OBSTETRICS

Risk factors for uterine atony/postpartum hemorrhage requiring treatment after vaginal delivery

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OBJECTIVE: We sought to identify risk factors for uterine atony or hemorrhage.

STUDY DESIGN: We conducted a secondary analysis of a 3-arm double-blind randomized trial of different dose regimens of oxytocin to prevent uterine atony after vaginal delivery. The primary outcome was uterine atony or hemorrhage requiring treatment. In all, 21 potential risk factors were evaluated. Logistic regression was used to identify independent risk factors using 2 complementary predefined model selection strategies.

RESULTS: Among 1798 women randomized to 10, 40, or 80 U of prophylactic oxytocin after vaginal delivery, treated uterine atony occurred in 7%. Hispanic (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.3—3.4), non-Hispanic white (OR, 1.6; 95% CI, 1.0—2.5), preeclampsia (OR, 3.2; 95% CI, 2.0—4.9), and chorioamnionitis (OR, 2.8; 95% CI, 1.6—5.0) were consistent independent risk factors. Other risk factors based on the specified selection strategies were obesity, induction/augmentation of labor, twins, hydramnios, anemia, and arrest of descent. Amnioinfusion appeared to be protective against uterine atony (OR, 0.53; 95% CI, 0.29—0.98).

CONCLUSION: Independent risk factors for uterine atony requiring treatment include Hispanic and non-Hispanic white ethnicity, preeclampsia, and chorioamnionitis.

Key words: postpartum hemorrhage, risk factors, uterine atony

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The incidence of postpartum hemorrhage in developed countries is increasing.[1-4] In the United States, one estimate of the overall rate of postpartum hemorrhage increased approximately 26%, from 2.3% in 1994 to 2.9% in 2006.[1] Uterine atony may specifically account for up to 80% of the cases of postpartum hemorrhage.[5,6] Unlike other causes of obstetric hemorrhage such as placental abnormalities that may be detected prenatally, uterine atony is difficult to predict.[7] Many risk factors for uterine atony and postpartum hemorrhage have been reported.[8-15] The specific risk factors examined and the magnitude of risk attributable to each of them vary across reports. Therefore confounding may be a major reason for the discrepancies. Furthermore, reports of true risk factors may be missed in some studies because of limited power to demonstrate statistical significance.

A greater understanding of well-defined independent risk factors may improve our ability to determine which women may be at risk for postpartum hemorrhage. This is important since obstetrical hemorrhage, primarily postpartum, is a significant cause of maternal morbidity and mortality worldwide.[8,16-19] Therefore the purpose of this study was to conduct a more comprehensive multivariable analysis to identify independent risk factors for uterine atony or postpartum hemorrhage. We applied multivariable statistical models that allowed us to identify probable independent risk factors that may be confirmed in larger studies.

Materials and Methods

We conducted a secondary analysis of a 3-arm double-blind randomized clinical trial of different doses of oxytocin.[20] The primary aim of the trial was to evaluate higher doses of oxytocin compared to a standard low-dose oxytocin regimen used for prophylaxis among women undergoing vaginal delivery. Women were randomized to a 10-(standard), 40-, or 80-U dose regimen of oxytocin at vaginal delivery. Women were excluded if they were <24 weeks' gestation, underwent cesarean delivery, had fetal demise, had pulmonary edema, or had coagulopathy or cardiomyopathy. Each regimen comprised the specified dose in 500 mL of a crystalloid solution administered rapidly over 1 hour after delivery of the placenta (ie, at a rate of 500 mL/h). The protocol was approved by the Institutional Review Board at the University of Alabama at Birmingham. All participating women granted informed consent. Information concerning patient demographic and clinical characteristics as well as

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TABLE 1
Distribution of demographic characteristics and potential risk factors (N = 1798)

Characteristic or factor	Prevalence, n (%)
Maternal age,[a] y	24.1 ± 5.4
Oxytocin dose, U	
10	659 (37)
40	481 (27)
80	658 (37)
Nulliparity	673 (37)
Hispanic	327 (18)
White and other	410 (23)
Black	1061 (59)
Obese (BMI ≥30)	1036 (58)
Overweight (BMI 25-30)	523 (29)
Normal, underweight	239 (13)
Augmentation	955 (53)
Induction	572 (32)
Spontaneous	271 (15)
Preeclampsia/eclampsia	218 (12)
MgSO4 use	188 (10)
Twins	13 (<1)
Chorioamnionitis	122 (7)
Hydramnios	43 (2)
Amnioinfusion	299 (17)
Epidural anesthesia	1504 (84)
Breast-feeding	1000 (57)
Spontaneous ROM	584 (33)
Prior cesarean	86 (5)
Operative deliveries	147 (8)
Anemia	44 (2)
Protracted second stage	108 (6)
Prolonged third stage	35 (2)
GA at delivery,[a] wk	38.8 ± 2.1
Total birthweight, g	
<2500	190 (11)
2500-3999	1499 (83)
≥4000	109 (6)

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TABLE 1
Distribution of demographic characteristics and potential risk factors (N = 1798) *(continued)*

Characteristic or factor	Prevalence, n (%)
GA at delivery, wk	
<37	223 (12)
37-41	1395 (78)
≥41	180 (10)

BMI, body mass index; *GA*, gestational age; *MgSO4*, magnesium sulfate; *ROM*, rupture of membranes.

[a] Mean ± SD.

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outcomes of interest, including postpartum hemorrhage or atony requiring therapy, was abstracted by trained research nurses. For this secondary analysis, we retained the same primary outcome: uterine atony or hemorrhage requiring treatment. Treatment included the use any use of uterotonics, or the need for transfusion, balloon tamponade, surgery, or interventional radiology procedure for uterine or arterial embolization. Transfusion was based on the need for whole or packed red cells prior to discharge home from the hospital. The diagnosis of uterine atony was made based on the discretion of the treating obstetrical team.

The study variables or exposures of interest consisted of a large set of 21 potential risk factors (including demographic characteristics) for uterine atony/hemorrhage (Table 1) identified from the published literature. The risk factors were defined accordingly: overweight was defined as a body mass index (BMI) of 25-29.9 kg/m^2 and obesity was defined as a BMI of ≥30 kg/m^2. Ethnicity was self-reported as Hispanic, black, white, or other. Chorioamnionitis was defined as the presence of clinical signs (primarily intrapartum fever) leading to a clinical diagnosis and antibiotic treatment of chorioamnionitis. Anemia was determined by a hemoglobin of <9 g/dL. Hydramnios was defined as an amniotic fluid volume of >25 cm or a greatest vertical pocket of >8 cm. Protracted second stage of labor was >1 hour from complete cervical dilation to delivery if multiparous and >2 hours between complete cervical dilation and delivery if nulliparous. A protracted third stage was defined as being >30 minutes from the times of delivery of the infant to delivery of the placenta.

Logistic regression analyses were conducted to individually evaluate each of the risk factors as predictors of the primary study composite. Risk factors identified as significant, either by statistical significance at a .05 level or by large effect (odds ratio [OR], >1.5 or <0.7) at the univariate level, were considered in multivariable logistic regression models. A parsimonious regression model of independent risk factors was derived using traditional backward model selection strategy whereby only factors significant at the .05 level at each stage were retained for further consideration.[21] Risk factors were progressively eliminated from the model until a parsimonious model comprising only factors statistically satisfying the specific selection criteria was obtained.

To identify additional risk factors that may not be statistically significant within the limitations of our sample size, we utilized a previously described modified backward selection strategy that gave premium to the magnitude of risk as well as to statistical significance.[22] A priori, factors associated with a minimally important change in the outcome (defined as OR, ≥1.5 or ≤0.67) or a P value < .05 were retained in the model. The minimally important difference was selected as we judged this level to be of public health significance. Variables with adjusted ORs (aORs) <1.5 and >0.67 were then progressively removed, starting with the variable with the highest P value until the final parsimonious models were obtained. Software (SAS, version 9.2; SAS Institute Inc, Cary, NC) was used for all statistical analyses.

RESULTS

Our study sample included all 1798 women randomized and analyzed in the primary trial. In all, 658 women were randomized to 80 U of oxytocin, 481

women to 40 U (this arm was terminated at interim review), and 659 to 10 U of oxytocin. The distribution of the population according to characteristics under study is presented in Table 1. Of note, the dose of prophylactic oxytocin did not influence the outcome in the primary trial. The study population consisted of women who were predominantly obese, black, underwent labor induction, and received an epidural.

The frequency of the primary outcome, treated uterine atony or hemorrhage, was 7% overall (118 women) and did not differ by study group.[20] The prevalence of this outcome by categories of each of the 21 potential risk factors for uterine atony/hemorrhage and the corresponding unadjusted OR (95% confidence interval [CI]) are presented in Table 2. BMI, race/ethnicity, labor induction, twins, preeclampsia, breast-feeding, anemia, protracted second stage, and chorioamnionitis were significantly associated with postpartum atony or hemorrhage in univariate analyses.

Using traditional backward selection (strategy A), Hispanic (aOR, 2.10; 95% CI, 1.30−3.37) and non-Hispanic white (aOR, 1.59; 95% CI, 1.00−2.53) ethnicity, preeclampsia (aOR, 3.15; 95% CI, 2.00−4.95), and chorioamnionitis (aOR, 2.83; 95% CI, 1.61−4.97) were the only independent risk factors for treated uterine atony or obstetric hemorrhage in the final parsimonious model (Table 3).

Applying the modified backward selection (strategy B) to identify additional risk factors, obesity, labor induction, twins, hydramnios, anemia, and protracted second stage of labor were identified as risk factors for uterine atony or obstetric hemorrhage (in addition to race/ethnicity, preeclampsia, and chorioamnionitis); amnioinfusion appeared protective based on the predefined criteria for selecting risk factors (Table 3).

Magnesium sulfate was used in 10% of the deliveries; however, preeclampsia is highly correlated with use of magnesium sulfate in our study sample (Spearman correlation 0.84, $P < .0001$). To avoid multicolinearity in the statistical models, these 2 factors were considered separately. When magnesium

TABLE 2
Incidence of outcome (treated uterine atony) for each factor and unadjusted OR (95% CI)

Factor	Incidence of uterine atony, n (%)	No uterine atony, n (%)	OR (95% CI)
Oxytocin dose, U			
10 (n = 659)	45 (7)	614 (93)	Referent
40 (n = 481)	31 (6)	450 (94)	0.9 (0.6−1.5)
80 (n = 658)	42 (6)	616 (94)	0.9 (0.6−1.4)
Obese (BMI ≥30) (n = 1036)	75 (7)	961 (93)	2.6 (1.2−5.7)
Overweight (BMI 25-30) (n = 523)	36 (7)	487 (93)	2.5 (1.1−5.6)
Normal, underweight (n = 239)	7 (3)	232 (97)	Referent
Hispanic (n = 327)	33 (10)	294 (89)	2.1 (1.3−3.3)
White and other (n = 410)	31 (8)	379 (92)	1.5 (1.0−2.4)
Black (n = 1061)	54 (5)	1007 (95)	Referent
Augmentation (n = 955)	52 (5)	903 (95)	1.2 (0.7−2.4)
Induction (n = 572)	54 (9)	518 (91)	2.3 (1.2−4.3)
Spontaneous (n = 271)	12 (4)	259 (96)	Referent
Birthweight, g			
<2500 (n = 190)	10 (5)	180 (95)	0.8 (0.4−1.5)
2500-3999 (n = 1499)	100 (7)	1399 (93)	Referent
≥4000 (n = 109)	8 (7)	101 (93)	1.1 (0.5−2.3)
Nulliparity (n = 673)	54 (8)	619 (92)	1.4 (1.0−2.1)
Parity (n = 1125)	64 (6)	1061 (94)	
Preeclampsia (n = 218)	31 (14)	187 (86)	2.8 (1.8−4.4)
No preeclampsia (n = 1580)	87 (6)	1493 (94)	
MgSO4 use (n = 188)	27 (14)	161 (86)	2.8 (1.8−4.4)
No MgSO4 use (n = 1610)	91 (6)	1519 (94)	
Twins (n = 13)	2 (15)	11 (85)	2.6 (0.6−12.0)
Singletons (n = 1785)	116 (7)	1669 (93)	
Chorioamnionitis (n = 122)	17 (14)	105 (86)	2.5 (1.5−4.4)
No chorioamnionitis (n = 1676)	101 (6)	1575 (94)	
Hydramnios (n = 43)	5 (12)	38 (88)	1.9 (0.7−5.0)
No hydramnios (n = 1755)	113 (6)	1642 (94)	
Amnioinfusion (n = 299)	13 (4)	286 (96)	0.6 (0.3−1.1)
No amnioinfusion (n = 1499)	105 (7)	1394 (93)	
Epidural anesthesia (n = 1504)	97 (6)	1407 (94)	0.9 (0.5−1.5)
No epidural (n = 294)	21 (7)	273 (93)	
Breast-feeding (n = 1000)	76 (8)	924 (92)	1.5 (1.0−2.2)
No breast-feeding (n = 751)	39 (5)	712 (95)	
Spontaneous ROM (n = 584)	36 (6)	548 (94)	0.9 (0.6−1.4)
Artificial ROM (n = 1212)	82 (7)	1130 (93)	

Wetta. Risk factors for uterine atony. Am J Obstet Gynecol 2013. *(continued)*

TABLE 2
Incidence of outcome (treated uterine atony) for each factor and unadjusted OR (95% CI) *(continued)*

Factor	Incidence of uterine atony, n (%)	No uterine atony, n (%)	OR (95% CI)
Prior cesarean (n = 86)	7 (8)	79 (92)	1.3 (0.6–2.8)
No prior cesarean (n = 1712)	111 (6)	1601 (94)	
Operative deliveries (n = 147)	12 (8)	135 (92)	1.3 (0.7–2.4)
Nonoperative delivery (n = 1651)	106 (6)	1545 (94)	
Anemia (hemoglobin <9) (n = 44)	5 (11)	39 (89)	1.9 (0.7–4.8)
No anemia (n = 1754)	113 (6)	1641 (94)	
Protracted second stage (n = 108)	14 (13)	94 (87)	2.3 (1.3–4.1)
No protracted second stage (n = 1690)	104 (6)	1586 (94)	
Prolonged third stage (n = 35)	4 (11)	31 (89)	1.9 (0.6–5.4)
No prolonged third stage (n = 1763)	114 (6)	1649 (94)	
Maternal age, y	24.7 ± 5.7	24.7 ± 5.3	1.0 (1.0–1.1)
GA at delivery, wk	38.9 ± 2.1	38.9 ± 2.1	1.0 (0.9–1.1)

BMI, body mass index; *CI*, confidence interval; *GA*, gestational age; *MgSO4*, magnesium sulfate; *OR*, odds ratio; *ROM*, rupture of membranes.

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sulfate replaced preeclampsia in the final models it was also associated with atony/postpartum hemorrhage with both strategy A (aOR, 3.0; 95% CI, 1.9–4.8) and strategy B (aOR, 2.4; 95% CI, 1.4–4.0). Results for the other covariates identified in prior models were similar.

In additional analyses not shown, we evaluated women with a history of a postpartum hemorrhage. There were only a small number of women, 7, who reported this history. When a history of postpartum hemorrhage was assessed using traditional backward selection (strategy A), it was not identified as a risk factor. However, using strategy B, the aOR was 2.0 (95% CI, 0.2–19.1). Overall the associations of other risk factors did not change materially, but the model became less stable because of the small number of women.

Comment

Of 21 demographic and clinical factors examined, maternal race/ethnicity, preeclampsia, and chorioamnionitis were consistent risk factors for uterine atony or postpartum hemorrhage requiring treatment in our cohort of women who underwent vaginal delivery. When we applied a modified model selection strategy that emphasized strength of association over statistical significance, we identified additional risk factors. Prophylactic oxytocin doses did not influence the results as reported in the primary paper.[20]

Uterine atony as the cause of primary postpartum hemorrhage is increasing in the United States and other countries such as Canada and Australia.[1,2,23] Interventions such as induction of labor, cesarean delivery, and operative vaginal delivery have been implicated, but the cause of this increase remains unclear.[24,25] Additionally, advanced maternal age, multiple gestation, prior hemorrhage, and prolonged labor have also been cited as risk factors.[25-27] Our current findings among women with vaginal delivery support labor induction and multiple pregnancy but not operative vaginal deliveries or advanced maternal age as likely independent risk factors. Furthermore, our findings are supportive of prior studies that identified obesity, white or Hispanic race/ethnicity, polyhydramnios, preeclampsia, anemia, and infection (chorioamnionitis) as potential independent risk factors but not those that identified black race or breast-feeding.[6,8,11,13-15] Because of its tocolytic effect, one would expect magnesium sulfate to be associated with an increase in the risk of atony or postpartum hemorrhage. Although our results also support studies suggesting such an association,[13] we are unable to delineate whether this is entirely or partially attributable to confounding with preeclampsia. The exact mechanism by which preeclampsia leads to atony or hemorrhage is open to speculation. Furthermore, because breast-feeding may have an uterotonic effect due to endogenous oxytocin surge, it would be expected to be associated with a reduction in the study outcome. We do not observe such an association after multivariable adjustments (breast-feeding is eliminated from the multivariable regression models), perhaps suggesting that at the doses of exogenous prophylactic oxytocin administered, there is no additional uterotonic benefit from breast-feeding. Our finding suggesting amnioinfusion as a protective factor for uterine atony is surprising and does not appear to have been previously reported. If confirmed, it is plausible that amnioinfusion may "wash away" bacteria and inflammatory mediators that may predispose to infection and subsequent uterine atony. We are unable to postulate a unifying biological explanation for uterine atony. Our findings would suggest that there are likely several pathways at play. For example, both chorioamnionitis and magnesium sulfate in the setting of preeclampsia may impair uterine contractility, resulting in uterine atony and hemorrhage.

Our report suffers from a number of limitations. First, we studied only women who delivered vaginally. Therefore our results are not directly applicable to women who underwent cesarean delivery. Although some of our findings are consistent with observations in women who delivered by cesarean, it is also possible that some of the discrepancies may be due to differences in mode of

TABLE 3
Results of multivariable adjusted analyses: complementary models

Factor	OR (95% CI) Strategy A (traditional backward)	Strategy B (modified backward)
Obese (BMI ≥30)	—	2.25 (1.41–3.62)
Overweight (BMI 25-30)	—	1.48 (0.92–2.38)
Normal, underweight	—	Referent
Hispanic	2.10 (1.30–3.37)	2.26 (1.41–3.62)
White and other	1.59 (1.00–2.53)	1.48 (0.92–2.38)
Black	Referent	Referent
Augmentation	—	1.08 (0.56–2.08)
Induction	—	1.60 (0.80–3.18)
Spontaneous	—	Referent
Preeclampsia	3.15 (2.00–4.95)	2.61 (1.60–4.25)
Twins	—	2.64 (0.54–12.9)
Chorioamnionitis	2.83 (1.61–4.97)	2.42 (1.35–4.34)
Hydramnios	—	1.75 (0.65–4.69)
Amnioinfusion	—	0.53 (0.29–0.98)
Anemia	—	2.46 (0.92–6.56)
Protracted second stage	—	1.73 (0.92–3.26)

All factors without adjusted results were dropped out of models based on specified modeling strategies.

BMI, body mass index; *CI*, confidence interval; *OR*, odds ratio.

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delivery. Second, our sample size may not be sufficient to evaluate potential risk factors that are less frequent. Our modified regression strategy (B) addressed this potential limitation; we were able to identify probable risk factors that did not meet traditional criteria for statistical significance but that were important contributors to the model and might attain statistical significance given a larger study population. Finally, as an exploratory secondary analysis, levels of significance for each statistical test were not adjusted for multiple comparisons. Because of the large number of statistical tests performed, it is possible that some of the observed associations occurred purely by chance. It is, however, reassuring that most of our findings are supported by the published literature.

In this study, we have simultaneously evaluated multiple potential risk factors using a well-characterized contemporary sample of women enrolled in a single-center trial. We identified a short list of consistent risk factors for uterine atony or postpartum hemorrhage after eliminating factors that may have been previously associated because of uncontrolled confounding. For example, studies that did not consider preeclampsia may find black race as a risk factor. Also, given ongoing temporal changes in obstetric demographics and practices including labor induction, epidural use, and cesarean delivery, it is plausible that contemporary risk factors may vary. The identification of independent risk factors for atony and postpartum hemorrhage will allow clinicians to better anticipate who may truly be at risk for postpartum hemorrhage and more efficiently plan preventive and therapeutic measures against adverse outcomes. Our findings suggest that among vaginal deliveries, women of Hispanic or non-Hispanic white backgrounds or whose deliveries are complicated by chorioamnionitis or preeclampsia are most at risk. Subsequent studies with relevant power are needed to confirm maternal obesity, labor induction, twins, hydramnios, anemia, and protracted second stage of labor as additional independent risk factors and amnioinfusion as a protective factor. The role of magnesium sulfate use independently of preeclampsia also warrants further clarification. ■

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