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Condensation: Higher maximum doses of oxytocin should be used cautiously in VBAC trials, and considering an upper limit of 20 mu/min seems reasonable.

Title: Higher maximum doses of oxytocin are associated with an unacceptably high risk for uterine rupture in patients attempting VBAC

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Objective: To more precisely estimate the effect of maximum oxytocin dose on uterine rupture risk in patients attempting VBAC by considering timing and duration of therapy.

Study design: A nested case-control study was conducted within a multicenter, retrospective cohort study of over 25,000 women with at least one prior cesarean delivery, comparing cases of uterine rupture to controls (no rupture) while attempting VBAC. Time-to-event analyses were performed to examine the effect of maximum oxytocin dose on the risk of uterine rupture considering therapy duration, while adjusting for confounders.

Results: Within the nested case-control study of 804 patients, 272 were exposed to oxytocin: 62 cases of uterine rupture and 210 controls. Maximum oxytocin ranges above 20mu/min increased the risk of uterine rupture 4-fold or greater (21-30mu/min: HR=3.92, 95%CI 1.06-14.52; 31-40mu/min: HR=4.57, 95%CI 1.00-20.82).

Conclusion: These findings support a maximum oxytocin dose of 20mu/min in VBAC trials to avoid an unacceptably high risk of uterine rupture.

Key words: VBAC, oxytocin, uterine rupture

Introduction:

While attempts at vaginal birth after cesarean (VBAC) have become a common part of obstetric practice, largely due to recently published, well-designed studies [1, 2] quantifying the relatively low rates of maternal and neonatal risks associated with VBAC, practitioners are facing the complex reality of the intrapartum management of these VBAC trials with little evidence for guidance. As the number of women with a prior cesarean rises[3], so does the number of labor inductions, creating a paradox between the large number of patients attempting VBAC who require oxytocin for labor induction or augmentation, and the small amount of published data on oxytocin use in VBAC trials. This frequently encountered clinical scenario leaves clinicians to extrapolate data and guidelines from management in patients without a uterine scar to those attempting VBAC.

Any assessment of the safety of oxytocin use in VBAC trials must consider both dose and time. While some studies have described a small, increased risk for uterine rupture associated with oxytocin use[2], others have reported no association between oxytocin and the risk for uterine rupture[4]. Most importantly, no studies have addressed the role that time may play in risk of uterine rupture imparted by oxytocin use. We sought to more precisely estimate the effect of maximum oxytocin dose on the risk of uterine rupture in patients attempting VBAC by considering timing and duration of oxytocin dose.

Materials and Methods:

From 1995 to 2000, a 17-center, retrospective cohort study was conducted in the northeastern United States, enrolling all patients with at least one prior cesarean delivery. Institutional Review Board approval was obtained at all sites. This study was conducted to assess the risks of VBAC-associated maternal morbidities, and to ascertain if uterine rupture could be predicted. Nested within this large cohort, a case-control study was designed, defining cases as patients experiencing a symptomatic uterine rupture, and then randomly selecting control patients from those who underwent a VBAC trial but did not experience a uterine rupture, in a ratio of 5:1, matched on hospital site. Details of the cohort study have been described elsewhere[1], but a brief description follows.

Participants were identified by International Classification of Disease 9th Revision (ICD-9) code, using the term "previous cesarean delivery, delivered". The sensitivity of this ICD code-based search was validated in pilot studies prior to study initiation. Trained research nurses extracted charts using closed-ended data extraction forms, and 3% of charts were re-extracted for quality assurance. Patients were excluded if the type of scar from their prior cesarean was either unknown or non-low-transverse. Extensive data was collected on maternal demographics, medical and obstetric history, antenatal and peripartum events, and maternal outcomes. During re-abstraction for the patients in the case-control study, detailed patient-level information was collected on labor progress in 15 minute intervals, including exams, medications, and dosing. Thus, labor curves can be effectively reconstructed for all of the patients in the case-control study.

The definition of symptomatic uterine rupture (case) was specified *a priori*, and equivocal cases were reviewed and status determined by the primary investigator. To distinguish these cases from less clinically relevant incidental findings of asymptomatic

uterine dehiscence and uterine "windows", cases of uterine rupture required a full-thickness scar separation and at least one of the following clinical markers: hemoperitoneum, signs of maternal hemorrhage (including systolic blood pressure <70, diastolic blood pressure <40, or heart rate >120), or nonreassuring fetal heart rate pattern immediately preceding surgery.

For this analysis, we studied all patients exposed to oxytocin in the nested case-control study, comparing patients who experienced a uterine rupture to those who did not. Cases and controls were compared on baseline characteristics, using χ^2 analysis for dichotomous variables and Student's t-test or Mann-Whitney U test, as appropriate, for continuous variables. Additionally, a sensitivity analysis of sociodemographics and oxytocin parameters was performed, comparing the controls used for this analysis to the group of patients who did not experience a uterine rupture in the larger cohort to ensure that the controls chosen at random were representative (data available upon request).

For the time-to-event analyses, patients were classified as having the event of interest (uterine rupture) or were censored (delivered). We considered three clinically relevant time periods by defining time-to-event three distinct ways. The first was duration of labor, where time zero was specified as time of labor floor admission. The second was duration of oxytocin exposure, where time zero was specified as time of initiation of oxytocin therapy for labor induction or augmentation, and the third was duration of maximum oxytocin exposure, where time zero was specified as initiation of maximum oxytocin dose.

Maximum oxytocin dose was categorized into clinically relevant ranges (1-5, 6-20, 21-30, 31-40 mu/min), specifying the range of 1-5mu/min as the reference. For all

time-to-event analyses, Kaplan-Meier plots were used for graphical illustration of the risk of uterine rupture over time by stratum of maximum oxytocin range. Dummy variables were created with the 4 dose ranges of maximum oxytocin and the lowest range was designated as the reference. Using each of the three periods of observation, Cox proportional hazard regression was used to model the effect of maximum oxytocin dose on the risk for uterine rupture, adjusting for relevant confounding effects identified in the unadjusted analysis. Data was nearly complete for all covariates. Imputed values were not used in the regression analysis for missing data since they represented less than 2% of the data for any given variable. The proportional hazards assumption was tested using the global test of Grambsch and Therneau[5]. All statistical analysis was completed with STATA software package (v 8, Special Edition; Stata Corporation, College Station, TX).

Results:

Within a cohort of 25,005 patients with a history of at least one prior cesarean delivery, 13,706 attempted VBAC. Of those who attempted VBAC, 134 experienced a uterine rupture and were defined as cases. At random, 670 of the 13,706 patients who attempted VBAC but did not experience a uterine rupture were selected as controls. For this analysis of all 272 patients in the nested case-control study exposed to oxytocin, 62 cases of uterine rupture were compared to 210 controls. The two groups were similar in age, gravidity, gestational age at delivery, care site, comorbidities, and tobacco and alcohol use. However, patients who experienced uterine rupture were less likely to have had a prior vaginal delivery (15.0% vs. 32.2%, p=0.009), had a higher rate of induction as

compared to augmentation (75.0 % vs. 58.6%, p=0.021), and were more likely to have had more than one prior cesarean delivery (18.3% vs. 9.1%, p=0.047) (Table 1).

The maximum dose of oxytocin exposure was divided into 4 ranges (1-5, 6-20, 21-30, and 31-40mu/min). Using the lowest dose range as reference, a Kaplan-Meier plot displayed divergent survival curves, with the greater divergence in uterine rupture risk seen as duration of exposure becomes longer (Figure).

When Cox proportional hazard models were built to estimate the effect of maximum oxytocin dose on risk of uterine rupture, the results varied depending on the time period used for the time-to-event analysis. Table 2 presents the Cox proportional hazard model of the effect of the designated dose ranges of maximum oxytocin on the risk for uterine rupture, when time of observation was defined as time from initiation of maximum oxytocin dose to event or censor. The final Cox model adjusted for three relevant covariates: history of a prior vaginal delivery, induction (vs. augmented) labor, and number of prior hysterotomies. Neither number of prior cesareans nor cervical dilation (<4 vs ≥ 4 centimeters dilated at the time of oxytocin initiation) remained significant in the final model. We found a dose-response relationship between increased maximum oxytocin dose exposure and increased risk of uterine rupture. The dose range 6-20mu/min had a slightly greater than 3-fold increase risk of uterine rupture (HR=3.34, 95%CI 1.01-10.98). And at ranges of maximum oxytocin doses over 20mu/min, the increase in risk of uterine rupture was 4-fold or greater (21-30mu/min: HR=3.92, 95%CI 1.06-14.52; 31-40mu/min: HR=4.57, 95%CI 1.00-20.82). These adjusted analyses estimate the attributable risk of uterine rupture to be 2.9% and 3.6% for maximum oxytocin dose ranges above 20 and 30 milliunits per minute, respectively

Conversely, when defining the observation period as duration of labor or duration of any oxytocin therapy (as opposed to duration of maximum oxytocin dose) for the Cox model, there appeared to be no association between maximum oxytocin dose and uterine rupture risk. Even at the highest range of maximum oxytocin dose (31-40mu/min), neither defining time as duration of labor (HR=1.62, 95%CI 0.40-6.59) nor defining time as duration of oxytocin exposure (HR=0.62, 95%CI 0.12-3.01) revealed a significant increased risk association.

Comment:

When the timing and duration of oxytocin dose is considered, increasing ranges of maximum oxytocin dose are associated with a progressively increasing risk of uterine rupture in patients attempting VBAC. This association with uterine rupture risk, estimated by time-to-event analysis, is greater in magnitude than that previously described by multivariable models that did not consider time or duration of therapy[2, 4, 6-9]. This finding warrants setting limits on oxytocin use in VBAC trials.

In a 2001, Goetzl et al [4] published a small, case-control study of patients undergoing a VBAC trial, and reported no difference in oxytocin dose and duration between the 24 patients who experienced a uterine rupture and the 96 who did not. Though they reported no difference in oxytocin duration or oxytocin dose between cases of uterine rupture and controls, they were unable to adjust for relevant confounding variables, unable to examine a wide range of maximum doses since the study was performed at a single center, and could not fully explore the effect of therapy duration

because they did not use time-based analyses. Additionally, the sample size restricted the study's power to identify a difference in oxytocin exposure.

Since then, two studies have identified that there is in fact a risk association between oxytocin and uterine rupture. Landon et al [2] performed a large, prospective cohort study of VBAC candidates, and found that augmentation and induction with oxytocin were associated with an increased risk of uterine rupture (adjusted OR 2.42, 95% CI 1.49-3.93, and adjusted OR 3.01, 95% CI 1.66-5.46, respectively). Cahill et al[10], in a secondary analysis of a large retrospective cohort, reported a dose-response relationship between maximum oxytocin dose and risk of uterine rupture, comparing VBAC candidates who were exposed to oxytocin to those who were not. However, neither study addressed the clinically and physiologically significant role of time or therapy duration, and thus may not have most accurately estimated the true risk association between oxytocin, or more specifically maximum oxytocin dose, and uterine rupture.

In this study, we considered the possibility that the association of maximum oxytocin dose exposure and the risk of uterine rupture might be most precisely estimated using time-to-event analysis. The nested case-control design of our study afforded several advantages. It allowed us to examine the risk of a rare outcome with sufficient power to adjust for several relevant confounding variables without over-fitting our multivariable models. Since the study was nested within a large, retrospective, multicenter cohort, it enabled us to choose controls from the same population as the cases, reducing the chance for selection bias.

To assure that the controls were truly a random sample from the entire cohort that did not experience a uterine rupture (non-event population), we performed a sensitivity analysis of oxytocin parameters. There was no significant difference between the controls used for this analysis and the larger sample from which they were drawn, specifically with regard to oxytocin exposure and demographic variables, further supporting the lack of significant selection bias.

Time-to-event analysis allowed us to consider three clinically relevant time frames in the assessment of maximum oxytocin dose and risk of uterine rupture. When event-time was defined as duration of labor or duration of oxytocin exposure, while clinically appropriate, these definitions of time of exposure likely incorporate left censoring and introduced selection bias. That is, due to variation in labor at time of presentation and variability in oxytocin initiation and management, these definitions likely incorporated patients who were at risk during time not observed, which could have biased the results in either direction. By defining time at risk as time from initiation of maximum oxytocin dose to uterine rupture or delivery, we were able to more precisely estimate the risk association since all of the time at risk was observed.

Despite these efforts to minimize selection bias, some may still exist. However, it is unlikely to have occurred with regard to selection of the cases, since the definition of uterine rupture was defined strictly and *a priori*, and equivocal cases were reviewed for classification. If significant bias occurred in random selection of the controls, the nonsignificant trends in the sensitivity analysis support an over-sampling in the higher ranges of maximum oxytocin which, if anything, would have falsely diminished the observed risk estimates in relation to the true risk of uterine rupture. Finally, despite the

large sample size, the outcome is a rare event which limits the precision of the risk estimates.

Given the results of our analyses, the magnitude of increased risk for uterine rupture at higher maximum dose ranges of oxytocin is concerning. As compared to previous risk estimates that suggested an approximately 1% attributable risk of uterine rupture at the highest range of maximum oxytocin doses, these results estimate the attributable risk to be 2.9% and 3.6% for maximum oxytocin dose ranges above 20 and 30 milliunits per minute, respectively. While an increase in uterine rupture risk of 1% seems clinically acceptable, 2.9% and 3.6% are less so. From this data, we believe that higher maximum doses of oxytocin should be used cautiously in VBAC trials, and that an upper limit of 20 mu/min seems reasonable.

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Figure Legend:

Title: Kaplan-Meier plot of risk for uterine rupture with increasing ranges of maximum oxytocin exposure

Key: Maximum oxytocin ranges:

1 - (6-20 mu/min)

2 - (21-30 mu/min)

3 - (31-40 mu/min)

Table 1: Baseline characteristics of cases and controls exposed to oxytocin

Variable	Cases (N=62)	Controls (N=210)	p
Maternal age (years)	31.3 ± 5.14	30.3 ± 5.40	0.186
Gravidity (mean)	3.21 ± 1.59	3.27 ± 1.51	0.785
Gestational age @ delivery (wk)	38.6 ± 4.90	38.7 ± 3.11	0.869
Delivery prior to 34 weeks (%)	1.7	3.4	0.496
Delivery after 41 weeks (%)	15.0	21.6	0.259
Birth weight (grams)	3442 ± 701.3	3454 ± 743.5	0.919
> 1 prior cesarean (%)	18.3	9.1	0.047
Prior vaginal delivery (%)	15.0	32.2	0.009
Prior cesarean for cephalopelvic disproportion (%)	10.0	10.6	0.898
Induction of labor (%)	75.0	58.6	0.021
Twin gestation (%)	1.7	0.5	0.344
Asthma (%)	8.1	10.9	0.511
Chronic hypertension (%)	3.2	6.2	0.365
Any gestational hypertensive disease (%)	11.7	6.7	0.210
Diabetes (%)	3.2	2.9	0.885
Alcohol use (%)	5.0	6.0	0.783
Tobacco use (%)	11.7	17.2	0.307
University hospital (%)	68.3	67.8	0.936
Obstetric residency (%)	25.0	36.0	0.110

Table 2: Cox proportional hazard model of effect of maximum oxytocin dose on risk of uterine rupture

Maximum oxytocin dose (mu/min)	Hazard Ratio	95% CI	p
1-5 (n=89)	ref	- -	- -
6-20 (n=119)	3.34	1.01-10.98	0.047
21-30 (n=48)	3.92	1.06-14.52	0.040
31-40 (n=16)	4.57	1.00-20.82	0.050

*Significant covariates in model: history of prior vaginal delivery, induction or spontaneous labor, number of prior hysterotomies