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Factors Associated with Higher Oxytocin Requirements in Labor

Heather A. Frey, MD, MSCI¹, Methodius G. Tuuli, MD, MPH¹, Sarah K. England, PhD¹,
Kimberly A. Roehl, MPH¹, Anthony O. Odibo, MD, MSCE¹, George A. Macones, MD, MSCE¹,
and Alison G. Cahill, MD, MSCI¹

¹Department of Obstetrics and Gynecology, Washington University in St. Louis, St. Louis,
Missouri

Abstract

Objective—To identify clinical characteristics associated with high maximum oxytocin doses in women who achieve complete cervical dilation.

Methods—A retrospective nested case-control study was performed within a cohort of all term women at a single center between 2004–2008 who reached the second stage of labor. Cases were defined as women who had a maximum oxytocin dose during labor >20 mu/min, while women in the control group had a maximum oxytocin dose during labor of ≤20 mu/min. Exclusion criteria included no oxytocin administration during labor, multiple gestations, major fetal anomalies, nonvertex presentation, and prior cesarean delivery. Multiple maternal, fetal, and labor factors were evaluated with univariable analysis and multivariable logistic regression.

Results—Maximum oxytocin doses >20 mu/min were administered to 108 women (3.6%), while 2864 women received doses ≤20 mu/min. Factors associated with higher maximum oxytocin dose after adjusting for relevant confounders included maternal diabetes, birth weight >4000 gm, intrapartum fever, administration of magnesium, and induction of labor.

Conclusions—Few women who achieve complete cervical dilation require high doses of oxytocin. We identified maternal, fetal and labor factors that characterize this group of parturients.

Keywords

labor management; labor induction; labor augmentation

Introduction

With approximately 43% of all pregnant women in the United States exposed to oxytocin during labor for either induction or augmentation, oxytocin is one of the most commonly utilized drugs in obstetrics [1, 2]. Controversy remains regarding the optimal dosing regimen of oxytocin [3–6], but in general the use of the *lowest effective dose* is recommended. The *lowest effective dose* is defined by an individual's response to the medication as measured by labor progress and uterine contraction pressures [7–9]. With the use of individual clinical

parameters to guide labor management, variations in oxytocin requirements during labor are frequently observed. While some women require very little oxytocin to effect cervical change, other women seem to require much higher doses to achieve a successful vaginal delivery [9, 10].

In the last few years, there has been rising concern within the obstetric community regarding the safety of oxytocin [8, 11, 12]. Reports of adverse events associated with oxytocin including tachysystole, hyponatremia, and adverse neonatal outcomes have led the Institute for Safe Medication Practices to issue a warning about oxytocin use in labor [13]. A number of proposed standardized regimens to minimize the risks associated with oxytocin use have been published, each containing varying recommendations for the maximum oxytocin dose that should be used [9, 12, 14]. Nevertheless, even advocates of standardized oxytocin regimens concede that a small percentage of women may need higher doses than those proposed in their guidelines [11]. However, there is minimal data regarding individual oxytocin response. In order to improve our understanding of oxytocin responsiveness and ultimately construct safe yet effective oxytocin guidelines, better characterization of the population of women who require higher doses of oxytocin to achieve a vaginal delivery is required. In this large nested case-control study, we sought to identify maternal, fetal and labor characteristics associated with high maximum oxytocin doses required to achieve complete cervical dilation.

Methods

This was a nested case-control study performed within a retrospective cohort of all consecutive women who reached the second stage of labor and delivered at term at a single tertiary center from 2004 through 2008. Women included in the case-control study were those who received oxytocin during labor. Cases were defined as women who received a maximum oxytocin dose >20 milliunits/minute (mu/min), while women with a maximum oxytocin dose ≤ 20 mu/min comprised the control group. Oxytocin dose >20 mu/min was selected to define high dose because this dose represented the 95th percentile for women in our cohort. Exclusion criteria included delivery prior to 37 weeks gestation, multiple gestations, history of cesarean delivery, nonvertex fetal presentation and pregnancies complicated by prenatally diagnosed major anomalies or intrauterine fetal demise. Approval for the study was granted by the Washington University School of Medicine Human Research Protection Office.

Formally trained obstetric research nurses abstracted detailed demographic information as well as historical medical, surgical and pregnancy data from each participant's medical record. Demographic data recorded included maternal age, race, parity, body mass index (kg/m^2) at time of hospital admission, and insurance coverage. History of diabetes during the pregnancy, either gestational or pregestational, was recorded as was the diagnosis of preeclampsia. At our institution, gestational diabetes is defined as glucose ≥ 140 g/dl on a screening glucose tolerance test followed by at least 2 abnormal values on a 3-hour glucose test using the National Diabetes Data Group definitions [15]. The diagnosis of preeclampsia is based on guidelines from the National High Blood Pressure Education Program Working Group that include blood pressure >140 mm Hg systolic or >90 mm Hg diastolic and

proteinuria [16]. At our institution, magnesium is only administered for seizure prophylaxis to women with severe disease. Actual infant birth weight, estimated fetal weight based on recent ultrasound if available or clinical Leopold examination at time of admission, and gestational age at delivery were also abstracted from the participant's chart.

Details regarding labor management that were collected for each woman included use of oxytocin for induction or augmentation of labor, Bishop score at the time of admission, use of regional anesthesia, and all medications administered during labor including cervical ripening and induction agents and magnesium. Specifically, the maximum oxytocin dose that each woman received was documented. Women were categorized as having an intrapartum fever if their maximum recorded temperature prior to delivery was 38.0° Celsius or higher.

Maternal, fetal and labor characteristics were compared between women who received a high maximum oxytocin dose (>20 mu/min) and women who received a lower maximum oxytocin dose (≤ 20 mu/min). The institutional protocol calls for initiation of oxytocin at the discretion of the treating obstetric provider. Two acceptable regimens of oxytocin dose are available (high- and low-dose), but the low-dose regimen is primarily used. The low-dose regimen includes an initial oxytocin infusion rate of 2 mu/min with an increase of 2 mu/min every 20 minutes, while the high-dose regimen involves at starting dose of 6 mu/min with an increase of 6 mu/min every 20 minutes. Clinical parameters such as labor progress, fetal heart rate, and uterine contraction adequacy (>200 Montevideo units in women with intrauterine pressure catheters), also influence oxytocin titration.

Odds ratios and 95% confidence intervals were calculated to estimate the association between each factor and risk for high oxytocin dose. Multivariable models were created to adjust for relevant confounders. Variables associated with maximum oxytocin dose >20 mu/min in univariable analysis ($p < 0.10$) as well as factors with biologic plausibility or previously reported in the literature to be associated with higher oxytocin use were initially considered in the model. Backward stepwise logistic regression was performed. Wald tests and likelihood ratio tests were used to compare hierarchical models. The final model included those factors that were independently associated with maximum oxytocin use >20 mu/min. The model's fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test. A receiver operating characteristic (ROC) curve was created to evaluate the ability of the final model to predict exposure to maximum oxytocin dose >20 mu/min.

To further delineate whether factors associated with higher oxytocin use differed among women who were induced and women who were augmented, a stratified analysis based on indication for oxytocin use was performed. In women who were induced, the relationship between the use of additional induction agents during labor other than oxytocin and maximum oxytocin dose was examined. Cervical dilation at the time oxytocin was initiated was evaluated in women whose labor was augmented with oxytocin.

Secondarily, we excluded women who reached the second stage of labor but were delivered by cesarean or operative vaginal delivery from our analysis. We evaluated the maternal, fetal

and labor factors associated with maximum oxytocin dose >20 mu/min among only women who had a spontaneous vaginal delivery using both univariable and multivariable analyses.

All women included in the term birth cohort who met inclusion criteria were included in this analysis and given this fixed sample size, an a priori sample size calculation was not performed. Statistical analyses were performed using Stata 10.0 (special edition, Stata-Corp, College Station, TX).

Results

Among women who reached the second stage of labor, 2,972 women (55.2%) were identified who were exposed to oxytocin during labor and met additional inclusion criteria. The overall distribution of maximum oxytocin dose among women included in this study stratified by use of oxytocin for induction or augmentation is presented in Figure 1. Among women included in this case-control study, 108 women (3.6%) had a maximum oxytocin dose >20 mu/min (dose range 21-40 mu/min, median 26 mu/min). The control group consisted of 2,864 women who received a maximum oxytocin dose ≤ 20 mu/min.

Maternal demographic and historical factors were compared between women who received a maximum oxytocin dose >20 mu/min and those who received a maximum oxytocin dose ≤ 20 mu/min. Multiple characteristics were found to be associated with high oxytocin dose including white race, maternal diabetes and preeclampsia. In addition, obese women (BMI 30-39.9 kg/m² and BMI ≥ 40 kg/m²) had an increased risk of exposure to a high maximum oxytocin dose when compared to non-obese women (BMI <30 kg/m²) (Table 1).

Induction of labor in comparison to augmentation of labor was associated with high oxytocin dose. However, an unfavorable Bishop score (≤ 6) at time of admission were similar in the groups. Women with an intrapartum fever or exposure to magnesium were more likely to have a maximum oxytocin dose >20 mu/min. Birth weight >4000 grams was associated with an increased risk of high oxytocin as well, while estimated fetal weight, gestational age and regional anesthesia use were not found to be risk factors (Table I).

After adjusting for confounders, five factors were independently associated with high maximum oxytocin dose: induction of labor, birth weight >4000 grams, maternal diabetes, intrapartum fever, and magnesium administration (Table II). Other factors considered in the logistic regression model included parity, maternal BMI, ethnicity, insurance status, estimated fetal weight >4000 grams, and preeclampsia, however these factors did not remain associated with high oxytocin use after adjusting for confounders. The final model including induction of labor, birth weight, maternal diabetes, intrapartum fever and magnesium use was evaluated using the Hosmer-Lemeshow goodness-of-fit test (p=0.61), and the ability of the model to predict high maximum oxytocin dose was tested with ROC analysis (Figure 2). Although each factor was independently associated with high oxytocin dose, the model was only modestly predictive of requiring a maximum oxytocin dose >20 mu/min (AUC=0.72).

In stratified analysis by induction or augmentation, white race, BMI, diabetes, preeclampsia, intrapartum fever, and magnesium use remained associated with high oxytocin use in the group of women who were induced. Delivery between 39⁰-40⁶ weeks gestation compared to

delivery between 37⁰-38⁶ weeks gestation was also associated with high maximum oxytocin dose in this subgroup (OR 1.70, 95% CI 1.01-2.87). Use of other cervical ripening or induction agents during labor in addition to oxytocin was evaluated in women who were induced. While prostaglandin use was not associated with an increased risk of high maximum oxytocin dose, use of an intracervical Foley catheter was associated with maximum oxytocin dose >20 mu/min (OR 2.48, 95% CI 1.38-4.30). When women who augmented were analyzed separately, delivery between 39⁰-40⁶ weeks gestation compared to delivery between 37⁰-38⁶ weeks gestation was associated with lower risk of high maximum oxytocin dose (OR 0.44, 95% CI 0.19-0.98). Because Bishop score at the time of admission is arguably less important than cervical examination at the time that oxytocin was started in women requiring labor augmentation, cervical dilation at the time oxytocin was initiated was evaluated. Cervical dilation $\geq$ 3 cm was more common in women who received a high maximum oxytocin dose (OR 2.41, 95% CI 1.02-5.69).

While the focus of this study was identifying characteristics of women who achieved complete cervical dilation but required oxytocin doses >20 mu/min, it is arguable that spontaneous vaginal delivery is an equally important outcome to consider. Within our cohort, 2,499 women had a spontaneous vaginal delivery (84.1%), of whom 90 (3.6%) were exposed to oxytocin doses >20 mu/min. In a secondary analysis, we excluded women who had a cesarean (n=59) or operative vaginal delivery (n=414) in the second stage of labor. We found that labor induction, birth weight >4000 gm, intrapartum fever, and magnesium administration were also independently associated with spontaneous vaginal delivery after controlling for confounders (Table III).

Discussion

Exposure to oxytocin doses greater than 20 mu/min is uncommon among women who successfully reach the second stage of labor and those who have a spontaneous vaginal delivery. Factors that were independently associated with exposure to higher doses of oxytocin included maternal diabetes, infant birth weight >4,000 grams, intrapartum fever, magnesium administration, and induction of labor. Stratified analysis by indication for oxytocin use demonstrated that Foley catheter use as an induction agent and cervical dilation $\geq$ 3 cm at the time oxytocin for augmentation was initiated were additional risk factors for exposure to high doses of oxytocin.

We found only one other published study to specifically evaluate clinical factors associated with oxytocin dose response. Twenty years ago, Satin et al. identified gestational age ($\geq$ 36 weeks), cervical dilation ($\geq$ 2 cm), and parity as important predictors of maximum oxytocin dosage among women undergoing induction or augmentation of labor with a high-dose oxytocin regimen. Maternal body surface area was associated with higher oxytocin dosage only among women undergoing induction of labor. Similar to our study, the investigators found that ability of these factors to predict maximum oxytocin dose was limited [17].

It is not surprising that the factors that we identified to be associated with higher oxytocin doses are also factors that are associated with poor labor progress [18-20] as this is the central factor used to guide oxytocin administration. However, published research from

other investigators provides further explanation as to how these clinical factors may modify the biologic effect of oxytocin in various ways. Compared to non-diabetic women, diabetic women have reduced myometrial muscle mass and decreased calcium channel receptors and calcium signaling in their myometrial tissues [21]. While both the diagnosis of preeclampsia and magnesium use were more common among women who received oxytocin doses >20 $\mu\text{u}/\text{min}$ in univariable analysis, only magnesium use was demonstrated to be independently associated with high oxytocin dose after controlling for confounders. In this term birth cohort, the only indication for magnesium use was severe preeclampsia. Although it is possible that preeclampsia itself affects uterine contractility, a more likely explanation is the inhibition of uterine contractility by magnesium. A frequently used tocolytic agent in the prevention of preterm labor [22], magnesium has been shown to decrease oxytocin induced contractions in vitro by blocking calcium channels [23, 24].

While we identified factors independently associated with high maximum oxytocin dose needed to achieve complete cervical dilation, our overall model explanatory value was modest. This suggests that there remain unmeasured factors such as maternal genetics [25] that may influence oxytocin responsiveness. Additionally, our study cohort included only women at term, but Satin et al. found that prematurity was a risk factor for higher maximum oxytocin dose [17]. We also did not have information about the length of time that an individual received the maximum oxytocin dose, thus we cannot draw conclusions about the effect of the interaction between maximum dose and duration of that dose. Furthermore, oxytocin dosing was ultimately at the discretion of the managing clinician despite the use of the institutional protocol designed to guide clinical care, which is a source of potential bias in our study. Lastly, we examined factors associated with high maximum oxytocin dose within a cohort of women who successfully achieved complete dilation, and secondarily women who had a vaginal delivery, thus we are unable to draw conclusions about the effects of high oxytocin doses on complications within the first stage of labor or factors associated with high maximum oxytocin doses among women who do not reach the second stage.

The strengths of this study include the detailed data, large sample size and careful design. The nested case-control study minimized selection and ascertainment bias, two major limitations of the traditional case-control design. The detailed complete data allowed us to evaluate multiple risk factors and control for confounding using multivariable logistic regression.

In conclusion, a higher maximum oxytocin dose may be required for some women to achieve complete cervical dilation. However, in our study only 3.6% of women who reached the second stage received oxytocin doses >20 $\mu\text{u}/\text{min}$. The clinical factors we identified to be significantly associated higher oxytocin requirements are similar to the risk factors for protracted labor progress, which is expected because of the clinical practice of using contractions and cervical dilation to guide oxytocin dosing. This study highlights the need to further define the relationship between oxytocin, contractions, and labor progress with the ultimate goal of optimizing oxytocin dosing for all women.

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Figure 1. Distribution of maximum oxytocin dosages among all women, and women with induced and augmented labor

Figure 2. Receiver operating characteristic curve of model including induction of labor, birth weight, magnesium administration, intrapartum fever and maternal diabetes

Table I
Association of maternal, fetal and labor characteristics with maximum oxytocin dose >20 mu/min in univariable analysis among all women who achieved complete cervical dilation

A. MATERNAL				
	Max oxytocin dose >20 mu/min (n=108)	Max oxytocin dose 20 mu/min (n=2864)	OR (95% CI)	p
<i>Age</i>				
18-34 years	86 (79.6)	2399 (83.8)	ref	
<18 years	13 (12.0)	265 (9.2)	1.37 (0.69-2.51)	0.30
>34 years	9 (8.3)	200 (7.0)	1.26 (0.55-2.55)	0.52
<i>Race</i>				
Black	68 (64.2)	2038 (72.2)	ref	
White	30 (28.3)	545 (19.3)	1.65 (1.03-2.60)	0.02
Other	8 (7.5)	240 (8.5)	1.00 (0.41-2.12)	0.99
<i>Parity</i>				
Multiparous	61 (56.5)	1572 (54.9)	ref	
Nulliparous	47 (43.5)	1292 (45.1)	0.94 (0.62-1.40)	0.74
<i>Body mass index</i>				
BMI <30	32 (30.2)	1170 (41.9)	ref	
BMI 30-39.9	55 (51.9)	1262 (45.2)	1.59 (1.00-2.57)	0.04
BMI 40	19 (17.9)	358 (12.8)	1.94 (1.02-3.68)	0.02
<i>Insurance</i>				
Non-private	85 (78.7)	2448 (85.5)	ref	
Private	23 (21.3)	416 (14.5)	1.59 (0.95-2.58)	0.05
<i>Any diabetes</i>				
No	96 (88.9)	2753 (96.1)	ref	
Yes	12 (11.1)	111 (3.9)	3.10 (1.50-5.88)	<0.01
<i>Gestational diabetes</i>	10 (9.3)	89 (3.1)	3.18 (1.43-6.37)	<0.01
<i>Pregestational diabetes</i>	2 (1.9)	22 (0.8)	2.44 (0.27-10.13)	0.22
<i>Preeclampsia</i>				
No	89 (82.4)	2615 (91.3)	ref	
Yes	19 (17.6)	249 (8.7)	2.24 (1.27-3.78)	<0.01
B. FETAL				
	Max oxytocin dose >20 mu/min (n=108)	Max oxytocin dose 20 mu/min (n=2864)	OR (95% CI)	p
<i>Gestational age</i>				
37 ⁰ -38 ⁶ weeks	34 (32.1)	937 (33.0)	ref	

A. MATERNAL				
	Max oxytocin dose >20 mu/min (n=108)	Max oxytocin dose 20 mu/min (n=2864)	OR (95% CI)	p
39 ⁰ -40 ⁶ weeks	62 (58.5)	1568 (55.2)	1.09 (0.70-1.72)	0.69
41 ⁰ weeks	10 (9.4)	337 (11.8)	0.82 (0.36-1.72)	0.58
<i>Estimated fetal weight at time of admission</i>				
4000 gm	81 (96.4)	2362 (98.9)	ref	
>4000 gm	3 (3.6)	27 (1.1)	3.24 (0.62-10.86)	0.08
<i>Birthweight</i>				
4000 gm	95 (88.0)	2687 (93.8)	ref	
>4000 gm	13 (12.0)	177 (6.2)	2.08 (1.05-3.82)	0.01
C. LABOR				
	Max oxytocin dose >20 mu/min (n=108)	Max oxytocin dose 20 mu/min (n=2864)	OR (95% CI)	p
<i>Induction</i>				
No	26 (24.1)	1579 (55.1)	ref	
Yes	82 (75.9)	1285 (44.9)	3.88 (2.45-6.31)	<0.01
<i>Bishops score</i>				
>6	7 (6.5)	297 (10.4)	ref	
6	101 (93.5)	2567 (89.6)	1.67 (0.77-4.30)	0.19
<i>Regional anesthesia</i>				
No	7 (6.5)	210 (7.3)	ref	
Yes	101 (93.5)	2654 (92.7)	1.14 (0.52-2.95)	0.74
<i>Magnesium administration</i>				
No	92 (85.2)	2689 (93.9)	ref	
Yes	16 (14.8)	175 (6.1)	2.67 (1.43-4.70)	<0.01
<i>Intrapartum fever</i>				
No	84 (80.0)	2561 (93.4)	ref	
Yes	21 (20.0)	182 (6.6)	3.52 (2.02-5.88)	<0.01

* Data presented as n (%)

Table II
Independent factors associated with maximum oxytocin dose >20 mu/min among all women who achieved complete cervical dilation

Variable	aOR (95%CI)	p
<i>Induction of labor</i>	3.39 (2.14-5.39)	<0.01
<i>Any diabetes</i>	2.33 (1.21-4.48)	0.01
<i>Birthweight >4000 gm</i>	1.98 (1.07-3.68)	0.03
<i>Magnesium administration</i>	2.08 (1.15-3.75)	0.02
<i>Intrapartum fever</i>	3.26 (2.01-5.62)	<0.01

* Variables initially placed in the model: parity, ethnicity, private insurance, maternal BMI, induction, estimated fetal weight >4000 gm, birthweight >4000 gm, preeclampsia, magnesium use during labor, maternal diabetes, intrapartum fever

Table III
Independent factors associated with maximum oxytocin dose >20 mu/min among all women who had a spontaneous vaginal delivery

Variable	aOR (95%CI)	p
<i>Induction of labor</i>	3.08 (1.89-5.03)	<0.01
<i>Birthweight>4000 gm</i>	2.13 (1.09-4.17)	0.03
<i>Magnesium administration</i>	2.11 (1.10-4.04)	0.03
<i>Intrapartum fever</i>	3.84 (2.17-6.79)	<0.01

* Variables initially placed in the model: parity, ethnicity, private insurance, maternal BMI, induction, estimated fetal weight >4000 gm, birthweight >4000 gm, preeclampsia, magnesium use during labor, maternal diabetes, intrapartum fever