

Risk of preterm delivery in relation to vaginal bleeding in early pregnancy

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Abstract

Objective: To examine the relationship between vaginal bleeding during early pregnancy and preterm delivery.

Methods: Study subjects ($N = 2678$) provided information regarding socio-demographic, biomedical, and lifestyle characteristics. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI).

Results: Any vaginal bleeding in early pregnancy was associated with a 1.57-fold increased risk of preterm delivery (95% CI: 1.16–2.11). Vaginal bleeding was most strongly related with spontaneous preterm labor (OR = 2.10) and weakly associated with preterm premature rupture of membrane (OR = 1.36) and medically induced preterm delivery (OR = 1.32). As compared to women with no bleeding, those who bled during the first and second trimesters had a 6.24-fold increased risk of spontaneous preterm labor; and 2–3-fold increased risk of medically induced preterm delivery and preterm premature rupture of membrane, respectively.

Conclusion: Vaginal bleeding, particularly bleeding that persists across the first two trimesters, is associated with an increased risk of preterm delivery.

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1. Introduction

Preterm delivery, delivery before 37 weeks gestation, complicates approximately 12% of all pregnancies and is a major determinant of perinatal morbidity and infant mortality [1]. As previously reported, first trimester vaginal bleeding was associated with a two-fold increased risk of preterm delivery [2]. These findings were corroborated by several other investigators [3–6] and are consistent with conclusions drawn from a meta-analysis on the subject [7].

Few studies have attempted to evaluate risk of specific preterm delivery sub-types (e.g., spontaneous preterm labor, preterm premature rupture of membranes and medically induced preterm delivery) [5,6]. A small emergent literature suggests the merits of evaluating putative preterm delivery risk factors, such as vaginal bleeding, for each of the major subtypes of preterm delivery, as well as for moderate and very preterm delivery, respectively [3–6]. Collectively, available data suggest possible heterogeneity of associations of preterm delivery subtypes with vaginal bleeding. Specifically, it appears that vaginal bleeding may be more strongly related with preterm premature rupture of the membranes, and very preterm delivery [3,4,6] than with other preterm delivery subtypes. On the basis of this emerging evidence, we used data from a large cohort to further evaluate the relation between vaginal bleeding during

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the first and second trimester with preterm delivery. We also completed stratified analyses in attempts to account for the possible heterogeneity in the etiology of preterm delivery [8–11].

2. Methods

2.1. *The Omega Study and study population*

The population for the present analysis was drawn from the participants of the Omega Study, a prospective cohort study of maternal dietary and other risk factors of adverse pregnancy outcomes including preeclampsia, gestational diabetes mellitus and preterm delivery. Women participating in the study attended prenatal care clinics affiliated with Swedish Medical Center (Seattle) and Tacoma General Hospital (Tacoma), in Washington State between December 1996 and October 2004. Women eligible for inclusion were those who initiated prenatal care prior to 20 weeks gestation, were 18 years of age or older, could speak and read English, and planned to carry the pregnancy to term and to deliver at either of the two study hospitals.

Enrolled participants were asked to take part in an hour-long interview in which trained research personnel used a structured questionnaire to elicit information regarding maternal socio-demographic and anthropometric characteristics, lifestyle habits, and medical and reproductive histories. Pregnancy outcome information was ascertained by reviewing participants' hospital labor and delivery medical records and clinic records after delivery. The procedures used in this study were approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital. All participants provided written informed consent.

During the study period, 3896 eligible women were approached, and 3000 (77%) agreed to participate. One hundred and fifty-two women who were lost to follow-up (delivery outcome unknown or medical record not found) were excluded from this analysis. Also excluded were women who experienced an abortion or fetal demise prior to 28 weeks of gestation ($n = 60$), and those with multi-fetal pregnancies ($N = 110$). A cohort of 2678 women remained for analysis.

2.2. *Pregnancy outcome, vaginal bleeding and other covariates*

The diagnosis of preterm delivery was made using American College of Obstetricians and Gynecologists (ACOG) guidelines [12]. Gestational age was based on the last menstrual period (LMP) and confirmed by ultrasound examination, conducted prior to 20 weeks gestation. If both LMP and ultrasound dating were available and the two agreed within 14 days, the former was used to assign gestational age. If the two dates differed by more than

14 days, the ultrasound date was used. A total of 233 preterm delivery cases were identified; of these 2 were subsequently excluded because information concerning the presence or absence of vaginal bleeding in pregnancy was not available. Using detailed information collected from medical records, preterm delivery cases were categorized according to the three pathophysiological groups previously described (i.e., spontaneous preterm labor and delivery, preterm premature rupture of membranes, and medically induced preterm delivery) [8,10,11]. Preterm delivery cases were also categorized according to gestational age at delivery (i.e., very preterm delivery, defined as delivery prior to the completion of 34 weeks gestation; and moderate preterm delivery, defined as delivery between 34 and 36 weeks gestation).

Using a structured questionnaire, interviewers collected information on maternal socio-demographic, behavioral, and medical characteristics, including vaginal bleeding during pregnancy. Interviewers asked participants to report if they experienced vaginal bleeding during the first and second trimester, respectively. Covariate information included maternal age, reproductive and medical histories, information on maternal educational attainment, annual household income, occupation, as well as smoking and alcohol consumption during pregnancy.

Women who reported no bleeding in the first and second trimesters comprised the referent group. Women who reported vaginal bleeding during either trimester were classified as having bled during pregnancy. A four-category variable was created to allow for the identification of women who never bled; bled in first trimester only, bled in second trimester only; and bled in both first and second trimesters. Maternal age at the time of interview was expressed in years. Parity was reported as the number of previous pregnancies lasting beyond 20 weeks gestation.

2.3. *Statistical analysis*

We first explored frequency distributions of maternal socio-demographic characteristics, medical and reproductive histories. Chi-square tests were used to evaluate differences in distribution of covariates according to preterm and term delivery status. To estimate the relative association between vaginal bleeding and risk of preterm delivery, logistic regression procedures were used to calculate maximum likelihood estimates of odds ratios (OR) and 95% confidence intervals (95% CI), and adjusted for potential confounding factors [13]. Confounders were defined as those factors which altered unadjusted odds ratios by at least 10%. Maternal marital, employment and smoking status during pregnancy were not confounders in this study population. These analytical procedures were also used in stratified analyses designed to assess risks of sub-types of preterm delivery (i.e., spontaneous preterm labor, preterm premature rupture of membrane, medically induced preterm delivery, very preterm delivery and moderate preterm delivery). Statistical analyses

Table 1

Characteristics of study members according to preterm delivery case and control status, Seattle and Tacoma, WA, 1996–2004

| Characteristic | Controls (n = 2445) | | Preterm cases (n = 233) | | p-Value |
|--|------------------------|------|----------------------------|------|---------|
| | n | % | n | % | |
| Maternal age (years) | | | | | |
| <20 | 15 | 0.6 | 5 | 2.1 | 0.008 |
| 20–34 | 1666 | 68.1 | 139 | 59.7 | |
| ≥35 | 658 | 26.9 | 70 | 30.0 | |
| Missing | 106 | 4.3 | 19 | 8.2 | |
| Maternal ethnicity | | | | | |
| White | 2001 | 81.8 | 182 | 78.1 | 0.524 |
| African American | 40 | 1.6 | 6 | 2.6 | |
| Other | 279 | 11.4 | 26 | 11.2 | |
| Missing | 125 | 5.1 | 19 | 8.2 | |
| Unmarried | 206 | 8.8 | 24 | 11.2 | 0.240 |
| ≤12 years education | 97 | 4.1 | 13 | 6.1 | 0.184 |
| Nulliparity | 1473 | 60.2 | 143 | 61.4 | 0.737 |
| Smoking during pregnancy | 140 | 5.7 | 18 | 7.7 | 0.216 |
| Pre-pregnancy body mass index (kg/m ²) | | | | | |
| <20.0 | 423 | 17.3 | 28 | 12.0 | <0.001 |
| 20.0–24.9 | 1331 | 54.4 | 119 | 51.1 | |
| 25.0–29.9 | 372 | 15.2 | 29 | 12.4 | |
| ≥30.0 | 197 | 8.1 | 36 | 15.5 | |
| Missing | 122 | 5.0 | 21 | 9.0 | |
| Annual household income (\$) | | | | | |
| <30,000 | 87 | 3.6 | 10 | 4.3 | 0.029 |
| 30,000–69,999 | 506 | 20.7 | 62 | 26.6 | |
| ≥70,000 | 1680 | 68.7 | 136 | 58.4 | |
| Missing | 172 | 7.0 | 25 | 10.7 | |
| Work during pregnancy | 1905 | 81.7 | 167 | 78.0 | 0.184 |
| Physical activities during pregnancy | 1983 | 84.8 | 186 | 86.9 | 0.410 |

were performed using SPSS (Version 14.0, SPSS Inc., Chicago, IL, USA) software. All reported p-values are two tailed, and confidence intervals were calculated at the 95% level.

Table 2

Odds ratio (OR) and 95% confidence intervals (CI) of the association between vaginal bleeding and risk of preterm delivery, Seattle and Tacoma, WA, 1996–2004

| | Controls (n = 2445) | | Preterm cases (n = 233) | | Unadjusted OR (95% CI) | Adjusted OR ^a (95% CI) |
|-----------------------|---------------------|------|-------------------------|------|------------------------|-----------------------------------|
| | n | % | n | % | | |
| Vaginal bleeding | | | | | | |
| No | 1807 | 74.4 | 149 | 64.5 | 1.00 (referent) | 1.00 (referent) |
| Yes | 622 | 25.6 | 82 | 35.5 | 1.60 (1.20–2.13) | 1.57 (1.16–2.11) |
| Trimester of bleeding | | | | | | |
| No | 1807 | 74.7 | 149 | 65.6 | 1.00 (referent) | 1.00 (referent) |
| First trimester only | 520 | 21.5 | 64 | 28.2 | 1.49 (1.10–2.03) | 1.40 (1.04–2.00) |
| Second trimester only | 64 | 2.6 | 7 | 3.1 | 1.33 (0.60–2.95) | 1.40 (0.63–3.15) |
| Both trimesters | 28 | 1.2 | 7 | 3.1 | 3.03 (1.30–7.10) | 3.29 (1.31–8.24) |

Sixteen controls and two cases were not included in the analysis of vaginal bleeding because of missing data. Twenty-six controls and six cases were not included in the analysis of trimester of vaginal bleeding occurrence because of missing data.

^a Adjusted for maternal age (continuous), nulliparity (yes/no), ethnicity (white, African American, other), education and smoking during pregnancy.

3. Results

Approximately 26% of women in this cohort of women with singleton pregnancies reported experiencing vaginal bleeding during the first or second trimester. Women who delivered preterm were older, reported having lower annual household income, and were heavier prior to the index pregnancy than women who delivered at term (Table 1). The two study groups were similar with regards to maternal race/ethnicity, marital status, and educational attainment. The groups were also similar with regards to their employment status, smoking and physical activity habits during pregnancy.

Any vaginal bleeding during early pregnancy was associated with a 60% increased risk of preterm delivery, overall (OR = 1.60, 95% CI: 1.20–2.13) (Table 2). This association remained after adjustments for potential confounding by maternal age, race/ethnicity, educational attainment, and smoking status during pregnancy (OR = 1.57, 95% CI: 1.16–2.11). As can be seen in Table 2, the vaginal bleeding-preterm delivery association was more pronounced for women who bled during both the first and second trimesters as compared with women who did not bleed (OR = 3.29, 95% CI: 1.31–8.24).

The relationship between vaginal bleeding and preterm delivery subtypes was also evaluated. Preterm delivery subtypes were defined as spontaneous preterm labor, preterm premature rupture of membrane, and medically induced preterm delivery. In this cohort 37.3% of preterm deliveries were preceded by spontaneous preterm labor; approximately 33.9% were preceded by preterm premature rupture of membrane and the remaining 28.9% were delivered preterm after medical intervention. Any vaginal bleeding during pregnancy was most strongly associated with spontaneous preterm delivery (OR = 2.10, 95% CI: 1.31–3.35). Women with bleeding during both trimesters as compared to those that did not bleed were 6.2 times more likely to experience spontaneous preterm labor (95% CI: 1.74–22.36). Vaginal bleeding, particularly bleeding in both the first and second trimesters, was associated with an

Table 3

Odds ratio (OR) and 95% confidence intervals (CI) of the association between vaginal bleeding and preterm delivery risk according to subtype, Seattle and Tacoma, WA, 1996–2004

| | Controls <i>n</i> | Spontaneous preterm delivery | | Preterm premature rupture of membranes | | Medically indicated preterm delivery | |
|-----------------------|----------------------|------------------------------|--------------------------|--|--------------------------|--------------------------------------|--------------------------|
| | | <i>n</i> | OR ^a (95% CI) | <i>n</i> | OR ^b (95% CI) | <i>n</i> | OR ^c (95% CI) |
| Vaginal bleeding | | | | | | | |
| No | 1807 | 54 | 1.00 (referent) | 52 | 1.00 (referent) | 43 | 1.00 (referent) |
| Yes | 622 | 33 | 2.10 (1.31–3.35) | 27 | 1.36 (0.82–2.24) | 22 | 1.32 (0.74–2.38) |
| Trimester of bleeding | | | | | | | |
| No | 1807 | 54 | 1.00 (referent) | 52 | 1.00 (referent) | 43 | 1.00 (referent) |
| First trimester only | 520 | 26 | 2.00 (1.20–3.31) | 21 | 1.25 (0.72–2.17) | 17 | 1.17 (0.62–2.25) |
| Second trimester only | 64 | 2 | 1.52 (0.36–6.48) | 3 | 1.54 (0.46–5.21) | 2 | 1.10 (0.23–5.33) |
| Both trimesters | 28 | 3 | 6.24 (1.74–22.36) | 2 | 3.52 (0.79–15.72) | 2 | 2.07 (0.27–15.92) |

Sixteen controls and two cases were not included in the analysis of vaginal bleeding because of missing data. Twenty-six controls and six cases were not included in the analysis of trimester of vaginal bleeding occurrence because of missing data.

^a Adjusted for maternal age (<20, 20–34, 35+), education, income, ethnicity (white, African American, other), physical activity, pre-pregnancy body mass index.

^b Adjusted for maternal age (<20, 20–34, 35+), nulliparity (yes/no), ethnicity (white, African American, other), income, pre-pregnancy body mass index.

^c Adjusted for maternal age (<20, 20–34, 35+), education, income, ethnicity (white, African American, other), physical activity, pre-pregnancy body mass index.

Table 4

Odds ratio (OR) and 95% confidence intervals (CI) of the association between vaginal bleeding and preterm delivery (PTD) risk according to severity, Seattle and Tacoma, WA, 1996–2004

| | Controls <i>n</i> | Moderate PTD (34–36 weeks) | | Very PTD (<34 weeks) | |
|-----------------------|----------------------|----------------------------|------------------------------|----------------------|------------------------------|
| | | <i>n</i> | OR (95% CI) | <i>n</i> | OR (95% CI) |
| Vaginal bleeding | | | | | |
| No | 1807 | 125 | 1.00 (referent) ^a | 24 | 1.00 (referent) ^a |
| Yes | 622 | 69 | 1.74 (1.25–2.41) | 13 | 1.34 (0.64–2.80) |
| Trimester of bleeding | | | | | |
| No | 1807 | 125 | 1.00 (referent) ^a | 24 | 1.00 (referent) ^b |
| First trimester only | 520 | 56 | 1.63 (1.15–2.33) | 8 | 1.04 (0.44–2.46) |
| Second trimester only | 64 | 6 | 1.61 (0.67–3.87) | 1 | 1.10 (0.14–8.37) |
| Both trimesters | 28 | 4 | 3.13 (1.05–9.38) | 3 | 6.46 (1.41–29.68) |

Sixteen controls and two cases were not included in the analysis of vaginal bleeding because of missing data. Twenty-six controls and six cases were not included in the analysis of trimester of vaginal bleeding occurrence because of missing data.

^a Adjusted for maternal age (<20, 20–34, 35+), education, physical activity, income, ethnicity (white, African American, other), pre-pregnancy body mass index.

^b Adjusted for maternal age (continuous), education, income, ethnicity (white, African American, other).

increased risk of preterm premature rupture of membrane (OR = 3.52, 95% CI: 0.79–15.72) and medically induced preterm delivery (OR = 2.07, 95% CI: 0.27–15.92), though these latter associations were not statistically significant (Table 3).

The association between vaginal bleeding and severity of preterm delivery was also studied. In this study population 84% of preterm cases delivered between 34 and 36 weeks gestation (i.e., moderate preterm). The remaining 16% of cases delivered prior to 34 completed weeks of gestation and thus were classified as very preterm deliveries. Any vaginal bleeding during pregnancy was associated with 74% increased risk of moderate preterm delivery (OR = 1.74, 95% CI: 1.25–2.41) and a 34% increased risk of very preterm delivery (OR = 1.34, 95% CI: 0.64–2.80), though only the former association was statistically significant. Bleeding during both trimesters

was associated with a 3.13-fold increased risk of moderate preterm delivery (OR = 3.13, 95% CI: 1.05–9.38); and a 6.46-fold increased risk of very preterm delivery (OR = 6.46, 95% CI: 1.41–29.68) (Table 4).

4. Discussion

Women who bled during early pregnancy experienced a 60% (OR = 1.60, 95% CI: 1.20–2.13) increased risk of delivering preterm, overall. This association was lower than the summary risk estimated reported in a meta-analysis of cohort studies (combined OR = 2.2, 95% CI: 2.1–2.4) [7], but higher than the estimate recently reported by Yang et al. (RR = 1.3, 95% CI: 1.1–1.6) [5]. In this study vaginal bleeding was more strongly related with spontaneous preterm labor (OR = 2.10) than with preterm premature rupture of

membranes (OR = 1.36) and medically induced preterm delivery (OR = 1.32). These findings are dissimilar to those reported by others who concluded that vaginal bleeding is most strongly related with preterm premature rupture of membranes [5]. Vaginal bleeding during both the first and second trimesters was more strongly associated with preterm delivery (OR = 3.29, 95% CI: 1.31–8.24) than bleeding in either trimester alone (OR = 1.4 for first trimester bleeding only; OR = 1.4 for second trimester bleeding only). These findings were largely consistent with others reported results [5]. In their study of women in North Carolina, Yang and colleagues reported that vaginal bleeding in both trimesters was associated with a 2.4-fold increased risk of preterm delivery (95% CI: 1.6–3.6). Consistent with our findings, the authors noted considerably weaker associations for bleeding limited to the first (OR = 1.2) or second (OR = 1.1) only.

Bleeding during both the first and second trimesters was associated with a greater than six-fold increased risk of spontaneous preterm labor and very preterm delivery. These findings are largely similar to those reported by others who have sought to assess risks of specific sub-types of preterm delivery in relation to vaginal bleeding in early pregnancy [2,4–6]. For instance, our results are similar to those reported by Yang and Savitz, who noted that vaginal bleeding in early pregnancy is more strongly associated with preterm delivery before 34 completed weeks' gestation than with moderate preterm delivery (i.e., delivery between 34 and 36 weeks gestation) [6]. Like these authors, it was noted that the risk of preterm delivery was most elevated among women who experienced bleeding during both first and second trimesters. However, these findings are not consistent with results reported by Weiss et al. [4]. In their large study of 16,506 women who participated in a prospective multi-center cohort study, the authors reported that heavy vaginal bleeding during the first trimester was associated with a three-fold increased risk of preterm delivery (OR = 3.0, 95% CI: 1.9–4.5) and a slightly higher risk for preterm premature rupture of membranes (OR = 3.2, 95% CI: 1.8–5.7).

The overall association of vaginal bleeding with preterm delivery (OR = 1.57) noted in our study is well within the range of reported associations from study populations in the US and elsewhere [7,14,15]. In a large prospective study of Korean women, Kim et al. [15] reported that vaginal bleeding during pregnancy was associated with a 2.6-fold increased risk of delivering preterm (OR = 2.6, 95% CI: 1.7–4.2). Variations in the magnitude of reported associations may be attributable to underlying differences in severity, and duration of vaginal bleeding, as well as uncontrolled confounding across studies. It is also possible that variations in the relative proportions of subtypes of preterm delivery across study populations may contribute to the inconsistent results reported to date.

The prospective study design and the very high successful follow-up rate (>90%) of enrolled subjects represent important strengths of our study. Prospective data collection excluded concerns about recall bias of vaginal bleeding.

Nevertheless, several other possible limitations of our study should be considered. First, the possibility that reported results may be confounded by unmeasured risk factors cannot be excluded. Of particular concern was the absence of detailed complete information on genital tract infection during the index pregnancy. Second, the generalizability of our results to other general obstetric populations is likely to be limited since the pregnancies studied were among well educated, predominately non-Hispanic white women. Unlike some investigators [5], we were not able to fully characterize all aspects of vaginal bleeding in pregnancy. For instance, we were not able to assess preterm delivery risk in relation to intensity (volume of blood loss), duration and number of episodes of vaginal bleeding. Misclassification of maternal vaginal bleeding is possible since women may confuse menstrual bleeding with early pregnancy vaginal bleeding. The quality and accuracy of early pregnancy vaginal bleeding may be enhanced with the use of daily pregnancy diaries [16], however, participant burden is very high and the generalizability of such studies may be limited.

Although biological mechanisms for the consistently observed associations between vaginal bleeding in early pregnancy and preterm delivery are currently unknown, available evidence suggest that vaginal bleeding may be a clinical manifestation of sub-clinical intrauterine infection secondary to deciduitis and localized placental hemorrhage [3]. Investigators have speculated that decidual thrombosis, ischemia and necrosis may all lead to vaginal bleeding which can trigger a pro-inflammatory response and stimulate tissue factor release and thrombin formation [3,17–19]. Consequently, thrombin is thought to act as an uterotonic agent that may stimulate uterine contractility leading to spontaneous preterm labor. Alternately, thrombin formation leading to a proteolytic cascade may induce the generation of matrix degrading enzymes implicated in the weakening and increased susceptibility to preterm premature rupture of membranes [3,20,21]. Although available data suggest promising biologically and clinically relevant hypotheses for the bleeding-preterm delivery associations, more studies are needed to identify precise causes of vaginal bleeding in pregnancy. Evidence-based counseling and therapeutic options for treating women with idiopathic vaginal bleeding in early pregnancy may arise from such studies.

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