OBSTETRICS

Adverse outcomes in twin pregnancies complicated by early vaginal bleeding

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OBJECTIVE: We sought to estimate the risks of adverse pregnancy outcomes associated with early vaginal bleeding in twin pregnancies.

STUDY DESIGN: In a retrospective cohort study of consecutive twin pregnancies undergoing anatomic survey, we compared women who reported vaginal bleeding at <22 weeks to those who did not. Exclusion criteria included monoamniotic pregnancies, twin-to-twin transfusion syndrome, and placenta previa. Primary outcomes included preeclampsia, abruption, preterm premature rupture of membranes (PPROM), preterm birth <34 weeks, and intrauterine growth restriction.

RESULTS: Of 2106 pregnancies meeting inclusion criteria, 175 reported vaginal bleeding. Twin pregnancies with early vaginal bleeding had significantly higher risks of abruption, PPROM, and preterm birth compared to twin pregnancies without bleeding. The findings were similar when twin pairs were stratified by parity or maternal comorbidities.

CONCLUSION: Twin pregnancies complicated by vaginal bleeding in early pregnancy have an increased risk of abruption, PPROM, and preterm birth <34 weeks.

Key words: adverse pregnancy outcomes, multiples, vaginal bleeding

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Vaginal bleeding in the first and second trimester of pregnancy is common. Rates in singleton pregnancies are estimated to be as high as 14-27%.[1-6] Although early vaginal bleeding can be associated with spontaneous abortion, most pregnancies result in a live birth.[4] Ongoing pregnancies complicated by vaginal bleeding have an increased risk of adverse outcomes.[1,2,4,7,8] Recent studies in singletons with early vaginal bleeding have described increased risks of preterm premature rupture of membranes (PPROM), preterm birth, preeclampsia, and placental abruption.[1,2,4,7-9]

★ EDITORS' CHOICE ★

Published studies examining early vaginal bleeding and adverse pregnancy outcomes have excluded twin pregnancies.[2-4,7] This leaves clinicians to extrapolate data from singletons to counsel women carrying twin pregnancies who have experienced earlier vaginal bleeding.[2-4,7] Our study aimed to estimate the risk of adverse outcomes in ongoing twin pregnancies with reported bleeding in the first half of pregnancy and to further characterize at-risk groups by assessing whether parity and maternal comorbidities modify risk.

Materials and Methods

We performed a retrospective cohort study of all consecutive twin pregnancies at 17-22 weeks presenting to Washington University Medical Center to undergo routine sonographic anatomic survey from 1990 through 2008. The Washington University School of Medicine Human Research Protection Office approved the study prior to its initiation.

Dedicated research nurses collected the data prospectively. The data were primarily extracted from medical records, and then supplemented by the patient. Each patient was approached and consented at the time of the second-trimester anatomic survey and agreed to provide detailed information on a structured form regarding medical history and obstetrical history (including vaginal bleeding in the current pregnancy). Each patient was also given a form to be completed after delivery reflecting pregnancy outcomes including antenatal complications, delivery complications, and neonatal outcomes. If the form was not completed and received within 4 weeks of the expected date of delivery, a research coordinator called the patient to obtain the information. The majority of patients (92%) delivered at our institution; if the patient could not be reached and delivered at an outside facility, the coordinator contacted the referring physician to obtain outcome data. Only twin pregnancies with complete outcome information were included in this study.

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TABLE 1
Characteristics of women with twin pregnancies with vaginal bleeding compared to women without vaginal bleeding

Characteristics	Bleeding n = 175	No bleeding n = 1931	*P* value
Age, y	31.4 ± 5.4	30.9 ± 6.0	.33
Age ≥35 y	30.3	28.7	.66
Gravidity	2.6 ± 1.5	2.6 ± 1.6	.70
Nulliparity	28.6	27.4	.75
Chorionicity			.02
Monochorionic diamniotic	17.0	24.7	
Dichorionic	83.0	75.3	
Gestational age at delivery, wk	33.6 ± 4.0	34.7 ± 4.2	< .01
BMI, kg/m^2	25.8 ± 7.4	25.8 ± 6.8	.97
BMI, ≥30 kg/m^2	29.1	28.1	.77
African American	14.3	21.4	.03
Tobacco use	6.9	10.2	.16
Alcohol use	11.5	12.7	.65
Chronic hypertension	2.3	3.1	.57
Gestational diabetes	9.7	5.9	.04
Pregestational diabetes	1.7	1.1	.45
History of preterm delivery	7.4	6.3	.55
Any anomaly[a]	3.4	2.1	.24

Data are mean ± SD or percent unless otherwise specified.
BMI, body mass index.

[a] Any major congenital anomaly identified in either twin.

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Study groups were defined by patient-reported vaginal bleeding any time during the pregnancy prior to the sonographic anatomic survey. Monoamniotic pregnancies, pregnancies affected by twin-to-twin transfusion syndrome,[10] presence of placenta previa defined as complete or partial previa,[11] singletons, and higher-order multiple gestations were excluded from the study. Women who underwent assisted reproductive therapies were included and were not evaluated separately. Gestational age was assigned based on the first day of a woman's last menstrual period. If the dating was not consistent with a first-trimester ultrasound or dating based on the anatomic survey (±7 days in the first trimester or ±10 days in the second trimester), the gestational age was reassigned.[11] The primary outcomes were preeclampsia defined by the American College of Obstetricians and Gynecologists,[12] placental abruption as diagnosed by the delivering physician at the time of delivery, PPROM,[13] preterm birth <34 weeks, and intrauterine growth restriction (IUGR) of any twin defined as birthweight ≤10th percentile for gestational age at delivery determined by the Alexander growth standard.[14] As part of the preplanned analysis, study groups were then stratified by known risk factors including parity (nulliparous vs multiparous) and presence of maternal comorbidities including chronic hypertension[15] and pregestational or gestational diabetes (defined as an abnormal 3-hour glucose tolerance test result using the National Diabetes Data Group cutoffs). Within strata risks were estimated. Finally, analyses of the primary outcomes stratified by chorionicity were performed.

Baseline characteristics of women with twin pregnancies complicated by vaginal bleeding <22 weeks and those without bleeding were compared using the Student *t* test or Mann-Whitney *U* test for continuous variables and the χ^2 or Fisher exact test for categorical variables as appropriate. Incidences of the primary outcomes were compared between study groups and the unadjusted relative risks with 95% confidence intervals (CIs) were estimated. Bivariable analyses were performed to identify potentially confounding factors. Logistic regression models were developed to estimate the independent risk of vaginal bleeding for each outcome adjusting for confounding factors that were identified historically and in the bivariable analyses. Backward stepwise selection was used to reduce the number of variables in the regression model by assessing the magnitude of change in the effect size of remaining covariates. Differences in the explanatory model were tested using the likelihood ratio test or Wald test.[16] Statistically significant variables were included in the final models and adjusted odds ratios (aOR) with 95% CI were obtained ($P < .05$ was considered significant). Analyses were repeated with stratification by parity and maternal comorbidities. Statistical analyses were performed using software (STATA 10.0, special edition; StataCorp, College Station, TX).

RESULTS

Of 2445 twin pregnancies, 2146 met study inclusion criteria. Of those, 2106 (98.1%) had complete outcome data available and were included in the final analysis. Of those included in the final analysis, 175 (8.3%) reported vaginal bleeding <22 weeks.

The 2 groups were similar on average in terms of age, gravidity, nulliparity, obesity (body mass index ≥30 kg/m^2), tobacco or alcohol use, having chronic hypertension or pregestational diabetes, having a history of preterm delivery, or having any major anomaly[11] diagnosed in the pregnancy. Women who reported vaginal bleeding were less likely to be of African American race and were more likely to have gestational diabetes (Table 1).

Women with twins who reported vaginal bleeding <22 weeks had increased risks of placental abruption (aOR, 7.21; 95% CI, 3.61–14.41), PPROM (aOR, 2.48; 95% CI, 1.68–3.68), and preterm

TABLE 2
Risk of adverse outcomes in twin pregnancies with vaginal bleeding

Outcome	Bleeding n = 175	No bleeding n = 1931	Unadjusted relative risk (95% CI)	Adjusted odds ratio (95% CI)	*P* value
Preeclampsia	25.1%	20.0%	1.26 (0.96–1.65)	1.40 (0.96–2.03)[b]	.08
Abruption	8.0%	1.1%	7.02 (3.66–13.48)	7.21 (3.61–14.41)[c]	< .01
PPROM	21.1%	9.7%	2.17 (1.58–2.98)	2.48 (1.68–3.68)[d]	< .01
Preterm birth (<34 wk)	31.7%	22.4%	1.42 (1.09–1.84)	1.72 (1.17–2.54)[e]	< .01
Any IUGR[a]	17.5%	22.3%	0.78 (0.53–1.16)	0.76 (0.47–1.23)[f]	.27

CI, confidence interval; *IUGR,* intrauterine growth restriction; *PPROM,* preterm premature rupture of membranes.

[a] Growth <10th percentile on Alexander curve for either twin; [b] Adjusted for gestational diabetes, gravidity, nulliparity, body mass index ≥ 30 kg/m^2, chronic hypertension, African American race, and any major anomaly; [c] Adjusted for gestational age at delivery; [d] Adjusted for body mass index ≥30 kg/m^2; [e] Adjusted for chorionicity, African American race, nulliparity, and history of preterm birth; [f] Adjusted for African American race.

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birth <34 weeks (aOR, 1.72; 95% CI, 1.17–2.54) that persisted after adjusting for potential confounding factors. There were no differences in the rates of preeclampsia or IUGR (Table 2). When stratified by chorionicity, there were no differences in the associations between bleeding and the primary outcomes.

When stratified by parity, nulliparous women who reported vaginal bleeding at <22 weeks had an increased risk of abruption (aOR, 11.31; 95% CI, 2.68–47.72) compared to nulliparous women without vaginal bleeding. The increased risks of PPROM and preterm birth did not reach statistical significance in nulliparous women. Multiparous women who reported early vaginal bleeding had statistically significant increased risks of abruption, PPROM, and preterm birth compared to multiparous women who denied vaginal bleeding (Table 3).

When stratified by medical comorbidities, women without chronic hypertension, pregestational diabetes, or gestational diabetes who reported vaginal bleeding at <22 weeks had increased risks of abruption, PPROM, and preterm birth <34 weeks compared to those without early vaginal bleeding. Rates of abruption, PPROM, and preterm birth in women with chronic hypertension, pregestational diabetes, or gestational diabetes who reported vaginal bleeding at <22 weeks were not significantly different from those who did not report vaginal bleeding at <22 weeks (Table 4).

Comment

We found that the incidence of women reporting vaginal bleeding in the first half of twin gestations was 8.3%. Women who experienced early vaginal bleeding but carried their pregnancies through anatomic survey were at increased risk of having placental abruption, PPROM, or preterm birth <34 weeks. Similarly, in the stratified analyses, multiparous women and those without comorbidities were at increased risk of abruption, PPROM, and preterm birth <34 weeks. When stratified by chorionicity, there were no differences in the primary outcomes. Surprisingly, women with dichorionic twin pregnancies experienced a higher rate of early vaginal bleeding.

No prior studies have evaluated associated pregnancy risks in continuing

TABLE 3
Risk of adverse outcomes in twin pregnancies with vaginal bleeding by parity

Outcome	Bleeding n = 175	No bleeding n = 1931	Unadjusted relative risk (95% CI)	Adjusted odds ratio (95% CI)	*P* value
Nulliparous (n = 580)	n = 50	n = 530			
Preeclampsia	32.0%	28.7%	1.12 (0.73–1.71)	1.18 (0.63–2.23)[b]	.59
Abruption	8.0%	0.8%	10.60 (2.73–41.1)	11.31 (2.68–47.72)[c]	< .01
PPROM	20.0%	11.9%	1.68 (0.92–3.07)	1.85 (0.88–3.89)[d]	.10
Preterm birth (<34 wk)	34.9%	28.3%	1.23 (0.79–1.91)	1.36 (0.70–2.64)[e]	.34
Any IUGR[a]	23.8%	22.5%	1.06 (0.59–1.88)	1.12 (0.53–2.37)[f]	.77
Multiparous (n = 1526)	n = 125	n = 1401			
Preeclampsia	22.4%	16.7%	1.34 (0.94–1.90)	1.47 (0.94–2.30)[b]	.09
Abruption	8.0%	1.3%	6.23 (2.94–13.19)	6.26 (2.81–13.93)[c]	< .01
PPROM	21.6%	8.9%	2.42 (1.67–3.52)	2.81 (1.76–4.48)[d]	< .01
Preterm birth (<34 wk)	30.2%	20.0%	1.51 (1.09–2.09)	1.83 (1.14–2.94)[e]	.01
Any IUGR[a]	14.3%	22.3%	0.64 (0.38–1.09)	0.60 (0.32–1.13)[f]	.11

CI, confidence interval; *IUGR,* intrauterine growth restriction; *PPROM,* preterm premature rupture of membranes.

[a] Growth <10th percentile on Alexander curve for either twin; [b] Adjusted for obesity and chronic hypertension; [c] Adjusted for gestational age at delivery; [d] Adjusted for obesity; [e] Adjusted for chorionicity, African American race, and history of preterm birth; [f] Adjusted for African American race.

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TABLE 4
Risk of adverse outcomes in twin pregnancies with vaginal bleeding by presence or absence of select comorbidities

Outcome	Bleeding n = 175	No bleeding n = 1931	Unadjusted relative risk (95% CI)	Adjusted odds ratio (95% CI)	*P* value
No comorbidities (n = 2106)	n = 155	n = 1752			
Preeclampsia	24.5%	18.4%	1.33 (0.99–1.79)	1.44 (0.98–2.12)[b]	.07
Abruption	8.4%	1.1%	7.73 (3.89–15.36)	7.96 (3.84–16.52)[c]	< .01
PPROM	20.6%	9.6%	2.15 (1.53–3.03)	2.45 (1.61–3.74)[b]	< .01
Preterm birth (<34 wk)	29.3%	22.0%	1.33 (0.99–1.79)	1.57 (1.04–2.39)[d]	.03
Any IUGR[a]	18.2%	22.5%	0.81 (0.54–1.22)	0.79 (0.47–1.30)[e]	.35
Comorbidities (n = 199)	n = 20	n = 179			
Preeclampsia	30.0%	35.8%	0.83 (0.42–1.69)	0.78 (0.28–2.12)[b]	.64
Abruption	5.0%	1.7%	2.98 (0.32–27.34)	3.06 (0.30–31.09)[c]	.34
PPROM	25.0%	11.2%	2.24 (0.94–5.31)	2.61 (0.85–8.02)[b]	.09
Preterm birth (<34 wk)	50.0%	25.9%	1.93 (1.10–3.40)	2.57 (0.83–8.01)[d]	.10
Any IUGR[a]	12.5%	20.3%	0.62 (0.16–2.35)	0.61 (0.13–2.89)[e]	.53

CI, confidence interval; *IUGR,* intrauterine growth restriction; *PPROM,* preterm premature rupture of membranes.

[a] Growth <10th percentile on Alexander curve for either twin; [b] Adjusted for obesity; [c] Adjusted for gestational age at delivery; [d] Adjusted for chorionicity, African American race, and history of preterm birth; [e] Adjusted for African American race.

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twin pregnancies complicated by vaginal bleeding in the first half of pregnancy. Prior to this study, prenatal counseling required extrapolation from singleton pregnancy data. In 2004, Yang et al[17] reported on the relationship between self-reported vaginal bleeding in the first or second trimester and preterm birth in singletons. This was a prospective cohort of 2802 women, 683 who reported bleeding. They found a 1.3-fold increased risk of preterm birth and a 1.7-fold increased risk of PPROM among all women reporting vaginal bleeding. The study did not evaluate abruption, preeclampsia, or IUGR.

A study by Weis et al[4] in 2004 reported on adverse outcomes after first-trimester vaginal bleeding in singletons. The study evaluated >16,000 pregnancies, of which 14% had reported vaginal bleeding. The authors found that pregnancies with any vaginal bleeding were more likely to experience a loss at <24 gestational weeks. After adjusting for confounders, those women who reported light bleeding (defined as spotting only) had an increased risk of preeclampsia, abruption, and preterm delivery. Women who reported heavy bleeding were at an increased risk of IUGR, abruption, PPROM, and preterm delivery.

Saraswat et al[7] carried out a systematic review in 2010 that included 14 studies assessing outcomes in pregnancies complicated by vaginal bleeding in the first trimester with ultrasound confirmed viability. Nearly all of the included studies excluded twins. The results of the review were similar to those in the study by Weis et al.[4] There was an increased risk of PPROM and preterm delivery. The systematic review also noted a nearly 2-fold increased risk of perinatal death.

Our study design offers several advantages. Our large sample size of continuing twin pregnancies at the time of sonographic anatomic survey allowed us to study adverse outcomes after early vaginal bleeding that had previously been evaluated almost exclusively in singletons. Additionally, information in the database was collected prospectively and complete follow-up was available in >98% of women with twins, which allowed us to evaluate the effects of confounding factors. Finally, study subjects were not recruited based on a history of vaginal bleeding and the cohort was established prior to inception of the research question, both of which should minimize selection bias.

The retrospective nature of the study is a potential limitation and the study groups differed in several baseline characteristics. Multivariable regression analysis, however, was used to adjust for these measured differences minimizing confounding and leaving only unmeasured potential residual confounders. The patients were asked to report vaginal bleeding on a questionnaire at the time of anatomic survey, which may lead to recall errors. We would offer, however, that errors should be nondifferential as the information was obtained prior to the anatomic survey and the outcomes of interest. We did not differentiate between first or second trimester of bleeding or quantify the amount of bleeding. While this restricts our ability to assess characteristics of bleeding as risk factors or predictors, it likely improves generalizability of the findings, as women do not always recall the week of bleeding and bleeding quantification is not consistent among different women. Prior studies in singletons have differentiated between light and heavy bleeding and trimester, and have found that adverse outcomes such at preterm birth and PPROM are similar, which

argues that presence of any vaginal bleeding may be the most suitable predictor of adverse outcomes.[1,2,4] While this is one of the largest samples of twins with robust follow-up data the absolute number of adverse events limits precision. Generalizability is limited to women presenting to anatomic survey with 2 live fetuses, as those with an earlier loss were excluded. An explanation for the overall lower rate of vaginal bleeding compared to prior studies in singletons may be that pregnancies complicated by vaginal bleeding that resulted in loss prior to anatomic survey were not included. Lastly, given that our institution is a tertiary care referral center with a large proportion of high-risk pregnancies, reflected by the rates of preeclampsia and preterm birth in the cohort, the results of the study may not be applicable to all populations.

In our study, we found that the incidence of reported early vaginal bleeding in continuing twin pregnancies is 8.3%, which is lower than reports in the literature in singleton gestations. Similar to singletons, however, women carrying twins who report vaginal bleeding early in pregnancy are at increased risk of abruption, PPROM, and preterm birth <34 weeks. In our cohort, surprisingly, women with monochorionic twin pregnancies were less likely to report vaginal bleeding. This may be related to higher early loss rate after vaginal bleeding, however, future studies are needed. With this information, physicians will be better equipped to specifically counsel women carrying twin pregnancies complicated by vaginal bleeding rather than relying on previous studies that have evaluated only singleton pregnancies. Further, this patient population is an at-risk group for preterm birth and may represent a reasonable target population for intervention trials to reduce the risk of preterm birth. ■

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