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Bleeding per vaginam is associated with funisitis in women with preterm, prelabour rupture of the fetal membranes

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Abstract

Objective—The objective of this study was to evaluate the risk of funisitis among women with preterm, prelabour rupture of the membranes (PPROM) and subsequent bleeding per vaginam (pv).

Design—Prospective cohort study.

Setting—University Hospital in the United States.

Population—157 women with PPROM, divided into those with bleeding pv during the hospital admission (46) and those without bleeding pv (111).

Methods—Pathologist blinded to bleeding pv status assessed placental pathology for funisitis.

Main Outcome Measures—Funisitis.

Results—Women with bleeding pv were more likely to have funisitis (67.4% vs. 36%, $p < 0.001$) compared to those without bleeding. Logistic regression demonstrated that bleeding pv predicted funisitis after controlling for gestational age at admission, latency period and gestational age of delivery.

Conclusions—Among women with PPROM, those with bleeding pv are more likely to have funisitis than those without bleeding pv.

Keywords

funisitis; pregnancy; PPROM; preterm premature rupture of the membranes; vaginal bleeding

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DISCLOSURE OF INTERESTS

None reported

CONTRIBUTION OF AUTHORSHIP

CAG analyzed the data, performed statistical analysis and wrote the manuscript; LNCJ collected data and wrote the manuscript; CBF analyzed the data and wrote the manuscript; RPH wrote the manuscript and provided reagents; GKS analyzed the data and wrote the manuscript; APM designed the study, obtained funding, recruited subjects, analyzed the data, performed statistical analysis and wrote the manuscript. All authors approved the final version of the manuscript.

INTRODUCTION

Preterm, prelabour rupture of membranes (PPROM) accounts for one third of premature deliveries. In the United States, PPRM occurs in 2–3% of all pregnancies and affects more than 120,000 pregnancies annually.¹ Amnionitis and placental abruption are common in women with PPRM, affecting 13–60% and 4–12% of pregnancies complicated by PPRM, respectively.¹ Histologic chorioamnionitis represents a maternal inflammatory response, while funisitis represents a fetal response to inflammation. Funisitis represents the infiltration of fetal immune cells into the umbilical cord, and is more closely associated with adverse neonatal outcome compared to chorioamnionitis alone^{2–10}. While funisitis is thought to be a late manifestation of chorioamnionitis, clinical symptoms of chorioamnionitis – fever and fundal tenderness -- are also late manifestations, and may not always occur despite histologic confirmation of chorioamnionitis. This situation presents a dilemma for obstetricians when attempting to manage PPRM patients expectantly.

Bleeding per vaginam (pv) in pregnancy has also been associated with poor pregnancy outcomes, including preterm delivery and PPRM. Bleeding pv in the first trimester doubles the risk for preterm delivery.¹¹ Furthermore, Harger et al demonstrated that bleeding pv in more than one trimester increases the odds for PPRM greater than seven-fold.¹² Although, the mechanism by which bleeding pv increases the risk for PPRM is not completely understood, disorders in decidual hemostasis are thought to play an important role.^{13–15} Placental abruption has also been associated with intrauterine infection. Several studies have shown that women with placental abruption have a higher rate of histological chorioamnionitis and funisitis.^{16,17} Women with idiopathic bleeding during pregnancy also demonstrate an increase incidence of chorioamnionitis and funisitis as compared to women with no bleeding in pregnancy.^{18,19} Women with PPRM are in a unique situation in that the risk of infection and risk for placental abruption is much higher once rupture has occurred, yet our ability to predict which PPRM subjects are at greatest risk of developing infection is limited.

We hypothesize that women with PPRM and bleeding pv are at increased risk for funisitis. The objective of this secondary analysis was to determine if women with PPRM who have bleeding pv during their hospitalization are at increased risk for funisitis at delivery compared to women with PPRM without bleeding pv.

METHODS

This study is a secondary analysis of a prospective cohort study of women hospitalized with PPRM at Duke University Medical Center from July 1997 through April 2007. The PPRM trial was approved by the Duke Institutional Review Board, and informed consent was obtained from all participants. PPRM was diagnosed with vaginal pooling of amniotic fluid or positive phenolphthalein (Nitrazine, Bristol-Myers Squibb, New York, NY) testing and positive fern testing. Women were excluded for active labour with cervical dilatation greater than 3 cm, clinical chorioamnionitis or evidence of extrauterine infection and known congenital malformation incompatible with life. At the time of presentation with PPRM, women with signs or symptoms of clinical chorioamnionitis were excluded and immediately delivered. The primary objective of the PPRM trial was to determine how maternal serum inflammatory markers changed during the latency period. Daily blood samples were obtained by Duke University General Clinical Research Center nurses and banked for cytokine analysis. Demographic data, delivery data, and neonatal outcomes were recorded. For this secondary analysis, subjects were divided into those with and without bleeding pv at some point during their antepartum hospital admission. Bleeding pv was defined as the presence of blood per vaginam at any time during the hospital admission for PPRM that

was noted in the hospital record by either nursing or physician staff. Funisitis was defined as the presence of neutrophils within the stroma of the umbilical cord. Histological confirmation of funisitis was determined after delivery upon routine placental examination by one of the staff pathologists at Duke University Medical Center. The pathologist was unaware of the patient's bleeding pv status.

Demographic and outcome data were collected and compared using Student t-test for continuous variables and categorical variables were compared using chi-square or Fisher's exact where appropriate. Logistic regression modeling was utilized to control for potential confounding and results reported as odds ratios and 95% confidence intervals. Data was analyzed using JMP for Macintosh (version 8.0.1, SAS Institute, Inc, Cary, NC). Survival analysis was performed for the predictors bleeding pv and funisitis on length of latency in days using GraphPad Prism for Macintosh (version 5.0a, GraphPad Software, San Diego, CA, USA) and JMP for Macintosh (version 8.0.1, SAS Institute, Inc, Cary, NC). Significance for all calculations was determined with a p-value < 0.05.

RESULTS

There were 169 women enrolled in the prospective PPRM trial with demographic and delivery data available for analysis. Of these 169 women, 157 women (92.9%) had placental pathology data available for the presence or absence of funisitis and the presence or absence of bleeding pv during the hospitalization for PPRM recorded.

Of the 157 subjects analyzed, 46 (29.3%) had bleeding pv during the hospital admission. There were no differences in race, insurance status, marital status, smoking history, prior history of preterm delivery, or use of cerclage among women with or without bleeding pv (Table 1). Women with bleeding pv were admitted with PPRM at an earlier gestational age compared to women without bleeding pv (Table 1). There were no differences between the groups in mode of delivery or length of latency period (Table 2). Women with bleeding pv delivered at an earlier gestational age compared to women without bleeding pv (28.6 ± 3.0 vs. 30.7 ± 3.4 weeks, $p < 0.001$). (Table 2) The positive predictive value (PPV) for bleeding pv and funisitis was 67.4% and the negative predictive value (NPV) for lack of bleeding pv and absence of funisitis was 67.6%.

There were no differences in the rate of clinically diagnosed chorioamnionitis between the two groups but women with bleeding pv were more likely to have pathologically diagnosed chorioamnionitis. In addition, women with bleeding pv had higher rates of funisitis compared to women without bleeding pv (Table 2). Univariate logistic regression was performed to calculate the odds ratios for various predictors for the outcome funisitis (Table 3). Multiple logistic regression demonstrated that bleeding pv predicted funisitis while controlling for gestational age at admission, length of latency, gestational age of delivery, mode of delivery, tobacco use, insurance and marital status, use of cerclage and history of prior preterm birth (Table 3).

Survival analysis for the predictors bleeding pv and funisitis were performed for the outcome, admission with PPRM to delivery (latency period). There was no difference in the survival curves for latency between women with and without bleeding pv ($p = 0.8297$ by Log-rank/Mantel-Cox analysis). For women with funisitis, there was a trend to shorter latency period, though the association was not statistically significant compared to women without funisitis ($p = 0.074$ by log-rank/Mantel-Cox analysis) (Figures 1 and 2). The survival analysis was then repeated using a Cox Proportional Hazards model. While controlling for gestational age at delivery, there were no differences in the survival curves for latency

between women with and without bleeding pv ($p=0.442$) and in the survival curves for latency between women with and without funisitis ($p=0.275$).

DISCUSSION

Women with PPRM whose admission is complicated by the presence of bleeding pv are more likely to deliver at an earlier gestational age and are more likely to deliver a baby with funisitis compared to women without bleeding pv. Bleeding pv in the setting of PPRM is most likely due to placental abruption and decidual necrosis as a result of intra-amniotic infection.

In 2005, Gomez et al conducted a retrospective cohort study of 114 women presenting with idiopathic bleeding pv and intact membranes.¹⁸ All women who underwent amniocentesis upon admission for evaluation of intrauterine infection were included. Women with positive amniotic fluid culture delivered at lower gestational age, were at increased risk of developing subsequent PPRM, and exhibited a higher rate of acute funisitis. Furthermore, women presenting with idiopathic bleeding pv <28 wks were more likely to have positive amniotic fluid culture compared to women > 28 wks. They concluded that intraamniotic infection is a risk factor for bleeding pv and subsequent PPRM and PTD.

Weiner et al performed proteomic analysis on amniotic fluid obtained from women undergoing amniocentesis prior to rescue cerclage placement and compared the proteome to a cohort of women undergoing genetic amniocentesis. Women requiring a rescue cerclage were more likely to have hemoglobin peaks found in the proteomic analysis obtained from the amniotic fluid compared to controls, suggesting the presence of decidual hemorrhage and intraamniotic bleeding. Furthermore, of women having a rescue cerclage, women with hemoglobin peaks identified on the amniotic fluid proteome had shorter latency and shorter prolongation of pregnancy compared to those women without hemoglobin peaks.²⁰

De Felice et al conducted a case control study comparing women with bleeding in either the first or second trimester compared to women without bleeding in pregnancy. Patients with bleeding pv had a higher rate of histological chorioamnionitis, decreased gestational age at delivery, increased incidence of preterm delivery, and decreased birth weight.¹⁹ In addition, recent work demonstrates that women with placenta previa who present with idiopathic bleeding pv are at risk for intra-amniotic infection and/or inflammation and preterm delivery.²¹ Together, the evidence suggest that the presence of bleeding pv during pregnancy increases the risk for intra-amniotic infection and/or inflammation and for preterm delivery

Ascending infection has been implicated as a possible etiology for PPRM. The inflammatory response associated with ascending infection may lead to deciduitis and bleeding pv.¹⁸ Bleeding pv associated with PPRM and infection is most likely secondary to placental abruption. Decidual activation from inflammation has been shown to increase decidual production of tissue factor, which is a potent pro-coagulant and leads to the formation of thrombin.^{13,15,22} Thrombin then promotes extra-cellular matrix degradation of the fetal membranes through the activation of matrix metalloproteinases (MMPs) and leads to neutrophil recruitment which in turn increases local cytokine activity.^{13,14} Furthermore, there is an increase in apoptosis among cells within the fetal membranes.^{23,24} Together, MMP-mediated collagenase activity and increases in cellular apoptosis lead to membrane weakening and PPRM.²⁵ Furthermore, thrombin has been shown to be a potent uterotonic agent, and together with the effects on fetal membrane integrity, may further increase the risk for preterm delivery.²⁶ Attempting to determine the timeline of association

between PPROM, bleeding pv and infection is difficult. Extensive research suggests that infection leads to placental abruption which results in PPROM and preterm delivery.

The findings of our study, further describe the association of bleeding pv with fetal markers of inflammation in the setting of PPROM. There is clinical significance in these findings. First, our population demonstrated a low incidence of clinically diagnosed chorioamnionitis despite having PPROM. Subsequently, the rate of histologic chorioamnionitis was quite high and in agreement with the published literature. This discrepancy is not unique to our study but further elaborates the need for markers of impending infection in women with PPROM. The presence of bleeding pv in women with PPROM, in combination with other clinical markers for chorioamnionitis, should alert providers to the increased risk for fetal inflammation and adverse neonatal outcomes. Despite the high rate of histologic chorioamnionitis and funisitis among PPROM subjects with bleeding pv, not all subjects with bleeding pv had signs of infection. Clinically, the findings of our study alert providers that women with PPROM who experience bleeding pv during hospitalization are at increased risk for delivering a fetus with fetal inflammation, which increases the risk for poor neonatal outcome.

Although our study represents a large cohort of women with PPROM who were prospectively enrolled, this is a secondary analysis of data. As a result, there are potential outcome variables that would be of interest that were not collected. Bleeding pv was defined as an episode that took place during hospitalization. Data are not available regarding episodes of bleeding pv prior to admission, nor the timing of bleeding pv during the hospitalization relative to delivery. The association of bleeding pv with funisitis may represent infection-induced decidual necrosis, though other causes of bleeding pv that are not due to infection cannot be determined. Furthermore, approximately 8% of women in the study did not have results for placental pathology. Finally, funisitis was treated as a categorical variable as the presence or absence of neutrophils within the stroma of the umbilical cord, rather than as a scaled variable based on the severity of funisitis.

Although there was a higher rate of funisitis and pathologically diagnosed chorioamnionitis in women with bleeding pv, there was not a difference in the rate of clinically diagnosed chorioamnionitis between the two groups. In addition, the rate of clinical chorioamnionitis in each group was low (15.2% and 17.1% in women with bleeding pv and without, respectively), while the rate of significant pathologic chorioamnionitis was quite high (78.3% and 46.8% in women with bleeding pv and without, respectively). Other studies have also found a poor correlation of histologic chorioamnionitis with clinical chorioamnionitis.^{27–30}

CONCLUSION

This analysis demonstrates that bleeding pv occurring during an antepartum admission for PPROM increases the risk for funisitis in the neonate. Among women with PPROM and bleeding pv, amniocentesis may be considered to determine the presence of intramniotic infection and guide decisions to proceed with delivery. Further research is needed to determine if bleeding pv and funisitis have an impact on rate of adverse neonatal outcomes.

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DETAILS OF ETHICS APPROVAL

This study was approved by the Institutional Review Board of Duke University (IRB #: 00011591 and IRB# 00011659 and has remained active since initiation of the study.

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Figure 1.
Survival analysis for predictor bleeding pv on latency period.

Figure 2.
Survival analysis for predictor funisitis on latency period.

Table 1

Demographic data

	Bleeding pv n=46	No bleeding pv n=111	<i>p</i>-value^b
Race, n (%)			0.357
Caucasian	18 (39.1)	42 (37.8)	
African American	25 (54.3)	59 (53.2)	
Hispanic	1 (2.2)	5 (4.5)	
Other/Unknown	2 (4.3)	5 (4.5)	
Medicaid Insurance, n (%)	22 (47.8)	58 (52.3)	0.800
Single, n (%)	18 (39.1)	58 (52.3)	0.202
Tobacco use, n (%)	9 (19.6)	23 (20.7)	0.870
Prior preterm del, n (%)	11 (23.9)	27 (24.3)	0.956
Cerclage, n (%)	4 (8.7)	9 (8.1)	0.916
Multiple gestation, n (%)	1 (2.2)	1 (0.9)	0.511
Gestational age admission, weeks ^a	26.5 ± 3.2	28.7 ± 3.6	<0.001

^aValues are mean ± SD

^bComparisons made by Student t-test for continuous variables; chi-square or Fisher's exact for categorical variables

Table 2

Delivery Outcomes

	Bleeding pv n=46	No bleeding pv n=111	p-value^c
Gestational age delivery, weeks ^a	28.6 ± 3.0	30.7 ± 3.4	<0.001
Latency period, days ^a	15.0 ± 13.5	14.3 ± 13.1	0.791
Birth weight, g ^a	1239 ± 516	1585 ± 638	<0.001
Cesarean delivery, n (%)	21 (45.7)	44 (39.6)	0.515
Preeclampsia, n (%)	0 (0)	1 (0.9)	0.402
Clinical chorioamnionitis, n (%)	7 (15.2)	19 (17.1)	0.903
Pathologic chorioamnionitis ^b , n (%)	36 (78.3)	52 (46.8)	<0.001
Funisitis, n (%)	31 (67.4)	36 (32.4)	<0.001

^aValues are mean ± SD

^bModerate or greater, Stage 2 or greater

^cComparisons made by Student t-test for continuous variables; chi-square or Fisher's exact for categorical variables

Table 3

Unadjusted and adjusted logistic regression analysis for outcome funisitis

Predictor	Denom/Numerator of OR	OR ^a (95% CI) <i>p</i> -value	aOR ^b (95% CI) <i>p</i> -value
Bleeding pv	Yes/no	4.31 (2.07, 8.97) <0.001	3.34 (1.43, 8.09) 0.005
Gestational age admission, weeks	1 week decrease	1.27 (1.15, 1.41) <0.001	1.01 (0.67, 1.55) 0.954
Latency, days	1 day decrease	1.02 (0.99, 1.06) 0.073	1.02 (0.97, 1.07) 0.523
Gestational age delivery, weeks	1 week decrease	1.34 (1.21, 1.52) <0.001	1.32 (0.86, 2.06) 0.195
Mode of delivery	Cesarean/vaginal	1.06 (0.55, 2.01) 0.870	1.27 (0.57, 2.92) 0.562
Tobacco use	Yes/no	0.90 (0.40, 1.97) 0.792	0.82 (0.29, 2.28) 0.699
Insurance status	Private/Medicaid	1.31 (0.69, 2.49) 0.406	1.11 (0.39, 3.23) 0.848
Marital status	Single/married	1.25 (0.66, 1.51) 0.488	1.24 (0.44, 3.53) 0.683
Cerclage	Yes/no	3.30 (1.02, 12.67) 0.046	2.08 (0.46, 10.26) 0.341
Prior preterm birth	Yes/no	1.48 (0.84, 1.76) 0.296	1.53 (0.61, 3.84) 0.360

^a Unadjusted OR^b Adjusted OR. Adjusted OR's were calculated for each listed predictor, while controlling for all other predictors in the listed table. This was then repeated for each predictor.