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Title: Trends and morbidity associated with oxytocin use in labour in nulliparas at term

Short title: Outcomes associated with oxytocin use in labour

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Abstract

Aim:

To determine the trends of oxytocin use at a population level within New South Wales and to assess the maternal and neonatal morbidities associated with the use of oxytocin.

Methods:

Trends in oxytocin use were assessed for women in NSW who were nulliparas at term with a singleton, cephalic baby between 1998 and 2008. Maternal and neonatal morbidities were assessed in 2007-2008 using linked hospital and birth data with regression analysis. Oxytocin was also assessed by indication for use being either induction or augmentation of labour.

Results:

The overall use of oxytocin increased from 10,291 (36.5%) of births in 1998 to 14,440 (45.4%) of births in 2008 ($p<0.0001$) with the increase entirely due to the increased use for induction of labour. The use of oxytocin was associated with an increase in regional analgesia (65 to 22%), instrumental delivery (21 to 18%) and caesarean section (29 to 14%) as compared to women who did not receive oxytocin in labour. Oxytocin was also associated with an increase in severe maternal (aOR 1.48, 95% CI 1.30 to 1.68) and neonatal morbidity (aOR 1.29, 95% CI 1.17 to 1.41). This increase in morbidity was maintained when both augmentation and induction were assessed separately

Conclusion:

Oxytocin has an important role in the management of labour. However its use should be carefully monitored with standardised treatment regimes to minimise maternal and neonatal morbidity.

Keywords: Oxytocin, Labour obstetric, Labour induced, Maternal morbidity, Neonatal morbidity

Introduction

Oxytocin is the commonest pharmacological agent used to either induce or augment labour. The role of endogenous oxytocin in labour is unclear but is thought to relate to oxytocin stimulating prostaglandin release within the uterus resulting in contraction of the uterine myometrium (1, 2).

Administration of oxytocin can be associated with complications such as uterine hyperstimulation and injudicious use of oxytocin has the potential to increase fetal hypoxia and acidosis and thereby result in adverse neonatal outcome (3-5). Oxytocin is the medication most commonly associated with preventable adverse neonatal outcome prompting recent concern about its use. In the United States this concern has resulted in oxytocin being added by the Institute for Safe Medication Practices to a list of medications "bearing a heightened risk of harm"(6). In addition the Food and Drug administration in the USA have placed a warning on oxytocin stating that the medication should be restricted to medically indicated inductions or augmentations and should not be used for elective induction of labour (7). With such concerns raised regarding the use of oxytocin, the aims of this study were to determine trends in oxytocin use at a population level. We also investigated whether oxytocin was a risk factor for neonatal and maternal morbidity, regardless of the context of use (induction or augmentation of labour).

Methods

The study population included nulliparous women attempting labour with a singleton, cephalic presenting fetus at term (37^0 to 41^6 weeks gestation) in NSW. The study was restricted to nulliparous women because of the different risk profiles and confounding of subsequent pregnancies by previous pregnancy. Exclusions were infants and their mothers with major congenital anomalies, stillbirths and those undergoing pre-labour caesarean section.

Data were obtained from two population datasets, 'birth data' from the NSW Midwives Data Collection (MDC), and 'hospital data' (for both the mother and the baby) related to the birth from the NSW Admitted Patients Data Collection (APDC). The MDC is a statutory population-based collection covering all births in NSW of at least 400 grams birth weight, or at least 20 weeks gestation, and includes information on maternal and infant characteristics, pregnancy, labour, delivery, and condition of the infant. The APDC is a census of all admissions in NSW public and private hospitals. Up to 20 diagnosis and procedures for each separation are coded according to the 10th revision of the International Classification of Diseases, Australian Modification (ICD-10-AM) and the Australian Classification of Health Interventions (ACHI). The NSW Centre for Health Record Linkage performed probabilistic data linkage between the two datasets. Linkage proportions were over 98%. Ethical approval was obtained from the NSW Population and Health Services Research Ethics Committee.

The primary outcomes considered were severe neonatal and maternal morbidity. We used composite indicators, the neonatal adverse outcome indicator (NAOI) and maternal morbidity outcome indicator (MMOI), which have been developed for use, and validated in, population health data.(8, 9) Consistent with the method used by the World Health Organisation,(10) the indicators incorporate both disease-specific (e.g. respiratory distress, cardiac failure) and management-based (ventilation, transfusion) criteria (see Appendix 1 for complete list).(8, 9)

Composite indicators, that incorporate both diagnoses and procedures, overcome the problem of under-ascertainment of individual adverse events and reduce the need to rely on single ICD codes that have limited clinical detail, lack clear definitions or are poorly validated.(9)

Oxytocin and prostaglandin use were defined as any record (in the birth data or hospital data) of use of either drug for induction or augmentation of labour. For labour inductions, a 10-item check box is used to report the indication for induction. A woman was considered to have received regional analgesia for labour if either an epidural/caudal or a combined spinal-epidural was recorded in the birth data. Maternal and neonatal characteristics were taken from the birth data, and hypertension and diabetes from either the birth or hospital data. Hospitals were grouped on the basis of similar rates of oxytocin use. Infant birth weight was classified as small or large for gestational age if it is below the 10th percentile or above the 90th percentile for gestational age, respectively.

Population trends in oxytocin use were determined for all pimipara at term from 1998 to 2008, inclusive. To investigate the effect of recent practices in oxytocin use on health outcomes, analyses were limited to 2007-2008 and to women who had the potential to be exposed to intrapartum oxytocin (i.e. births in midwifery lead units and homebirths were excluded). The association between oxytocin and adverse outcomes was assessed both overall, and (to explore any confounding by indication) separately among 'low risk' women, and women with hypertension. Low risk women were those without medical conditions who delivered a single, live-born infant of average size (10-90th birth weight for gestational age percentile) at 39-41 weeks gestation (when adverse outcomes are at their nadir) and, if labour was induced, where the indication was reported as 'other'. The hypertension analysis included women with chronic hypertension, gestational hypertension or preeclampsia from either birth or hospital data.

Analysis

Trends in oxytocin use were assessed by negative binomial regression. To examine the predictors of severe neonatal and maternal morbidity, separate logistic regressions were performed. The effect of oxytocin use was examined both overall and by augmentation and induction.. Explanatory variables which were significant at P<0.2 were entered into a logistic regression model, and the least significant removed in a stepwise manner until only variables significant at p<0.05 by the likelihood ratio test remained. Results are expressed as adjusted odds ratios (aOR) and 95% CI. Analyses were conducted in SAS, version 9.1 (SAS Institute, Cary NC, USA).

Results

From 1998 to 2008, inclusive, 322,640 nulliparous women gave birth at term in NSW. The overall use of oxytocin among these women increased from 10,291 (36.5%) in 1998 to 14,440 (45.4%) in 2008 (trend p<0.0001) with the increase entirely due to increased use for induction of labour 17.6% in 1998 to 26.2% in 2008 (trend p<0.0001) (Figure 1). Oxytocin use for augmentation declined to 2003, but then returned to a rate of 19% as it was in 1998.

In the period 2007 to 2008, 61,227 nulliparous women gave birth in hospitals that use oxytocin for labour management. Of these, 48.5% received oxytocin to induce (28.2%) or augment (20.3%) labour. Compared with women who did not receive oxytocin during labour, women receiving oxytocin were older (median age 29.4 vs. 28.0 years), and more likely to have hypertension and/or diabetes (Table 1). Use of regional analgesia during labour was higher in women receiving oxytocin (65.3% vs. 22.3%) (Table 1), with the majority of this being use of epidurals (63.4% vs. 20.7%). Caesarean delivery was more common among women receiving oxytocin (29.4% vs. 14.2%).

Overall, 2,223 (3.6%) newborns suffered severe morbidity (4.3% among those exposed to oxytocin vs. 3.0% in the unexposed, crude OR 1.46 (95% CI 1.34, 1.59)), while 1,025 (1.7%) mothers suffered severe morbidity (2.1% and 1.3% respectively, crude OR 1.57 (95% CI 1.39, 1.78)). After adjustment for confounders, oxytocin was associated with *neonatal* morbidity overall, and the increase in risk (~30%) was similar for oxytocin use in both induction and augmentation (Table 2). A similar pattern was observed when the analysis was restricted to low risk women and women with hypertension. Oxytocin use was also associated with increased risk of *maternal* morbidity overall, with a higher point estimate associated with oxytocin for induction (aOR=1.54) than augmentation (aOR=1.38) although the confidence intervals overlap (Table 2). The low risk and hypertension subgroup analyses for maternal morbidity, found somewhat attenuated and more similar ORs for induction and augmentation, although most did not reach statistical significance (Table 2). When analysed as any oxytocin use the risk for maternal morbidity was increased in hypertensive women by 34% and in low risk women was increased by 28% (Table 2)

Discussion

Our study demonstrates that since 1998 there has been a sustained and significant increase in the use of oxytocin in NSW for nulliparas at term. For the most recent years available nearly half of all such women attempting labour received oxytocin. This usage was associated with an increase in both maternal and neonatal morbidity regardless of whether the indication for use was induction or augmentation of labour. Even for low risk nulliparous women at term there was an increase in both maternal and neonatal morbidity associated with oxytocin. For newborns at term, there was an absolute increase in severe morbidity risk from 3.0% to 4.3% and for mothers from 1.3% to 2.1%. With almost 270,000 women delivering at term in Australia (11), these increases translate to a significant burden for families and health resources.

Adverse effects associated with oxytocin use have been widely reported, are implicated in professional liability claims and are almost exclusively mediated through its dose-related effects on uterine activity (6, 7). Although some clinical trials with strict patient selection criteria and tightly run protocols have not found an increased risk of adverse perinatal outcomes, (12-15) these benefits are not observed when extended to a broader population without strict administration protocols. A strength of this study is the use of validated, population data that allow examination of the birthing experience for an entire population, incorporating all the variations in practice around the use of oxytocin and allowing assessment of rare outcomes. Few other population studies have information on the type of drug used and have been unable to differentiate induction and augmentation. A notable exception is a population-based study from Sweden which assessed the use of oxytocin in labour and also reported an increased risk of adverse neonatal outcomes (apgar score <7 at 5 minutes (OR 2.3, 95% CI 1.8-29), umbilical arterial pH <7.05 (OR 2.9, 95% CI 2.0-2.7) NICU admission (OR 1.6, 95% CI 1.5-1.7)). When assessing maternal outcomes there was an increase in the use of epidural analgesia and caesarean section for women receiving oxytocin. However, other significant maternal morbidities were not reported (16).

We think that our data reflect a change in decision making by caregivers. Our findings suggest that the morbidity associated with oxytocin is not a result of pathology that requires its use but an independent effect of its large and indiscriminate use. Risk of adverse outcomes were increased even among low risk women. It is well recognised internationally that there is considerable variation in practice with respect to method of oxytocin administration, dosage, infusion protocols, and maximal dose administered. (2, 7, 17-19). There is also no consistency in practice with respect to whether oxytocin is ceased once labour is initiated or in the duration of oxytocin use before caesarean section is considered for either failed induction of labour or prolonged labour (20). It has been observed but not quantified that such practice variations also occur in Australia. With the concerns raised regarding the use of oxytocin, both for induction and augmentation of labour, it is imperative

that standardised regimes are developed and implemented to help minimise maternal and fetal complications (7, 21, 22).

Several limitations need to be borne in mind when interpreting the results of our study. First, despite our best efforts to adjust for risk factors, the results may be subject to residual confounding such that the adverse outcomes in-part reflect the reason for intervention rather than its consequence. However, the consistency of the estimate of risk (increased by approximately 30% across risk strata including low risk women) and irrespective of the use of oxytocin for induction or augmentation argues in favour of a true effect. Second, detailed clinical information was not available including the dose and duration of oxytocin infusion, duration of labour and the severity of the associated medical problems. Both a prolonged latent stage and a prolonged first stage of labour are associated with adverse maternal and neonatal outcomes (23). Third, only a single indication for induction is collected. And finally, it is unclear whether use of oxytocin in the management of prelabour ruptured membranes at term is recorded as induction or augmentation of labour and this may vary between hospitals. And finally,

The increase in oxytocin use observed in NSW was primarily due to the use of oxytocin for induction of labour, which increased by 49%. This finding of an increase in rates of induction of labour has also been reported in the UK, USA and Canada (24-28), but has not translated into improvements in maternal or neonatal outcomes (28-30). Also of note is the doubling of the caesarean section rate among women exposed to oxytocin (29%) compared to those who did not receive oxytocin (14%). Therefore the clinical indication and need for oxytocin induction should be considered carefully and balanced against the potential harms associated with its use when considering planned elective delivery.

In conclusion oxytocin has an integral role in the management of labour. However, it remains a potentially dangerous drug. The use of oxytocin should be carefully monitored with a

standardised treatment regimen to minimise maternal and neonatal adverse outcomes. Further research is required within Australia to determine the variations in obstetric practice with regard the use of oxytocin.

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References

1. Blanks AM, Thornton S. The role of oxytocin in parturition. BJOG: An International Journal of Obstetrics & Gynaecology. 2003 Apr;110 Suppl 20:46-51.

2. Smith JG, Merrill DC. Oxytocin for induction of labor. Clin Obstet Gynecol. 2006 Sep;49(3):594-608.

3. Simpson KR, James DC. Effects of oxytocin-induced uterine hyperstimulation during labor on fetal oxygen status and fetal heart rate patterns. American Journal of Obstetrics & Gynecology. 2008 Jul;199(1):34.e1-5.

4. Johnson N, van Oudgaarden E, Montague I, McNamara H. The effect of oxytocin-induced hyperstimulation on fetal oxygen. British Journal of Obstetrics & Gynaecology. 1994 Sep;101(9):805-7.

5. Crane JM, Young DC, Butt KD, Bennett KA, Hutchens D. Excessive uterine activity accompanying induced labor. Obstetrics & Gynecology. 2001 Jun;97(6):926-31.

6. Clark SL, Simpson KR, Knox GE, Garite TJ. Oxytocin: new perspectives on an old drug. American Journal of Obstetrics & Gynecology. 2009 Jan;200(1):35.e1-6.

7. Hayes EJ, Weinstein L. Improving patient safety and uniformity of care by a standardized regimen for the use of oxytocin. American Journal of Obstetrics & Gynecology. 2008 Jun;198(6):622.e1-7.

8. Lain SJ, Algert CS, Nassar N, Bowen JR, Roberts CL. Incidence of severe neonatal outcomes: use of a composite indicator in a population cohort. Maternal and Child Health Journal. 2011;Online First: 20 April 2011 DOI 10.1007/s10995-011-0797-6.

9. Roberts CL, Cameron CA, Bell JC, Algert CS, Morris JM. Measuring maternal morbidity in routinely collected health data: development and validation of a maternal morbidity outcome indicator. Med Care. 2008 Aug;46(8):786-94.

10. Say L, Pattinson RC, Gulmezoglu AM. WHO systematic review of maternal morbidity and mortality: the prevalence of severe acute maternal morbidity (near miss). Reprod Health. 2004;1:3.

11. Laws PJ, Li Z, Sullivan EA. Australia's mothers and babies 2008. Perinatal statistics series no 24 Cat no PER 50. Canberra: AIHW; 2010.

12. Wei S-Q, Luo Z-C, Xu H, Fraser W. Early amniotomy and early oxytocin for prevention of, or therapy for, delay in the first stage of labour compared with routine care (Review). Cochrane Database Syst Rev. 2009(2).

13. Alfirevic Z, Kelly AJ, Dowswell T. Intravenous oxytocin alone for cervical ripening and induction of labour. Cochrane Database Syst Rev. 2009(4):CD003246.

14. Wei S-Q, Luo Z-C, Xu H, Fraser WD. The effect of early oxytocin augmentation in labor: a meta-analysis. Obstetrics & Gynecology. 2009 Sep;114(3):641-9.

15. Wei S-Q, Luo Z-C, Qi H-P, Xu H, Fraser WD. High-dose vs low-dose oxytocin for labor augmentation: a systematic review. American Journal of Obstetrics & Gynecology. 2010 Oct;203(4):296-304.

16. Oscarsson ME, Amer-Wahlin I, Rydhstroem H, Kallen K. Outcome in obstetric care related to oxytocin use. A population-based study. Acta Obstetricia et Gynecologica Scandinavica. 2006;85(9):1094-8.

17. Arnott N, Harrold J, Lynch P. Variations in oxytocin regimes in Scottish labour wards in 1998. Journal of Obstetrics and Gynaecology. 2000;20(3):235-8.

18. Clark S, Simpson KR, Knox GE, Garite TJ. Oxytocin: new perspectives on an old drug. American Journal of Obstetrics & Gynecology. 2009;200:35e1-e6.

19. ACOG. ACOG Practice Bulletin No. 107: Induction of labor. Obstetrics & Gynecology. 2009 Aug;114:386-97.

20. Selin L, Almstrom E, Wallin G, Berg M. Use and abuse of oxytocin for augmentation of labor. Acta Obstetricia et Gynecologica Scandinavica. 2009;88(12):1352-7.

21. Clark S, Belfort M, Saade G, Hankins G, Miller D, Frye D, et al. Implementation of a conservative checklist-based protocol for oxytocin administration: maternal and newborn outcomes. American Journal of Obstetrics & Gynecology. 2007 Nov;197(5):480.e1-5.

22. Clark SL, Belfort MA, Dildy GA, Meyers JA. Reducing obstetric litigation through alterations in practice patterns. Obstetrics & Gynecology. 2008 Dec;112(6):1279-83.

23. Cheng YW, Delaney SS, Hopkins LM, Caughey AB. The association between the length of first stage of labor, mode of delivery, and perinatal outcomes in women undergoing induction of labor. American Journal of Obstetrics & Gynecology. 2009 Nov;201(5):477.e1-7.

24. Mealing NM, Roberts CL, Ford JB, Simpson JM, Morris JM. Trends in induction of labour, 1998-2007: a population-based study. Australian & New Zealand Journal of Obstetrics & Gynaecology. 2009 Dec;49(6):599-605.

25. Foley ME, Alarab M, Daly L, Keane D, Rath A, O'Herlihy C. The continuing effectiveness of active management of first labor, despite a doubling in overall nulliparous cesarean delivery. American Journal of Obstetrics & Gynecology. 2004 Sep;191(3):891-5.

26. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, et al. Births: Final data for 2005. Natl Vital Stat Rep. 2007;56:1-103.

27. Roberts CL, Taylor L, Henderson-Smart D. Trends in births at and beyond term: evidence of a change? British Journal of Obstetrics & Gynaecology. 1999 Sep;106(9):937-42.

28. Patterson JA, Roberts CL, Ford JB, Morris JM. Trends and induction of labour among primipara at term. Australian & New Zealand Journal of Obstetrics & Gynaecology (submitted for publication). 2011.

29. Cammu H, Martens G, Ruyssinck G, Amy J-J. Outcome after elective labor induction in nulliparous women: a matched cohort study. American Journal of Obstetrics & Gynecology. 2002 Feb;186(2):240-4.

30. Confidential enquiry into maternal and child health. Perinatal mortality 2005: England, Wales and Northern Ireland. London 2007.

Figure 1: Trend in use of oxytocin among nullipara at term (37-41 weeks, 1998-2008)

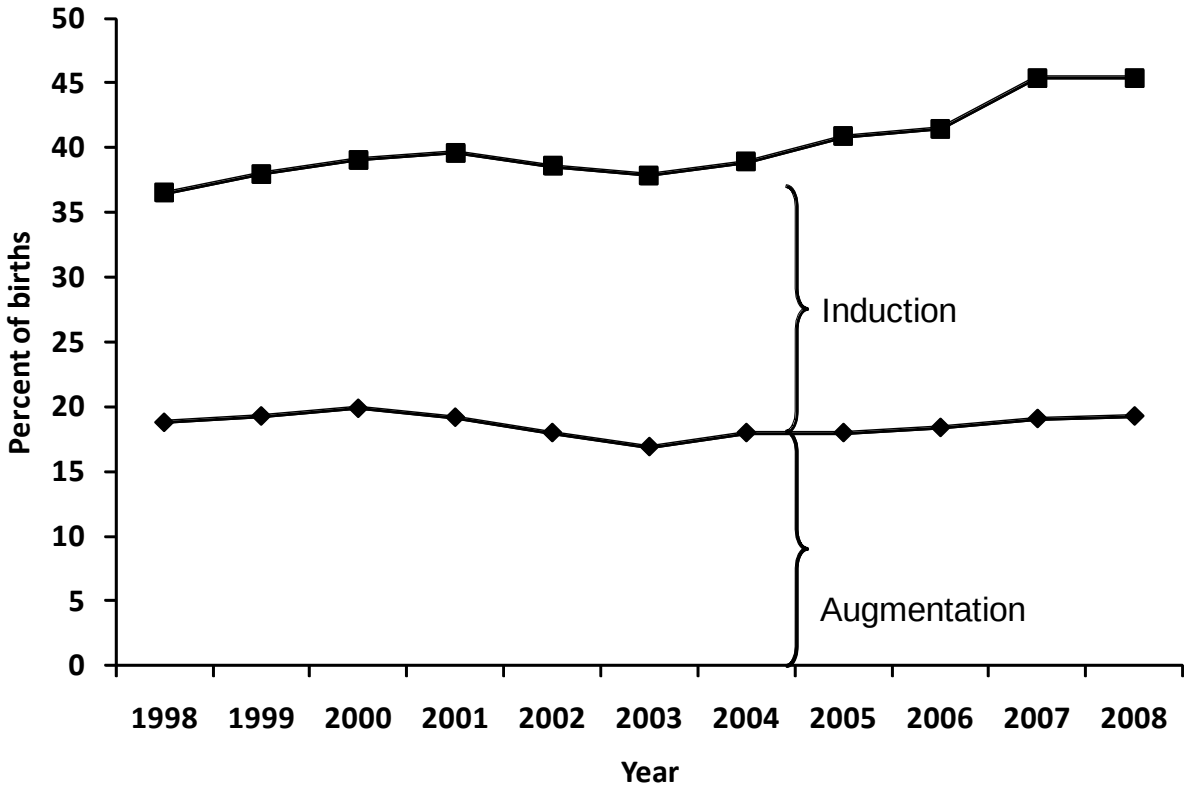

Table 1 Maternal and birth characteristics by oxytocin usage

	Oxytocin N=29711 N (%)	No Oxytocin N=31516 N (%)
Maternal Age		
<20	1557 (5.2)	3045 (9.7)
20-34	27530 (92.7)	27972 (88.8)
35+	623 (2.1)	499 (1.6)
Maternal Smoking		
Yes	2539 (8.5)	3833 (12.2)
Hypertension		
Any	4297 (14.5)	3027 (9.6)
Diabetes		
Any	2098 (7.1)	1389 (4.4)
Hospital Level		
Tertiary obstetric	13843 (46.6)	12925 (41.0)
Small/Medium	3382 (11.4)	6507 (20.6)
Large	4500 (15.1)	5411 (17.2)
Private	7986 (26.9)	6673 (21.2)
Gestational Age		
37	1430 (4.8)	1793 (5.7)
38	3808 (12.8)	4415 (14.0)
39	6743 (22.7)	8318 (26.4)
40	9948 (33.5)	11323 (35.9)
41	7782 (26.2)	5667 (18.0)
Birth weight percentile		
0.0-9.9	2867 (9.6)	3827 (12.1)
10.0 - 90.0	24025 (80.9)	25724 (81.7)
90.1 - 100	2805 (9.4)	1944 (6.2)
Regional Analgesia		
Yes	19414 (65.3)	7035 (22.3)
Onset of labour		
Spontaneous (augmentation)	12437 (41.9)	25884 (82.1)
Induction	17274 (58.1)	5632 (17.9)
Prostaglandin		
Yes	7222 (24.3)	4562 (14.5)
ARM		
Yes	16966 (57.1)	9334 (29.6)
Mode of delivery		
Normal vaginal	11651 (39.2)	21445 (68.0)
Instrumental	9337 (31.4)	5609 (17.8)
Caesarean	8723 (29.4)	4462 (14.2)

*Referent group is not having the exposure, unless otherwise stated

Table 2 Adjusted odds ratio for effect of oxytocin use on neonatal and maternal morbidity, 2007-2008

	Oxytocin	Neonatal morbidity		Maternal morbidity	
		Adjusted OR*	95% CI	Adjusted OR*	95% CI
Overall					
N=61227	Augmentation	1.26	(1.12, 1.42)	1.38	(1.18,1.63)
	Induction	1.31	(1.18, 1.46)	1.54	(1.35,1.78)
	Any Oxytocin†	1.29	(1.17,1.41)	1.48	(1.30,1.68)
Hypertension					
N=5172	Augmentation	1.21	(0.85,1.73)	1.28	(0.79,2.07)
	Induction	1.34	(1.01,1.78)	1.37	(0.93,2.02)
	Any Oxytocin†	1.30	(1.00,1.68)	1.34	(0.94,1.91)
Low Risk Women					
N=24499	Augmentation	1.36	(1.16,1.60)	1.30	(1.03,1.65)
	Induction	1.44	(1.14,1.82)	1.22	(0.86,1.73)
	Any Oxytocin†	1.38	(1.19,1.60)	1.28	(1.03,1.60)

* Referent group is no oxytocin. ORs are adjusted for factors with in Table 1.

† Oxytocin use for either augmentation or induction

Appendix 1. Components of neonatal adverse outcome indicator (NAOI) and maternal morbidity outcome indicator (MMOI) (8, 9)

Neonatal adverse outcome indicator	Maternal morbidity outcome indicator
Diagnoses	
Birth trauma (intracranial haemorrhage paralysis due to brachial plexus injury, skull or long bone fracture)	Acute abdomen
Birthweight < 1,500 g	Acute renal failure
Broncho-pulmonary dysplasia	Acute psychosis
Cerebral infarction	Cardiac arrest, failure or infarction
Death (before discharge home)	Cerebral oedema or coma
Gestational age < 32 weeks	Disseminated intravascular coagulopathy
Hypoxic ischemic encephalopathy	Cerebro-vascular accident
Intraventricular haemorrhage (grades 2-4)	Major complications of anaesthesia
Necrotising enterocolitis	Obstetric embolism
Other respiratory: primary atelectasis, respiratory failure	Shock
Periventricular leukomalacia	Sickle cell anaemia with crisis
Pneumonia	Status asthmaticus
Respiratory distress syndrome	Status epilepticus
Seizure	Uterine rupture
Sepsis/ septicaemia (streptococcus, staphylococcus, *E. coli*, unspecified Gram-negative)	
Procedures	
Any body cavity surgical procedure	Assisted ventilation including tracheostomy
Any intravenous fluids	Curettage in combination with a general anaesthetic
Central venous or arterial catheter	Dialysis
Pneumothorax requiring an intercostal catheter	Evacuation of haematoma
Resuscitation	Hysterectomy
Transfusion of blood or blood products	Procedures to reduce blood flow to uterus
Ventilatory support (mechanical ventilation and/or continuous positive airway pressure)	Reclosure of disrupted Caesarean section wound
	Repair of bladder or cystostomy
	Repair of intestine
	Repair ruptured or inverted uterus
	Transfusion of blood or coagulation factors