were recoded to the reference value in the logistic regression analyses. Very few cases with missing data (n=52).
		(*d*) If applicable, describe analytical methods taking account of sampling strategy (R) NA
		(*e*) Describe any sensitivity analyses (R) NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (R) Potentially eligible: 15 545 Confirmed eligible: 15 493 Included/analyzed: 15 493
		(b) Give reasons for non-participation at each stage (R) Cases with missing data for estimated date of delivery were excluded (n=52)
		(c) Consider use of a flow diagram (R) Not useful in this study.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (R) Given in Table 1. The study participants represent the total population of women fulfilling the inclusion criteria in a Norwegian region of 320 000 people. The study population is heterogeneous with regard to obstetric risk (overall caesarean section rate 12,5%), social status and ethnicity.
		(b) Indicate number of participants with missing data for each variable of interest (R) Cases with missing data for estimated date of delivery were excluded from the study population (n=52) Recoded to the reference category of the variable and included in the analyses: Birth weight 3 cases. Maternal age 2 cases. Lie at delivery 8 cases. Duration of second stage of labour 92 cases.
Outcome data	15*	Report numbers of outcome events or summary measures (R) Table 1. Outcome event, the dependant variable, anal sphincter injury: 1014 cases.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (R) Table 2 and 3. Confounders: paragraph 4 in Material and Methods.
		(*b*) Report category boundaries when continuous variables were categorized (R) Table 1

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (R) NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses R) NA
Discussion		
Key results	18	Summarise key results with reference to study objectives (R) Fulfilled.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (R) Bias regarding main outcome: We do not know the magnitude of underreporting of anal sphincter tear grade 3 and 4, however believe this to be low. Bias regarding main exposure: The quality system of the department relies on honest reporting by midwives and obstetricians, and has been a cornerstone in the systematic interdisciplinary work towards better clinical outcomes since 1996. We have reason to believe that ownership to the concept has resulted in good adherence to the reporting routines, and we believe the reporting of oxytocin augmentation to be a robust measure of what was actually practised. The midwives plotting the information were not aware of any research issue related to oxytocin augmentation. We consider the other main exposure variables to be robust: It is unlikely that reports of episiotomy, instrumental delivery and birth weight are skewed in any direction. The same applies to the possible confounders age, ethnicity, occiput posterior position and epidural analgesia. We believe that the reporting of these variables reflects the actual practice. Therefore we consider the estimates for risks related to anal sphincter tear grade 3 and 4 to be precise with little bias. Our stratified approach, modified model, takes care of the interaction problems between episiotomy, operative vaginal delivery, birth weight and oxytocin augmentation.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (R) Fulfilled.
Generalisability	21	Discuss the generalisability (external validity) of the study results. (R) The study participants represent the total population of women fulfilling the inclusion criteria in a Norwegian region of 320 000 people. The study population is heterogeneous with regard to obstetric risk (overall caesarean section rate 12,5%), social status and ethnicity. This adds value to the external validity of the study results. We encourage other study groups to make research on the effect of oxytocin augmentation on anal sphincter injury in other populations.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if

	applicable, for the original study on which the present article is based
	(R) No specific funding.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.