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VAGINAL BLEEDING DURING THE FIRST 20 WEEKS OF PREGNANCY AND THE RISK OF PRETERM DELIVERY

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VAGINAL BLEEDING DURING THE FIRST 20 WEEKS OF PREGNANCY AND THE RISK OF PRETERM DELIVERY

By

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ABSTRACT

VAGINAL BLEEDING DURING THE FIRST 20 WEEKS OF PREGNANCY AND THE RISK OF PRETERM DELIVERY

By

Veronika Skorokhod

This study examined associations between vaginal bleeding in the first 20 weeks of pregnancy and risk of preterm delivery (PTD) in two ethnic/racial groups. Data were from the Pregnancy Outcomes and Community Health (POUCH) Study (1998-2004, 5 Michigan communities) and included only women enrolled/interviewed at 20-27 weeks of pregnancy (78% of the cohort; 1,735 non-Hispanic White and 619 African-American). Maternal reports of bleeding in the first half of pregnancy were grouped by time of bleeding (weeks 1-13 only; weeks 14-20 +/- weeks 1-13), duration (≤24 hrs; >24 hrs) and amount (spotting/slight; ≥usual menstrual period).

The prevalence of bleeding in weeks 1-20 was similar in non-Hispanic Whites (24.4%) and African-Americans (23.4%). In addition these ethnic/racial groups did not differ with respect to timing, duration and amount of bleeding. The risk of PTD was increased among women who bled in "weeks 14-20 +/- weeks 1-13" (non-Hispanic White odds ratio=2.0), for >24 hrs (non-Hispanic White odds ratio=2.0; African-American odds ratio=1.7), and with amounts "≥ usual menstrual period" (non-Hispanic White odds ratio=2.7; African-American odds ratio=2.2). There were no significant interactions by ethnicity/race. These results suggest that bleeding is associated with increased risk of PTD but ethnic/racial disparities in PTD risk are more strongly linked to pathways that do not involve bleeding in the first 20 weeks of pregnancy.

DEDICATION

To my wonderful parents, who always believe in me

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KEY TO ABBREVIATIONS

APHUO	Antepartum Hemorrhage of Unknown Origin
AVB	Antenatal Vaginal Bleeding
A/OR	Adjusted Odds-Ratio
A/RR	Adjusted Risk-Ratio
BMI	Body Mass Index
BW	Body Weight
CI	Confidence Interval
D/P	During Pregnancy
GA	Gestational Age
GT	Genital Tract
GW	Gestational Week(s)
LMP	Last Menstrual Period
MI	Medically Induced Delivery
N/S	Not Specified
OR	Odds Ratio
PTD	Preterm Delivery
PTL	Preterm Labor
PPROM	Preterm Premature Rupture of Membrane
Ref	Reference Group
RR	Relative Risk
VB	Vaginal Bleeding

CHAPTER 1.

BACKGROUND

1.1 Introduction

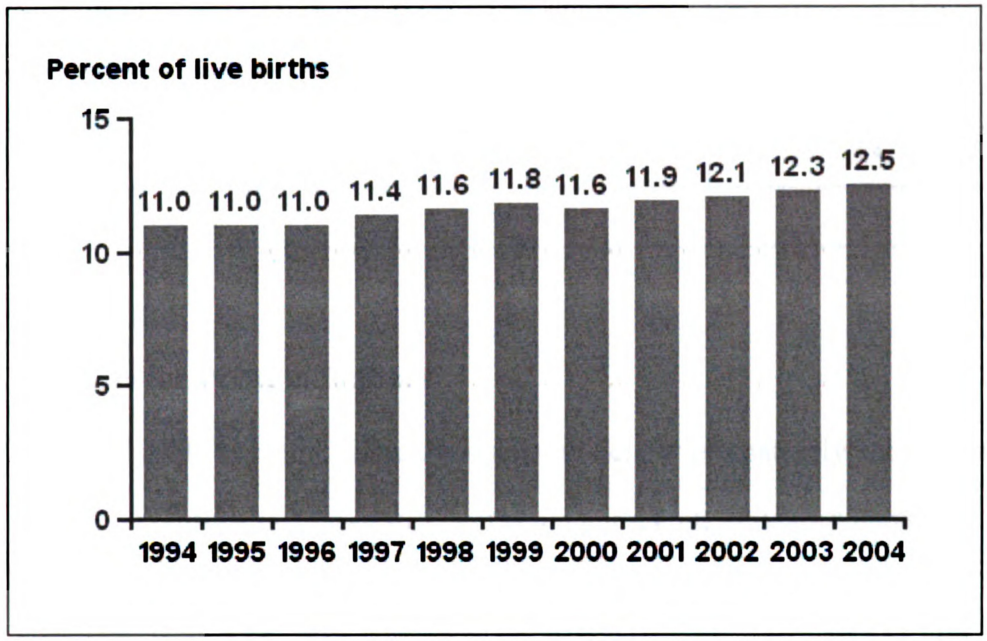
Preterm birth currently remains an important issue in prenatal care, since 70-80% percent of all perinatal deaths and a similar proportion of perinatal illnesses occur in the infants delivered preterm (1,2). The numbers of preterm infants born all over the world remains high and the problem of preterm delivery is by no means resolved. Although a large number of studies have been conducted and many factors that increase the risk of preterm delivery discovered (8,13,19,33) the causes of preterm delivery are not fully understood and, at this time, often little can be done in order to prevent preterm birth.

1.2 Preterm Delivery

Preterm delivery (defined as live birth before 37 completed weeks of pregnancy) is a major public health concern (3). In 2004 in the United States 1 in 8 babies (12.5% of live births) were born prematurely with 2% of these born very prematurely (live birth before 34 completed weeks of pregnancy) (4). Preterm delivery rates are especially high among poor, inner city, and minority pregnant mothers. The rate of preterm birth in the United States in 2002-2004 (average) was the highest for African-American infants (17.6%), followed by Native American (13.4%), Hispanic (11.8%), non-Hispanic White (11.3%), and Asian (10.4%) (4). Despite improvement in many health indicators, the rate of preterm delivery in the US showed no improvement from 1994-2004 (Figure 1.1).

In fact it continues to increase, reaching 12.7% in 2005 (5) and 12.8% in 2006 (6).

Figure 1.1. Preterm Deliveries in the US between 1994 and 2004



Preterm delivery is the second leading cause of infant death in the US. In 2004, 36.5% of all infant deaths in the US were preterm-related (4). Surviving infants are likely to be at a high risk of damage to the central nervous system resulting in serious disorders such as cerebral palsy, chronic respiratory problems and infections, as well as long-term neurological and developmental impairments, mental and cognitive dysfunctions, increased rate of cardiovascular disorders, hypertension, and diabetes. They may end up with lifelong handicaps, varying in degree from slight to severe (Table 1.1).

Table 1.1. Rough Guide for Survival and Handicaps among Premature Babies

Gestational Age at Delivery (weeks)	Survival (%)	Handicaps (%)
24	60	60
26	95	40
28	96	25
30	97	15
32-36	98+	<3

1.3 Risk Factors for Preterm Delivery

It is impossible to predict which women will deliver prematurely but there are risk factors associated with an increased risk, and some but not all of these factors are modifiable. Risk factors for preterm delivery include demographic characteristics, obstetric history, certain maternal medical conditions, and behavioral factors. Demographic factors for preterm delivery include African-American race (4,8), extremes of maternal age (under 17 or over 35 years old) (9-11), low socioeconomic status (12). Obstetric history includes multiple gestations (14,15), short cervix (less than 2 cm at less than 24 weeks of gestation) (16,17), incompetent cervix, malformation of the uterus (8), certain birth defects in a baby, and previous history of preterm delivery (18). Maternal medical conditions include diabetes (28), hypertension (32,33), clotting disorders (64,72-74). Infections in genitourinary tract also pose a risk (8,19-25). Behavioral factors include smoking during pregnancy (22-24), alcohol consumption in pregnancy (8,13), illegal drug use (especially cocaine) while pregnant (25,26), low pre-pregnancy weight, obesity (28,29), low or excessive weight gain during pregnancy (8).

In addition preterm delivery can be associated with stressful life situations and certain occupational factors. Some studies have found an association between high levels of stress caused by anxiety, depression, major life events, such as loss of a job, death of a family member, divorce, and higher rates of delivering preterm (13,27-30). The theory is that severe stress can lead to the release of hormones that can trigger uterine contractions and subsequent preterm delivery. There is evidence that extremely physically demanding jobs or long working hours play a role in preterm delivery. Women who had to stand for long periods of time (over 40 hours per week) or had extremely tiring jobs were more likely to deliver preterm (31,32).

Despite the progress in the field of obstetrics and gynecology, the predictive value of currently substantiated risk factors for preterm delivery is rather low and there are no effective treatments to substantially prolong gestation once preterm labor begins.

1.4 Ethnicity/Race and Preterm Delivery

The risk of preterm delivery varies among women in different ethnic/racial groups. African-American women are at the highest risk of delivering preterm followed by Native American and Hispanic women. The risk is the lowest for Asian and non-Hispanic White women (4,50). Furthermore women born in the US (except for some Asian and non-Hispanic White) are at a higher risk of delivering preterm compared to foreign-born women of the same ethnicity/race (50,51).

It seems that father's ethnicity/race may also affect pregnancy outcomes (51,53). Compared to women partnered with men of the same race, non-Hispanic White women partnered with African-American men are at a higher risk of delivering preterm; however

African-American women partnered with White men do not appear to be at an elevated risk (51). While black women in general are known to have the highest risk of delivering preterm this risk varies significantly once their ancestry and nativity are taken into account. The risk appears to be the highest in the US-born black women compared with foreign-born black women (50-52).

The cause for a high risk of preterm delivery among African-American women remains uncertain. Many suspected demographic and socioeconomic risk factors have been compared between African-American and White women but these risk factors seem to account for very little ethnicity/race difference in the rates of preterm delivery (54,55).

There is a number of medical conditions that are associated with preterm delivery for which African-American women appear to be at a higher risk. African-American women are significantly more likely to be obese (26-29), to be affected by both chronic and gestational diabetes (28,30), and have higher risk of developing hypertension (31-33) than non-Hispanic White women. All of these conditions are also known to be risk factors for development of preeclamsia, which in turn is one of the causes for preterm delivery (33). In addition compared to women from other ethnic/racial groups African-American women have higher rates of preterm delivery associated with prevalent reproductive tract infections during pregnancy, particularly bacterial vaginosis, *Trichomonas vaginalis* and *Chlamydia trachomatis* (22-25).

Furthermore preterm delivery can be associated with stressful life situations (13,39-42). While African-American women are subjected to more stress (43,44). they may also have more adverse health effects due to stress (45,47). Cardiovascular reactivity is one of the indicators of susceptibility to stress and in at least two studies

African-American women had higher levels of cardiovascular reactivity than White women (45,46).

It is very important to understand why African-American women are at increased risk of preterm delivery in order to implement effective interventions. One area that has not been commonly investigated is the role of bleeding in preterm delivery among African-American women versus White women.

1.5 Antenatal Vaginal Bleeding

Vaginal bleeding is a common complication that may occur at any time during pregnancy. There are many different reasons why a woman may experience antenatal vaginal bleeding. The likely cause of vaginal bleeding changes over the course of pregnancy. Vaginal bleeding in the first trimester of pregnancy is not uncommon, occurring in 20-30% of all pregnancies (56). It can be associated with normal implantation of an embryo into the uterine wall (known as implantational bleeding), cervical changes due to pregnancy or it can be caused by more serious factors, such as miscarriage (15-20% of pregnancies) (57), ectopic pregnancy (1 in 60 pregnancies) (58) or molar pregnancy (1 in 1,000 pregnancies) (59).

Vaginal bleeding in the second and third trimesters of pregnancy is less common. Causes for vaginal bleeding later in pregnancy are different from those in early pregnancy. Most common causes of vaginal bleeding during second and/or third trimester are problems with a placenta, such as placental abruption (about 1% of pregnancies) (60) or placenta previa (1 in 200 pregnancies) (61). Other causes include problems with the cervix, uterine rupture, and premature labor.

Antenatal vaginal bleeding can also be caused by conditions unrelated to pregnancy, such as vaginal or sexually transmitted infections (8,19-21), abnormalities of cervix or vagina, carcinoma or cervical polyps (52), and various kinds of trauma (63). Different maternal inherited or acquired bleeding disorders can also result in antenatal vaginal bleeding. They include hemophilia (extremely rare cause, occurs in 1 in 10,000 women) (64) or thrombophilia (72-74). Certain gynecological procedures, such as Chorionic Villus Sampling (CVS) and Amniocentesis can cause bleeding as well. However in about 50% of pregnancies the cause of vaginal bleeding is unknown (65,66). Antenatal vaginal bleeding has been associated with adverse pregnancy outcomes, such as preterm delivery, low birth weight, stillbirth, and perinatal death (75).

1.6 Underlying Mechanisms for Antenatal Bleeding and Preterm Delivery

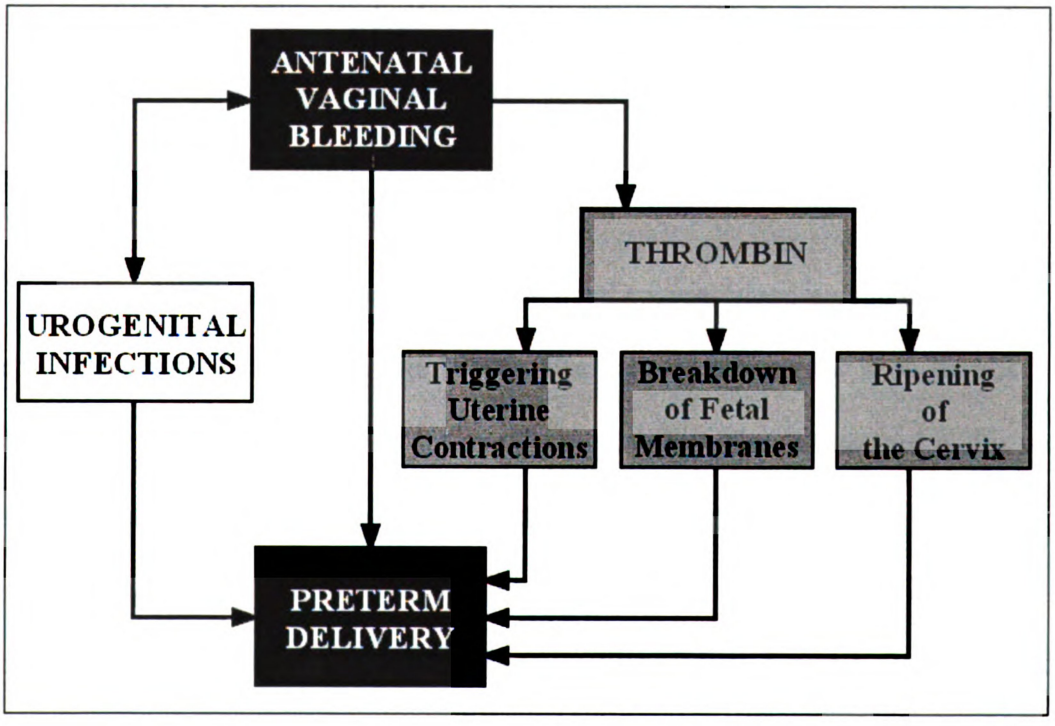
The reason for the association between antenatal vaginal bleeding and adverse pregnancy outcomes, including preterm delivery remains unclear. Different underlying mechanisms have been suggested (67) (Figure 1.2).

Some cases of preterm delivery may result from thrombin activation (68-71). Thrombin is a coagulation protein that has many effects in the coagulation cascade. Its primary role is to convert fibrinogen (a soluble protein that is produced by the liver and found in blood plasma) to an active form that assembles into fibrin (a protein involved in the clotting of blood), as well as catalyzing many other coagulation-related reactions. In addition to its activity in the coagulation cascades, thrombin promotes platelet activation. Thrombin is also known as a potent uterotonic agonist (69). Due to the difficulties in the direct measurement of thrombin, indirect measures have been used in

studies to assess the coagulation cascade and activated thrombin production. Most often studies use the TAT test: thrombin–antithrombin III (TAT) complex levels measure the amount of activated thrombin bound to antithrombin III, an endogenous thrombin antagonist (68,69).

The bleeding causes the generation of thrombin, which causes an outpouring of enzymes capable of ripening the cervix and damaging fetal membranes, resulting in preterm premature rupture of membrane, and leading to preterm delivery (70). On the other hand thrombin also binds to receptors on uterine muscle cells to trigger contractions, which may promote preterm labor (71).

Figure 2.1. Underlying Mechanisms for Antenatal Vaginal Bleeding and Preterm Delivery



Thrombophilia is an abnormality in the coagulation pathways that predisposes an individual to thrombosis. It can be inherited, acquired or combined. Maternal thrombophilias increase risk of several adverse pregnancy outcomes including early or late spontaneous abortions, pre-eclampsia, placental abruption, and intrauterine growth restriction (72,73). The most common inherited thrombophilias consist of Factor V Leiden and the prothrombin gene mutation G20210A, and more rare ones include deficiencies of protein C, S and antithrombin III. Recently, deficiency of protein Z has been linked to pregnancy complications, including preterm delivery. It is possible for more than one inherited thrombophilia to be present (73,74).

Importantly, in the addition to the direct effects of bleeding and thrombin, bleeding might also result from other underlying problems, such as infection or inflammation, which in turn can lead to preterm delivery (67). In these cases bleeding may be more of a marker than a cause. These distinctions can be difficult to determine.

1.6 Summary of Literature Review

Studies on the association between antenatal vaginal bleeding and the risk of preterm delivery date back to the late 1950's. The focus in this review is on studies conducted starting from early 1980's, since the availability of an ultrasound in this more recent period made it possible to obtain better estimates of gestational age.

The majority of studies were conducted in various parts of the US, however there were also studies conducted in Australia, Brazil, China, Egypt, Finland, Germany, India, Israel, Korea, Pakistan, Saudi Arabia, and United Kingdom. Sample sizes for these studies range from 75 to 16,506 women. Some studies reported gestational age at the enrollment into the study. It ranged from 10 to 29 gestational weeks (76,78,79,84).

Bleeding history was mostly collected by maternal questionnaires/interview at the various stages of pregnancy; however some studies used reviews of medical records instead or in addition to the maternal self-report. The majority of studies defined preterm delivery as "live birth at less then 37 completed weeks of gestation". Studies that assessed timing of bleeding, did it primarily by trimesters but some studies referred to the first or second half of pregnancy (80,91). Most studies reported assessing heaviness of bleeding episodes (78-81,84) but only one study reported taking duration of bleeding episodes into account (79).

The potential confounders most frequently taken into consideration were maternal age, ethnicity/race, education, parity, marital status, cigarette smoking, and alcohol consumption during pregnancy. Some studies also considered medical insurance status, and elements of medical and obstetric histories. Most studies reported the prevalence of antenatal vaginal bleeding. It ranged between 4.9% and 35.5% (76,78-80,82-84).

The majority of studies have found a moderate to severe increase in the risk of preterm delivery associated with antenatal vaginal bleeding (76-84,86-94), particularly bleeding during first trimester of pregnancy only (78,85), and during the second half of pregnancy (91,92). One study reported significant increase in the risk of vaginal bleeding during the second half of pregnancy for women that had some bleeding during the first half (91). A very limited number of studies have assessed ethnicity/race–specific differences for the risk of preterm delivery in association with antenatal vaginal bleeding. Studies that did found ethnicity/race-specific odds-ratios to be greater in non-Hispanic White than in African-American women (79,80).

There were some differences in results of prior studies. One study found

a significant association between preterm delivery and vaginal bleeding during the second but not first trimester of pregnancy (83). While most of the studies that accounted for heaviness of bleeding episodes found that the risk of delivering preterm was notably higher among women with heavier bleeding episodes (78-80,84), one study found no association between heaviness of bleeding episodes and preterm delivery (84).

A number of factors may potentially account for the differences in the results of prior studies. First, there have been differences in times in pregnancy when bleeding history was assessed. Information on bleeding was typically gathered by asking study participants, and recall bias may have occurred in women queried after delivery or late in pregnancy following other complications. Second, many studies have failed to include characteristics of bleeding in their analysis, particularly duration of bleeding episodes. It is important to take these characteristics into account, since they may influence the association between antenatal vaginal bleeding and the risk of preterm delivery. Third, studies have used different definitions of preterm delivery, and bleeding characteristics, particularly there was great variability in defining heaviness of bleeding episodes. Finally, studies differed with respect to study design, sample size, and confounders selected during data collection and statistical analysis.

Among studies on the association between antenatal vaginal bleeding and the risk of preterm delivery very few studies attempted to separate preterm delivery into its clinical subtypes (i.e. preterm labor, premature rupture of membrane, and medically induced delivery) (78,79,93,95). Only one study considered both bleeding characteristics (timing, duration, and heaviness), and clinical subtypes of preterm delivery (79). One more study assessed the relation between heaviness of bleeding and the risk of preterm

premature rupture of membrane (78). It has been found that antenatal vaginal bleeding increases the risk of preterm delivery in all subgroups but especially for preterm labor (79,93,95).

At present time the desirability of separating preterm delivery into its clinical subtypes remains an open topic. Some researchers maintain that such separation should be made (95,96) while others oppose it (97). Based on the results of some prior studies it has been recommend that the subtypes should be examined first, and then combined back together only if they turn out to be homogenous (95,96). It is further recommended that preterm labor and preterm premature rupture of membrane could be combined into spontaneous preterm delivery, however medically induced preterm delivery should be kept separately (95,96).

More studies are needed in order to further understand the association between vaginal bleeding during pregnancy and the risk of preterm delivery, the underlying mechanism for this association, and implications for prenatal care. Consideration of preterm delivery's clinical subtypes might provide additional insights into these associations.

1.7 Study Aims and Strengths

Study Aims

The aim of this study is to consider associations between antenatal vaginal bleeding and the risk of preterm delivery. This aim will be operationalized by considering characteristics of bleeding (timing, duration, and heaviness of bleeding episodes), ethnicity/race-specific effect, influence of potential confounding factors, and clinical

subtypes of preterm delivery (preterm labor, premature rupture of membrane, and medically induced delivery).

Study Strengths

Major strengths of this study are prospective design, the fact that women were not selected based on their bleeding history, and the large sample size. In addition estimates of gestational age based on the last menstrual period were confirmed using estimates by an early ultrasound for 90% of study participants. Furthermore, recall bias was minimized due to the fact that bleeding information was collected early in pregnancy; and differential reporting was impossible, since at the time of the interview the outcome of the pregnancy was unknown. Obtaining information by self-report has its limitations and strengths. Although there is subjectivity in recalling bleeding, self-report is potentially more accurate and complete than information obtained from medical records.

Table 1.2. Studies on Association between Antenatal Vaginal Bleeding and Preterm Delivery

First Author **Year of Publication** **Study Details:** **Name** **Design** **Location** **Time Frame** **Sample Size**	**Gestational Age at Enrollment** **Exclusion/Inclusion Criteria**	**Bleeding History Assessment** **Bleeding Characteristics Considered** **PTD Definition**	**Ethnic/Race-Specific Analysis** **Confounders Used**	**Study Results**
McCormack et al, 2008 Retrospective Observational study Western Australia (Subiaco) 01/1998 -12/2004 N=28,014	N/S Exclusion: multiple gestations, deliveries at <24 GW, identifiable bleeding causes (placenta praevia, placenta percreta/increta/accrete, placental abruption, trauma).	Hospital database. Timing. < 37 GW	No. Maternal age, ethnicity, smoking d/p, illegal drugs use d/p, medical conditions (renal disease, essential hypertension, hyperthyroidism, hypothyroidism, diabetes), reproductive history (gravidity, parity, miscarriages).	OR=4.31, 95%CI: 3.8-4.8, p<0.001.

Table 1.2. (cont'd).

Harlev et al, 2008 Israel N=134	2nd half of pregnancy Inclusion: singleton gestations, hospital admission due to VB at the 2nd half of pregnancy, presence of prenatal care, unidentifiable bleeding causes.	Hospital records. Timing (2nd half of pregnancy). < 37 GW	No. N/S	PTD: 56.7% vs. 7.3%; mean GA: 33.6±5.7 vs.39.2±2.1 (GW); p<0.001. PROM: OR=3.4, 95% CI: 1.8–6.2; p<0.001.
Hossain et al, 2007 Omega Study Prospective Cohort Washington State, USA 12/1996-10/2004 N=2,678	N/S Inclusions: singleton pregnancies, maternal age ≥18 years, prenatal care at <20 GW, proficiency in English, delivery at the study hospitals, no abortion or fetal loss at <28 GW.	Self-report in-person at enrollment. Timing (by trimesters: 1st only, 2nd only, both 1st & 2nd). < 37 GW (subdivided into: 1) <34 & 34-36 GW 2) PTL, PROM, MI).	No. Maternal age, education, annual household income, occupation, medical & reproductive histories, smoking, alcohol use d/p.	Overall PTD: OR=1.57, 95%CI: 1.16–2.11. PTL: OR=2.10, 95% CI: 1.3-3.3 PPROM: OR=1.36, 95% CI: 0.8-2.2 MI: OR=1.32, 95% CI: 0.7-2.4. Timing (1st&2nd trimesters): OR=6.24, 95% CI: 1.7-22.4.

Table 1.2. (cont'd).

Boggess et al, 2006 North Carolina, USA 12/1997-07/2001 N=661	GW < 26 N/S	Self-Report in-person within 48 hrs of delivery for all study women; abstraction of medical records for a subgroup of study women. <u>Timing</u> (by trimesters: 1st (<14GW), 2nd (14-24GW), both 1st & 2nd). < 35 GW	No. Maternal age, race, marital status, insurance status, smoking, bacterial vaginosis, prior PTD.	Timing (1st&2nd trimesters): OR=1.4, 95% CI: 0.9-2.5.
Kim et al, 2005 Prospective study Korea N=2,645	N/S <u>Exclusion:</u> multiple gestations.	N/S	No. Demographic & socio-economic factors, drugs & alcohol abuse, previous & current medical histories, current pregnancy complications.	OR=2.6, 95%CI: 1.7-4.2 (among nulliparous women)

Table 1.2. (cont'd).

Magann et al, 2005 Review (9 studies)	Various. Exclusion: multiple gestations, any known bleeding cause.	N/S Timing (2nd half of pregnancy). < 37 GW	No. N/S	OR=3.17, 95%CI: 2.8-3.6
Weiss et al, 2004 FASTER trial Prospective Cohort USA 1999-2000 N=16,506	GW: 10-14 Exclusion: multiple gestations.	Self-report in-person at enrollment. Heaviness (light, heavy). N/S	No. Maternal age, race, education, marital status, reproductive history.	PTD: Heaviness: light: OR=1.3, 95%CI: 1.1-1.7 heavy: OR=3.0, 95%CI: 1.9-4.5. PROM: Heaviness: light: OR=1.3, 95%CI: 0.9-1.9 heavy: OR=3.2, 95%CI: 1.8-5.7.

Table 1.2. (cont'd).

Yang et al, 2004 PIN Study Prospective Cohort North Carolina, USA 01/1995-08/2000 N=2,802	GW: 24-29 Exclusion: multiple gestations, didn't speak English, maternal age <16 years, no telephone access, delivery not at study site.	Self-report by phone within 2 wks of enrollment. Timing* (by trimesters: 1st only, 2nd only, both 1st & 2nd), Duration* (by days: single, multiple), Heaviness* (light, heavy). * for 3 episodes only. Live birth at <37 GW (subdivided into: 1) ≤34 & 35-36 GW 2) PTL, PROM, MI).	Yes: White, African-American. Maternal age, education, marital status, household income, smoking, alcohol use, illegal drug use d/p, GT infection d/p, parity, prior adverse pregnancy outcomes, exercise d/p.	Overall: VB-PTD: RR=1.3, 95%CI: 1.1-1.6. Timing: 1st trimester-PTD≤34GW: RR=1.6, 95%CI: 1.1-2.4 1st trimester-PPROM: RR=1.9, 95%CI: 1.1-3.3 Both trimesters-PTL: RR=3.6, 95%CI: 1.9-6.8. RACE: 1) Any PTD: White: RR=1.4, 95%CI: 1.1-1.9 African-American: RR=1.2, 95%CI: 0.9-1.7. 2)PPROM: White: RR=2.6, 95%CI: 1.3-5.1 African-American: RR=1.0, 95%CI: 0.4-2.3.

Table 1.2. (cont'd).

Yang et al, 2001 NMIHS 1988 Study Prospective Cohort USA (excluding Montana and South Dakota) 1988 N=8,671	N/S <u>Exclusion:</u> multiple gestations.	Maternal questionnaires, birth certificates. <u>Severity & Timing</u> (less severe; severe in 1st half of pregnancy, severe in 2nd half of pregnancy, severe in both halves). Live birth at <37 GW (subdivided into: <32, 32-33, 34-36 GW)	Yes: White, African-American. Maternal age, race, education, marital status, employment d/p, annual household income, smoking, alcohol use, illegal drugs use d/p, bacterial vaginosis, parity, prior adverse pregnancy outcomes, minerals & supplements use d/p, medical treatment f/getting pregnant, infant gender, prenatal care in current pregnancy.	Overall PTD: Severity/Timing: less severe: A/OR=1.6 95%CI: 1.2-2.1 severe/1st half: A/OR=1.6, 95%CI: 1.2-2.3 severe/2nd half: A/OR=1.7, 95%CI: 1.0-2.9 severe/both halves: A/OR=4.4, 95%CI: 2.3-8.6. RACE: White: less severe: A/OR =1.7, 95%CI: 1.2-2.4 severe/1st half: A/OR=1.6, 95%CI: 1.0-2.5 severe/2nd half: A/OR=1.7, 95%CI: 0.9-3.2 severe/both halves: A/OR=4.6, 95%CI: 2.0-10.6 African-American: less severe: A/OR=1.3, 95%CI: 1.0-1.8 severe/1st half: A/OR=1.6, 95%CI: 1.0-2.5 severe/2nd half: A/OR=1.0, 95%CI: 0.5-1.8 severe/both halves: A/OR=2.5, 95%CI: 1.2-5.4.

Table 1.2. (cont'd).

Leung et al, 2001 Retrospective Hong-Kong, China 1995-1998 N=75	N/S <u>Inclusion:</u> singleton gestations, 1st APHUO at <34 GW, no listed pathologies.	Review of medical records. <u>Timing, Heaviness</u> (mild, heavy). < 37 GW	No. N/S	APHUO at <34 GW is associated w/high risk of PTD at <34 GW. No Heaviness-PTD association.
Arafa et al, 2000 Retrospective Alexandria, Egypt Jan-Oct 1998 N=1,503	N/S <u>Exclusion:</u> multiple gestations, VB in 3rd trimester only.	Maternal questionnaires during postpartum hospital stay. <u>Timing</u> (by trimesters: 1st only, 2nd only). < 37 GW	No. Maternal age, socio-economic status, reproductive history (parity, abortion, stillbirth, anemia, preeclampsia), prenatal care in current pregnancy.	Timing: 1st trimester: OR=1.6, A/OR=1.6, 95%CI: 0.8-3.2 2nd trimester: OR=6.4, A/OR=7.3, 95%CI: 3.1-17.1.

Table 1.2. (cont'd).

Berkowitz et al, 1998 New York City, USA 1986-1994	N/S Exclusions: race other than white, black or Hispanic; tocolytic agents use w/delivery at >37 GW.	Hospital database. N/S < 37 GW (subdivided into PTL, PROM, MI).	No. Maternal age, race, birth place, marital status, type of insurance coverage, smoking, alcohol abuse, illegal drugs use, medical & reproductive histories, antepartum complications, pre-pregnancy BMI.	PPROM: A/OR=2.8, 95% CI: 2.1-3.8 PTL: A/OR=3.6, 95% CI: 2.6-4.8 MI: A/OR=3.7, 95% CI: 2.5-5.5.
Ananth et al, 1994 Meta-Analysis (12 studies published: 1950-04/1992) Australia, Brazil, Denmark, Finland, Germany, India, Israel, Saudi Arabia, UK, USA	Various. Exclusion: studies not in English; primary focus: placenta previa, abruption placentae, PPROM.	N/S Timing and Heaviness (assessed by some studies but not by all). < 37 GW	No. N/S	ALL studies (12): A/RR=2.3, 95%CI: 2.1-2.5. COHORT studies (11): A/RR=2.2, 95%CI: 2.1-2.4. CASE-CONTROL study (1): A/RR=3.0, 95%CI: 1.9-4.6.

Table 1.2. (cont'd).

Chan et al, 1999 Retrospective Case-Control Hong-Kong, China 1991-1996 N=1,436	N/S <u>Exclusion:</u> multiple gestations, known bleeding cause.	Computer database. <u>Timing</u> (>24 GW). < 37 GW	No. Maternal age, education, family income, smoking, parity, maternal height and weight.	PTD: Cases: 114 (15.8%) Controls: 34 (4.7%), p<0.001.
Karim et al, 1998 Karachi, Pakistan N=268	N/S <u>Inclusion:</u> singleton gestations, hospital-based population.	N/S <u>Timing</u> (by trimesters: 1st only, 2nd only). < 37 GW	No. N/S	2nd trimester VB significantly associated with PTD.

Table 1.2. (cont'd).

Siplä et al, 1992 Prospective Cohort Finland (northern part) 07/1985 -06/1986 N=8,718	2nd trimester but <25 GW Exclusion: multiple gestations, miscarriage at <24 GW.	In-person maternal questionnaire: GW 24, & ±1 visit to delivery; hospital records. Timing (by trimesters: 1st only, 2nd only, both 1st & 2nd), Heaviness (light, heavy). < 37 GW	No. Maternal age, education, marital status, social class, employment, smoking, alcohol use, reproductive history (parity, induced abortions, miscarriages), infertility, contraception b/pregnancy.	Heaviness: light: A/OR=2.1, 95%CI: 1.5-2.8 heavy: A/OR=2.3, 95%CI: 1.4-3.8. Timing: 1st trimester only: A/OR=1.8, 95%CI: 1.3-2.5 2nd trimester only: A/OR=2.1, 95%CI: 1.9-4.6.
Williams et al, 1991 Cohort Boston, USA 1977-1980 N=12,197	N/S Inclusion: VB in 1st trimester only.	In-person maternal interview & review of medical records. Timing (1st trimester only). < 37 GW	No. N/S	RR=2.3, 95%CI: 1.9-2.8

Table 1.2. (cont'd).

Strobino et al, 1989 Cohort New York City, USA 1975-1985 N=3,531	2nd trimester N/S	Self-report in-person. Timing, Duration, Heaviness (light, heavy). Live birth at <36 GW	No. Maternal age, education, payment status (public/ private), smoking, alcohol use, working d/p, reproductive history, gynecological complications history, maternal weight.	Heaviness: light: A/OR=1.3, 95%CI: 0.9-1.9 heavy: A/OR=0.9, 95%CI: 0.4-2.2.
Hertz et al, 1985 Cohort Denmark 1977-1978 N=438	< 20 GW Exclusion: multiple gestations.	N/S N/S < 37 GW	No. N/S	RR=2.1, 95%CI: 1.0-4.8

Table 1.2. (cont'd).

Berkowitz et al, 1985 Case-Control Connecticut, USA 1977-1978 N=488	N/S <u>Inclusion:</u> singleton live births.	Maternal interview during postpartum hospital stay. N/S Live birth at <37 GW	No. N/S	RR=3.1, 95%CI: 2.0-4.8
Batzofin et al, 1984 Case-Control Boston, USA 1978-1979 N=7,229	N/S <u>Inclusion:</u> VB at <20 GW only; significant VB (by physician).	Retrospective medical records only (computer form). <u>Timing</u> (<20 GW), <u>Heaviness</u> (significant only). < 37 GW	No. N/S	RR=2.07, $P=3.1x10^{-9}$

Table 1.2. (cont'd).

Berkowitz et al, 1983 Cohort Jerusalem, Israel 1975-1976 N=16,583	N/S <u>Exclusion:</u> multiple gestations, GA <28 GW, infants w/BW<1000g.	Maternal interview during postpartum period. <u>Timing</u> (by month), <u>Heaviness</u> (spotting, light, heavy). < 37 GW	No. N/S	RR=6.8, 95%CI: 5.2-8.3

CHAPTER 2.

VAGINAL BLEEDING IN THE FIRST 20 WEEKS OF PREGNANCY AND THE RISK OF PRETERM DELIVERY

2.1 Introduction

Vaginal bleeding is common complication that may occur at any time during pregnancy. There are many different reasons for antenatal vaginal bleeding. The likely cause of vaginal bleeding changes over the course of pregnancy.

Vaginal bleeding in the first trimester of pregnancy is not uncommon, occurring in 20-30% of all pregnancies (56). It can be associated with normal implantation of an embryo into the uterine wall (known as implantational bleeding), cervical changes due to pregnancy or it can be caused by more serious factors, such as miscarriage (15-20% of pregnancies) (57), ectopic pregnancy (1 in 60 pregnancies) (58) or molar pregnancy (1 in 1,000 pregnancies) (59).

Vaginal bleeding in the second and third trimesters of pregnancy is less common. The most common causes of vaginal bleeding during the second and/or third trimester are problems with placenta, such as placental abruption (about 1% of pregnancies) (60) or placenta previa (1 in 200 pregnancies) (61). Other causes include problems with cervix, uterine rupture, and premature labor.

Antenatal vaginal bleeding can also be caused by conditions unrelated to pregnancy, such as genitourinary tract infections (8,19-25), abnormalities of cervix or vagina, carcinoma or cervical polyps (62), and various kinds of maternal trauma (63). Different maternal inherited or acquired bleeding disorders can also result in antenatal vaginal bleeding, they include hemophilia (extremely rare cause, occurs in 1 in 10,000

pregnancies) (64), and thrombophilia (72-74). Certain gynecological procedures, such as Chorionic Villus Sampling (CVS) and Amniocentesis can also cause bleeding. However in about 50% of pregnancies the cause of vaginal bleeding is unknown (66,80). Antenatal vaginal bleeding has been associated with adverse pregnancy outcomes, such as preterm delivery, low birth weight, stillbirth, and perinatal death (75-87,82-92) but the reason for this association remains unclear (80,90).

Multiple studies have reported positive association between antenatal vaginal bleeding and preterm delivery (76-92), particularly severe bleeding (78-80,84,86). Fewer studies have examined variations in bleeding patterns as they relate to the risk of preterm delivery (79,86). Bleeding in the first half of pregnancy may indicate a prolonged underlying process or a maternal predisposition. A recent study reported significant increase in risk of vaginal bleeding in the second half of pregnancy for women that experienced some vaginal bleeding during the first 20 weeks of pregnancy (91).

In this study we focused on bleeding patterns in the first half of pregnancy among women who were interviewed at 20-27 weeks of gestation as part of prospective study on preterm delivery. We were particularly interested in comparing ethnic/racial groups to examine whether a bleeding-preterm delivery pathway contributes to ethnic/racial disparities in the risk of preterm delivery.

2.2 Subjects and Methods

Study Protocol

The Pregnancy Outcomes and Community Health (POUCH) Study is a prospective cohort study of women enrolled from 52 clinics in five economically diverse

Michigan communities. Enrollment took place during 1998-2004. A total of 3,038 women were enrolled in their 15-27 weeks of pregnancy; however 19 women were lost to follow-up. Exclusion criteria included multi-fetal pregnancy, lack of competency in English, maternal age less less than 15 years, known congenital abnormalities at the time of enrollment, and pre-pregnancy diabetes mellitus. The POUCH study protocol was approved by the institutional review boards of Michigan State University, Michigan Department of Community Health, and all nine delivery hospitals. All study participants provided informed written consent.

At enrollment each woman met with a study nurse and completed detailed in-person interview, and a self-administered questionnaire. The following information was ascertained: demographics (including self-reported ethnicity/race), socioeconomics, reproductive history, medical conditions, substance abuse, and events during current pregnancy. Information on vaginal bleeding during current pregnancy was also collected at this time. Women were asked if they had any vaginal bleeding at any time during current pregnancy, and for those who did some additional information was collected, including the week(s) in pregnancy when bleeding began, number of days/hours it continued for, and how heavy it was (spotting, slight; about the same as usual menstrual period; or heavier than usual menstrual period). Such information was collected for to up to seven bleeding episodes.

Study Sample

Our study sample contained non-Hispanic White and African-American POUCH cohort women enrolled/interviewed at 20-27 weeks of pregnancy. Women enrolled before 20 completed weeks of pregnancy were excluded (446 women) because of the

focus on vaginal bleeding in the first 20 weeks of pregnancy. In addition we excluded women from ethnic/racial groups other than non-Hispanic White and African-American due to small numbers (48 Asian, 89 Mexican, 45 other Hispanic, 33 Native American and 4 other). After these exclusions our sample contained 2,354 women (78% the cohort; 1,735 non-Hispanic White, and 619 African-American).

Outcome and Exposure Measures

Preterm delivery was defined as live birth before 37 completed weeks of gestation, and was further subdivided into the following categories: preterm labor (PTL), i.e. onset of labor that was not preceded by the rupture of membrane; premature rupture of membrane (PROM), i.e. rupture of membranes that occurred at any time before the onset of labor; and medically induced delivery (MI), i.e. delivery due to medical intervention that was not preceded by preterm labor or premature rupture of membrane.

Gestational age was based on the first day of the last menstrual period (LMP), and/or on estimate from an early ultrasound (performed at or before 25th week of pregnancy). Both of these estimates were available for 90% of women. In case these two estimates differed by more than two weeks (12.8% of women) or if LMP estimate was unavailable (4% of women) the ultrasound estimate of gestational age was used.

Vaginal bleeding during pregnancy was summarized by three variables: duration, heaviness, and timing of bleeding episodes. Duration of bleeding episode was divided into two mutually exclusive categories: up to 24 hours, and over 24 hours. In case multiple bleeding episodes were reported longest episode was used for the classification. Heaviness (amount of blood lost during a single bleeding episode) was divided into two mutually exclusive categories: "spotting/slight", and "same or heavier than usual

menstrual period". In case of multiple episodes classification was made based on the most severe one. Timing was divided into two categories "bleeding in weeks 1-13 only" (i.e. first trimester), and "bleeding in weeks 14-20 +/- weeks 1-13". Preliminary analysis revealed a similar risk of preterm delivery in women with bleeding during 14-20 gestational weeks only, and those with bleeding during 14-20 gestational weeks and during 1-13 gestational weeks. As a result these two groups of women were combined into a single group.

The potential confounding variables included maternal age, education, parity, marital status, Medicaid status, cigarette smoking, and alcohol consumption during pregnancy. Information on all confounders was obtained in a detailed in-person interview, and a self-administered questionnaire at the time of enrollment into the study.

Analytic Strategy

The prevalence of bleeding (by timing, duration, and heaviness) was compared across two ethnic/racial groups (African-American versus non-Hispanic White) using a Chi-square test. Logistic regression models were used to examine the relation between vaginal bleeding and preterm delivery. Separate ethnicity/race-specific logit models were constructed for each of the three bleeding variables (timing, duration, and heaviness). Bleeding variables were categorized into three levels with "no bleeding" as a referent category. Statistical analyses were conducted with and without adjustment for potential confounders. The potential confounders that were adjusted for in the logistic regression models included maternal age (categorized as 15-19, 20-29, and >30 years of age), education (<12, =12, and >12 completed years of schooling), parity (no previous live birth, previous live birth/preterm, and previous live birth/term), Medicaid status (yes/no),

marital status (married/living with husband, married/not living with husband, not married/living with partner, and not married/not living with partner), cigarette smoking during pregnancy (no smoking during pregnancy, quit smoking before enrollment, smoking up to ½ pack per day at enrollment, and smoking over ½ pack per day at enrolment), and alcohol use during pregnancy (yes/no).

Polytomous regression was used to assess the relations between bleeding and delivery outcome, i.e. three preterm delivery subtypes (preterm labor, preterm rupture of membrane, medically induced), and term (referent category). Separate models were constructed for each of the tree bleeding variables (timing, duration and heaviness). Bleeding variables were categorized into three levels with "no bleeding" as a referent category. All statistical analysis were performed using Statistical Analysis System Software (Release 9.1.2, SAS Institute, Inc., and Cary, NC).

2.3 Results

The distributions of selected maternal socio-demographic and pregnancy history characteristics of study participants are presented in Table 2.1. Among study women 84.1% were enrolled into the study in their 20th-24th week of pregnancy, 46.7% were insured by Medicaid, and 10.4% delivered preterm.

The history of any vaginal bleeding in the first 20 weeks of pregnancy was very similar in non-Hispanic White (24.4%) and African-American (23.4%) (Table 2.2). Distribution of timing, duration, and heaviness of bleeding were also similar in both groups. Percentages in African-American women versus non-Hispanic White were not statistically different.. In the ethnicity/race-specific analysis, risk of preterm delivery was

increased in all bleeding groups; however it was especially high in women with bleeding "in weeks 14-20 +/- weeks 1-13" (14.3% among non-Hispanic White and 13.7% among African- American women), women with bleeding that lasted for over 24 hours (14.4% among non-Hispanic White and 21.6% among African-American), and women with the amount of bleeding described as "same or greater then usual menstrual period" (18.1% among non-Hispanic White and 26.1% among African-American) (Table 2.3). Within the bleeding groups there was no significant ethnic/racial difference in the risk of preterm delivery. Ethnicity/race-specific odds ratios (OR) for preterm delivery in association with bleeding appeared greater in non-Hispanic White (OR range 1.6-2.7) than in African-American women (OR range 1.0-2.2) (Table 2.3); however this was due to the fact that the "no bleeding" group in African-American women had a higher risk of preterm delivery (13.9%) compared to that in non-Hispanic White (7.6%): OR=2.0, 95% CI: 1.4-2.7. Adjustment for potential confounders, including maternal age, education, parity, marital status, Medicaid status, cigarette smoking, and alcohol consumption during pregnancy did not change odds-ratio estimates by more than 10%. Since there was no significant interactions between ethnicity/race and any of the bleeding characteristics (p=0.34 for timing, p=0.50 for duration, and p=0.51 for heaviness) African-American and non-Hispanic White women were combined for further analysis.

Table 2.4 shows the association between vaginal bleeding in the first 20 weeks of pregnancy and the risk of preterm delivery in the model that combined racial/ethnic groups. The risk appeared to be increased in all bleeding groups but especially high in women with amount of bleeding described as "same or greater then usual menstrual period" (OR=2.4, 95% CI: 1.5-4.0), and women with bleeding that lasted for over 24

hours (OR=1.8, 95% CI: 1.3-2.7). As for the timing of bleeding, the risk of preterm delivery appeared to be the same in both groups: bleeding "in weeks 1-13 only" and "in weeks 14-20 +/- weeks 1-13" (OR=1.6, 95% CIs: 1.1-2.2 and 1.0-2.5 respectively).

The results of analysis for the association between vaginal bleeding in the first 20 weeks of pregnancy and preterm delivery subtypes, i.e. preterm labor (PTL), preterm premature rupture of membrane (PPROM), medically induced (MI), are presented in Table 2.5. Of all preterm deliveries 41.2% were preceded by PTL, 26.1% were preceded by PROM, and the remaining 32.7% were delivered with medical intervention. Women with bleeding "in weeks 14-20 +/- weeks 1-13" were at high risk of both PROM (OR=1.9, 95% CI: 0.9-4.1) and medically induced delivery (OR=1.8, 95% CI: 0.9-3.7). However risk of PTL was higher in women with bleeding "in weeks 1-13 only" (OR=1.9, 95% CI: 1.2- 3.0). Women with bleeding that lasted for over 24 hours were at high risk of medically induced delivery (OR=2.1, 95% CI: 1.2- 3.8) and PROM (OR=1.9, 95% CI: 1.0-3.7). The risk of PTL was lower, and very similar in both groups: women with bleeding that lasted for up to 24 hours, and women with bleeding that lasted for over 24 hours (OR=1.7, 95% CI: 1.0-2.9 and OR=1.6, 95% CI: 0.9-2.9 respectively). Women with the amount of bleeding described as "same or greater then usual menstrual period" were at very high risk of PTL (OR=3.4, 95% CI: 1.8-6.5). Risk of PROM in this group was lower but still very high (OR=2.5, 95% CI: 1.1-6.1). However the risk of medically induced delivery was higher in women with the amount of bleeding described as "spotting/slight" (OR=1.7, 95% CI: 1.0-2.8). Overall the strongest association was found between heavy bleeding (described as "same or greater than usual menstrual period") and both spontaneous subtypes of preterm delivery (for PTL: OR=3.4, 95% CI: 1.8-6.5 and

for PROM: OR=2.5, 95% CI: 1.1- 6.1). Medically induced delivery was most strongly related to bleeding that lasted for over 24 hours (OR=2.1, 95% CI: 1.2-3.8).

Table 2.1. Selected Sociodemographic and Pregnancy History Characteristics of Study Participants

Maternal Characteristics	N (%)
AGE	
15-19	355 (15.1)
20-29	1,325 (56.3)
≥30	674 (28.6)
RACE	
White Non-Hispanic	1,735 (73.7)
African-American	619 (26.3)
PARITY	
No Previous Live Birth	1,024 (43.5)
Previous Live Birth/Preterm	105 (4.5)
Previous Live Birth/Term	1,225 (52.0)
EDUCATION (years) †	
< 12	409 (17.4)
= 12	698 (29.7)
> 12	1,244 (52.9)
MEDICAID †	
Have Medicaid	1,100 (46.7)
Do not have Medicaid	1,251 (53.1)
GESTATIONAL AGE AT ENROLLMENT (wks) ‡	
20-22	1,180 (50.1)
23-24	800 (34.0)
25-27	374 (15.9)
GESTATIONAL AGE AT DELIVERY (wks)	
< 35	79 (3.4)
35-36	166 (7.0)
≥37	2,109 (89.6)

Table 2.1. (cont'd)

Maternal Characteristics	N (%)
MARITAL STATUS †	
Married, living w/husband	1,182 (50.2)
Married, not living w/husband	14 (0.6)
Not married, living w/partner	533 (22.6)
Not married, not living w/partner	618 (26.3)
CIGARETTE SMOKING IN PREGNANCY †	
No smoking during pregnancy	1,689 (71.8)
Quit smoking before the enrollment	242 (10.3)
Smoking (≤ ½ pack p/day) during pregnancy	282 (12.0)
Smoking (>½ pack p/day) during pregnancy	137 (5.8)
ALCOHOL CONSUMPTION IN PREGNANCY †	
Yes	443 (18.8)
No	1,896 (80.5)

* Women other than non-Hispanic White and African-American are not included.
† Missing values: education-3, Medicaid-3, marital status-7, smoking-4, alcohol-15.
‡ Women enrolled into study during 15-19 weeks of pregnancy are not included.

Table 2.2. History of Vaginal Bleeding in the First 20 Weeks of Pregnancy by Maternal Ethnicity/Race

	Non-Hispanic White (N=1,735)	African-American (N=619)
	N (%)	N (%)
TIMING		
No Bleeding in weeks 1-20	1,311 (75.6)	474 (76.6)
Bleeding in weeks 1-13 only	298 (17.2)	94 (15.2)
Bleeding in weeks 14-20 +/- weeks 1-13	126 (7.2)	51 (8.2)
DURATION *		
No Bleeding	1,311 (75.6)	474 (76.7)
Short: ≤ 24 hours	223 (12.8)	93 (15.1)
Long: > 24 hours	201 (11.6)	51 (8.2)
HEAVINESS †		
No Bleeding	1,311 (75.6)	474 (76.7)
Light: Spotting/Slight	340 (19.6)	121 (19.6)
Heavy: ≥ Menstrual Period	83 (4.8)	23(3.7)

* 1 African-American has missing data.
† 1 African-American and 1 non-Hispanic White have missing data.

Table 2.3. Association between Bleeding in the First 20 Weeks of Pregnancy and a Risk of Preterm Delivery by Maternal Ethnicity/Race

	Non-Hispanic White (N=1,735)			African-American (N=619)		
	Term	Preterm		Term	Preterm	
	N (%)	N (%)	OR (95% CI)	N (%)	N (%)	OR (95% CI)
TIMING						
No bleeding in weeks 1-20	1,211 (92.4)	100 (7.6)	Ref	408 (86.1)	66 (13.9)	Ref
Bleeding in weeks 1-13 only	261 (87.6)	37 (12.4)	1.7 (1.2, 2.6)	77 (81.9)	17 (18.1)	1.4 (0.8, 2.5)
Bleeding in weeks 14-20+/-1-13	108 (85.7)	18 (14.3)	2.0 (1.2, 3.5)	44 (86.3)	7 (13.7)	1.0 (0.4, 2.3)
DURATION *						
No bleeding	1,211 (92.4)	100 (7.6)	Ref	408 (86.1)	66 (13.9)	Ref
≤ 24 hours	197 (88.3)	26 (11.7)	1.6 (1.0, 2.5)	80 (86.0)	13 (14.0)	1.0 (0.5, 1.9)
> 24 hours	172 (85.6)	29 (14.4)	2.0 (1.3, 3.2)	40 (78.4)	11 (21.6)	1.7 (0.8, 3.5)
HEAVINESS †						
No bleeding	1,211 (92.4)	100 (7.6)	Ref	408 (86.1)	66 (13.9)	Ref
Spotting / Slight	300 (88.2)	40 (11.8)	1.6 (1.1, 2.4)	103 (85.1)	18 (14.9)	1.1 (0.6, 1.9)
≥ Menstrual Period	68 (81.9)	15 (18.1)	2.7 (1.5, 4.9)	17 (73.9)	6 (26.1)	2.2 (0.8, 5.7)

* 1 African-American has missing data.
† 1 African-American and 1 non-Hispanic White have missing data.
NOTE: Term is a reference category.

Table 2.4. Association between Vaginal Bleeding in the First 20 Weeks of Pregnancy and Preterm Delivery

	Term	Preterm	
	N (%)	N(%)	OR (95% CI)
TIMING			
No bleeding in weeks 1-20	1,619 (90.7)	166 (9.3)	Ref
Bleeding in weeks 1-13 only	338 (86.2)	54 (13.8)	1.6 (1.1, 2.2)
Bleeding in weeks 14-20+/-1-13	152 (85.9)	25 (14.1)	1.6 (1.0, 2.5)
DURATION *			
No bleeding	1,619 (90.7)	166 (9.3)	Ref
≤ 24 hours	277 (87.7)	39 (12.3)	1.4 (0.9, 2.0)
> 24 hours	212 (84.1)	40 (15.9)	1.8 (1.3, 2.7)
HEAVINESS †			
No bleeding	1,619 (90.7)	166 (9.3)	Ref
Spotting / Slight	403 (87.4)	58 (12.6)	1.4 (1.0, 1.9)
≥ Menstrual Period	85 (80.2)	21 (19.8)	2.4 (1.5, 4.0)

* 1 missing value in Term.
† 2 missing values in Term.
NOTE: Term is a reference category.

Table 2.5. Association between Vaginal Bleeding in the First 20 Weeks of Pregnancy and the Risk of Preterm Delivery by Its Subtypes

	Term	PTL		PROM		Medically Induced	
	N (%)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
TIMING							
No bleeding in weeks 1-20	1,619 (90.7)	67 (3.8)	Ref	45 (2.5)	Ref	54 (3.0)	Ref
Bleeding in weeks 1-13 only	338 (86.2)	26 (6.6)	1.9 (1.2, 3.0)	11 (2.8)	1.2 (0.6, 2.3)	17 (4.3)	1.5 (0.9, 2.6)
Bleeding in weeks 14-20+/-1-13	152 (85.9)	8 (4.5)	1.3 (0.6, 2.7)	8 (4.5)	1.9 (0.9, 4.1)	9 (5.1)	1.8 (0.9, 3.7)
DURATION *							
No bleeding	1,619 (90.7)	67 (3.8)	Ref	45 (2.5)	Ref	54 (3.0)	Ref
≤ 24 hours	277 (87.7)	20 (6.3)	1.7 (1.0, 2.9)	8 (2.5)	1.0 (0.5, 2.2)	11 (3.5)	1.2 (0.6, 2.3)
> 24 hours	212 (84.0)	14 (5.6)	1.6 (0.9, 2.9)	11 (4.4)	1.9 (1.0, 3.7)	15 (6.0)	2.1 (1.2, 3.8)
HEAVINESS †							
No bleeding	1,619 (90.7)	67 (3.8)	Ref	45 (2.5)	Ref	54 (3.0)	Ref
Spotting / Slight	403 (87.4)	22 (4.8)	1.3 (0.8, 2.2)	13 (2.8)	1.2 (0.6, 2.2)	23 (5.0)	1.7 (1.0, 2.8)
≥ Menstrual Period	85 (80.2)	12 (11.3)	3.4 (1.8, 6.5)	6 (5.7)	2.5 (1.1, 6.1)	3 (2.8)	1.1 (0.3, 3.5)

* 1 missing value in Term.
† 2 missing values in Term.
NOTE: Term is a reference category.

2.4 Discussion

A number of previous studies have reported increased risk of preterm delivery associated with antenatal vaginal bleeding (76-95), particularly during the first trimester of pregnancy (78,85,93), and during the second half of pregnancy (91,92). It has also been reported that vaginal bleeding during the first half of pregnancy significantly increases the risk of vaginal bleeding during the second half of pregnancy (91).

A very limited number of studies have assessed ethnic/race–specific differences in the relations between preterm delivery and antenatal vaginal bleeding. Those studies reported that odds-ratios were greater in White than in African-American women (79,80). Similarly in our study we found that ethnic/race-specific odds-ratios for preterm delivery in association with vaginal bleeding during the first 20 weeks of pregnancy were greater in non-Hispanic White than in African-American women; however this was primarily due to the higher risk of preterm delivery in "non-bleeders" (reference group) among African-American women compared to non-Hispanic White and there were no statistically significant interactions by race/ethnicity. Thus our study suggests that ethnic/racial disparities in the risk of preterm delivery are not mediated by pathways associated with vaginal bleeding in the first 20 weeks of pregnancy.

It is important to take bleeding characteristics (i.e. timing of bleeding, duration and heaviness of bleeding episodes) into account, since they may influence association between antenatal vaginal bleeding and the risk of preterm delivery. Many studies on antenatal vaginal bleeding and the risk of preterm delivery assessed timing of bleeding episodes (76,77,79-83,85,86,90-93) and some assessed heaviness (78-81,84,86); however only one study considered duration of bleeding episodes (79). While most of the

studies that considered heaviness of bleeding episodes found that the risk of preterm delivery was notably higher in women with heavier bleeding episodes (78-80,84) some studies found no association between heaviness of bleeding episodes and the risk of preterm delivery (81-86). Our detailed analyses using bleeding characteristics were consistent with previous findings, and suggested a dose effect with higher risk of preterm delivery as severity of bleeding increased. It was noted in our study that associations between the risk of preterm delivery and less severe bleeding were evident but weaker, an important nuance for prenatal care.

There are a number of factors that may potentially account for some of the differences in results of prior studies. First, many studies failed to include characteristics of bleeding in their data analysis. Second, studies used different definitions of bleeding characteristics, especially for heaviness of bleeding episodes. Finally, different study designs, various sample sizes, and degrees of control for potential confounders in both data collection and statistical analysis were used by different authors.

Among the many studies on vaginal bleeding during pregnancy and risk of preterm delivery very few have attempted to separate preterm delivery into its clinical subtypes, (i.e. PTL, PROM, and MI) (78,79,93,95). It has been reported that antenatal vaginal bleeding increases the risk of PTD in all subgroups but especially for PTL (79, 93,95). Only one study looked at the association between vaginal bleeding and risk of preterm delivery using both bleeding characteristics (timing, duration, and heaviness), and clinical subtypes of preterm delivery (79). One more study assessed the relation between heaviness of bleeding and the risk of PPROM (78).

In our study we found that both heavy bleeding (described as "same or greater than usual menstrual period"), and bleeding that lasted for over 24 hours were strongly associated with the risk of both spontaneous subtypes of preterm delivery (PTL and PROM). We also found increased risk of PROM in a group with bleeding described as "spotting/slight". All these findings were consistent with findings from other studies (78, 79). We also found strong associations between bleeding that lasted for over 24 hours and the risk of medically induced delivery and between bleeding "in weeks 1-13 only" and the risk of PTL. These findings contradicted the findings reported by Yang et al (79).

There has been much debate in the literature as to whether preterm delivery should be separated into its clinical subtypes. While some researchers insist on separation (95,96) others stand against it, arguing that these subtypes may not be etiologically different, may be confounded by differences in access to medical care, and may be subject to misclassification (97). Some investigators recommend that the subtypes be examined first, and if they appear to be homogenous, combine them back together (95, 96). In at least two studies, results showed that the overall set of risk factors associated with preterm labor and premature rupture of membrane was the same but different from those for medically induced preterm delivery. Given these findings the authors recommended that preterm labor and preterm premature rupture of membranes be combined into spontaneous preterm delivery and that medically induced preterm delivery be considered separately (95,96).

Our study has its strengths and limitations. Major strengths of this study are the large sample size, prospective design, the fact that women were not selected into the study based on their bleeding history, and confirmation of gestational age estimates based

on the last menstrual period using early ultrasound estimates for 90% of study women. Furthermore, the interval from period of bleeding during the first 20 weeks of pregnancy to time of maternal interview was short, thus minimizing recall bias; women were able to report up to seven bleeding episodes, and prospective collection eliminated the possibility of differential reporting based on women's knowledge of pregnancy outcome. Reliance on maternal self-report for information about vaginal bleeding episodes has its limitations and strengths. While there is subjectivity in recalling bleeding, self-report is potentially more accurate and complete than information obtained from medical records. It is possible that women might mistake an early vaginal bleedings as a menstrual period or vise versa but confirmation of gestational dates by ultrasound helps to reduce bias introduced by these types of mistakes. However potential reporting bias could be introduced by the possibility that women known to be at higher risk of delivering preterm, such as those with prior preterm deliveries, might over-report their vaginal bleeding because of increased anxiety during the current pregnancy. It is important to note that our study did not include women who miscarried prior to 20 weeks of pregnancy, and women who suffered fetal loss sometime between 20th and 27th weeks of pregnancy.

More studies are needed in order to further understand the association between vaginal bleeding during pregnancy and preterm delivery and the underlying mechanism for this association in order to be able to make recommendations for prenatal care. This study points to the importance of carefully considering bleeding characteristics, ethnic/racial differences, and clinical subtypes of preterm birth in pathways to preterm delivery.

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