Published in final edited form as:

J Matern Fetal Neonatal Med. 2011 June ; 24(6): 778–786. doi:10.3109/14767058.2010.530707.

Vaginal bleeding in early pregnancy and preterm birth: systemic review and analysis of heterogeneity

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Abstract

Objective—To systemically review published studies of vaginal bleeding and the risk of preterm birth (PTB) and explore sources of heterogeneity between them.

Methods—The literature was searched for peer-reviewed articles from 1980–2009 in which the primary analysis was the risk of PTB among low risk subjects with and without bleeding. Heterogeneity was assessed through I^2 statistics and sources of heterogeneity were explored through subgroup analyses and meta-regression.

Results—218 studies were initially identified, 64 reviewed and 23 included. The pooled Odds Ratio for PTB was 1.74, though significant heterogeneity was present ($I^2=49.7\%$). Meta-regression demonstrated a significant association between a study's incidence of bleeding and quality assessment and subsequent odds ratio, such that studies with a lower quality assessment or lower incidence of bleeding demonstrated an increased odds of preterm birth.

Conclusions—Bleeding in early pregnancy is associated with an increased risk of PTB, however excessive heterogeneity exists among published studies. The heterogeneity arises in part from differences in the reported incidence of bleeding within study populations. Presumably studies that identify bleeding in a larger percentage of subjects consequently dilute the magnitude of the risk.

Keywords

Vaginal bleeding; preterm birth; metaanalysis; metaregression; systemic review; threatened abortion; preterm premature rupture of membranes

Introduction

Preterm birth complications approximately 12% of pregnancies [1] and is a leading cause of neonatal morbidity and mortality. Although many cases of preterm birth remain idiopathic, many occur secondary to clinical or subclinical intrauterine bleeding events, and bleeding in the chorion-decidual interface is one of the four major hypothesized pathways of spontaneous preterm birth [2]. Additionally, histologic evidence of prior chorion-decidual

bleeding is more common in the placentas of infants with preeclampsia or IUGR [3], two of the major causes of indicated preterm deliveries. Though many cases of chorion-decidual bleeding are subclinical, many will present with clinically recognized vaginal bleeding, and the presence of clinical vaginal bleeding during pregnancy has been associated with subsequent preterm birth in prior studies.

Bleeding events that occur in early pregnancy are usually not directly observed by care providers, and thus one is often dependent upon a patient's self report and qualitative assessment of the bleeding event. This can create obvious problems for both clinicians and researchers in that a patient's self report can be subject to an array of biases and recall errors. Consequently it is not surprising that variation in preterm labor risks are present in different studies of vaginal bleeding during pregnancy. Such differences, however, potentially can be accounted for by differences in patient populations and study designs. For example, prospective studies may identify a larger total number of patients with vaginal bleeding than retrospective studies, though they may also identify patients with lesser degrees of bleeding which may be of less consequence. Both prospective and retrospective studies can also differ in their definitions of bleeding or preterm birth, the trimester in which bleeding occurs, and many other features. These differences can pose barriers to the study of vaginal bleeding and preterm birth, making comparisons between studies difficult.

In addition to providing a pooled estimate of the risk of preterm birth after a bleeding event, meta-analytic methods can be used to explore the degree and sources of heterogeneity among included studies. The identification of factors associated with increased heterogeneity can assist future researchers in the development of study design or the formation of standard definitions for bleeding events or outcomes, as well as assist in the interpretation of the literature. Our hypothesis was that clinical vaginal bleeding would be associated with an increased risk of preterm birth, though with significant heterogeneity among the studies. We additionally hypothesized that subgroups of studies or subjects could be identified in which this heterogeneity was reduced.

Methods

The planning and performance of the systemic review was in accordance with the "Meta-analysis of Observational Studies in Epidemiology" (MOOSE) guidelines[4]. Published studies were identified through a computerized search of PubMed, MEDLINE, and the Cochrane database conducted in April 2009. The search strategy was formulated with the assistance of a medical librarian at the University of Rochester School of Medicine, and is presented in Figure 1. The references of selected studies, review articles, and book chapters were searched by hand for additional publications.

Studies were included if they were published in a peer-reviewed journal between 1980 and 2009. Publications prior to 1980 were excluded due to concerns of underreporting of early preterm births due to historical changes in the lower limit of neonatal viability. Despite this limitation, 5 studies [5–9] were still encountered that excluded subjects who delivered at less than 28 weeks. A consensus decision was made to include these studies, though to also perform a sensitivity analysis to determine if their exclusion would impact the final results.

Included studies were required to have a comparison group without clinical vaginal bleeding, with case series being excluded. English language was an inclusion criteria, though no identified publications ended up being excluded for this indication. Because one of the aims of the study was to access differences in study design, no *a priori* exclusion criteria were used for study quality assessments. Instead, different methods of ascertainment of vaginal bleeding and study design were analyzed in subgroup analyses and meta-regression. Additionally the quality of included studies was assessed through the Newcastle Ottawa scale (www.ohri.ca/programs/clinical_epidemiology/oxford.htm) and study quality subgroups were analyzed. Abstracts and unpublished studies were not included.

Studies were included if the association between vaginal bleeding and preterm birth was the primary outcome of the study, as reflected in the title or abstract. Unfortunately this necessitated excluding some well-known studies of preterm birth in which bleeding was included in a secondary analysis. Only including publications in which bleeding and PTB was the primary outcome, however, eliminated potential concerns of multiple analyses within included publications. Additionally, searching for all publications on the subject of preterm birth to identify those in which bleeding may have been included as a secondary analysis was not determined to be practical, and thus it was preferable to exclude all secondary analyses rather than include select publications from outside of a systemic review process.

Subjects in included studies needed to have experienced vaginal bleeding prior to 24 weeks estimated gestational age (EGA). Studies that included vaginal bleeding in all three trimesters were included if specific results were provided within individual trimesters, in which case they were included with only the pooled 1st and 2nd trimester results included in the statistical analysis. Studies that were limited to subjects with bleeding in only the 1st or 2nd trimester subjects were included in the primary analysis but were then also analyzed in separate subgroups.

Included studies evaluated the relationship between bleeding and preterm birth in low-risk, generalizable patient populations. Studies that were entirely limited to specific subpopulations of patients, such as those undergoing infertility or invasive procedures or with only specific risk factors, were excluded, though we did not seek to exclude studies that may have included such patients among their total population. Publications also had to classify their exposure only according to the presence or absence of vaginal bleeding. Two publications subdivided their subjects with vaginal bleeding into those with or without elevated maternal serum alpha-fetoprotein [10] or umbilical cord IgM [11] without reporting the overall association between bleeding and preterm birth, and were thus excluded. We also excluded studies that were limited to subjects with placenta previa or “abruption”, though no studies were ultimately excluded secondary to being limited to abruption. A consensus decision was made to include three studies that were limited to primagravidas [12–14], though with the decision to perform a sensitivity analysis to determine if their inclusion altered the primary outcome. If two publications evaluated the same patient population, only the most recent publication was included. Of note, two included publications had the same primary author but analyzed two separate study populations[15–16].

The Odds Ratio (OR) and 95% confidence intervals for PTB in subjects with or without VB was calculated from all included studies. The summary ORs were calculated by fixed- and random-effects models using the Mantel-Haenszel and DerSimonian-Laird methods, respectively. Study heterogeneity was assessed by I^2 statistics, and sources of heterogeneity were explored by sensitivity and subgroup analysis. Planned secondary analyses were performed for the outcomes of preterm premature rupture of membranes (PPROM), spontaneous preterm birth, and “early” and “late” preterm births. Planned subgroup analyses were performed for subjects with bleeding in only the 1st or 2nd trimester, and “light” versus “heavy” bleeding (defined variably between studies), prospective versus retrospective study designs as well as study quality subgroups. For the subgroup analyses, the OR’s of studies that only included subjects in a particular trimester (i.e. only patients with 1st trimester bleeding) were included with the calculated OR’s from the same trimester from studies that included patients with bleeding in both trimesters but provided data on individual subgroups. For the “light” and “heavy” bleeding subgroups, studies were included in which separate data was presented for these two different groups, defined variably between studies.

A sensitivity analysis was performed to assess the impact of individual studies. A cumulative meta-analysis was performed to assess the chronologic addition of studies. Publication bias was assessed through a Funnel Plot. Meta-regression was performed within cohort studies with the log(OR) for preterm birth as the dependent variable and study characteristics as independent variables. All analyses were performed on Stata 10 (College Station, Texas, USA), supplemented by the user-defined commands: metan, metabias, metafunnel, metacum, and metareg. User defined commands were uploaded on and thus current to March 2010, primarily through www.stata-press.com/data/mais.

Results

206 studies were identified through the initial search result, and an additional 12 studies were identified through a hand search of references, for a total of 218 potentially eligible publications. 154 of these were able to be excluded by title or abstract review alone, leaving 64 publications for review. Of these, 41 were excluded after manuscript review. The causes of exclusion are presented in Table I, with the absence of a control group being the most common reason. The final result of the literature search was 23 publications [5–9, 12–15, 17–30]. Details regarding included studies are presented in Table II. The total number of subjects was 152,512, of whom 19,201 had vaginal bleeding and 10,625 had preterm birth.

The forest plot for the relative risk of preterm birth among all studies is presented in Figure 2. The pooled OR in a random effects model was 1.74, with a 95% confidence interval that did not include the null hypothesis. However, moderate heterogeneity was also present ($I^2=49.7\%$). A visual analysis of the cumulative meta-analysis demonstrated that this risk has been relatively stable since the early 1980’s (data not shown). In sensitivity analysis the exclusion of any one study did not cause the pooled OR to become non-significant, nor increase to more than 2.0. There were no meaningful differences when two studies that only enrolled primigravidas [12–13] were excluded (pooled OR=1.77, $I^2=50.3\%$), as well as after the exclusion of five studies which only included subjects who had achieved at least 28 weeks gestational age [6–9] (pooled OR=1.81, $I^2=53.8\%$). Of note, 9 studies did not provide

a specific lower gestational age cut-off, and cut-offs for the other studies ranged from 20–25. Individual gestational age groups in this regard were too small for individual subgroup analyses. Publication bias or small-study effects did not appear to be present either through the visual inspection of a funnel plot (Figure 3) or Egger's test ($p=0.67$).

The included studies were classified according to different aspects of study design. The included studies were a mix of those that utilized “population samples” (i.e. all subjects with or without vaginal bleeding within a comprehensive cohort) and those that utilized “samples of convenience” (i.e. subjects with vaginal bleeding who presented to a clinic or ultrasound unit were compared to a group of subjects without bleeding). The stratified forest plot for these two study types is presented in Figure 4. Although there were no meaningful differences in the pooled ORs between groups, there were dramatic differences in heterogeneity, which was minimal in studies of convenience ($I^2=0\%$) and severe in population samples ($I^2=65.4\%$). Table III presents the results of subgroup analyses of prospective versus retrospective study design as well as study quality. Meaningful differences were not present between studies with prospective versus retrospective study designs, though the OR for prospective studies was slightly lower than that of retrospective studies. Studies were further subdivided into those that had less than the maximum score on the Newcastle Ottawa scale (NOS) of quality. Of note, most studies with scores of <9 still fell within the acceptable range, and thus would not be considered to be of “low” quality per se. Studies with quality scores <9 demonstrated an increased OR of preterm birth than those with higher scores, and also demonstrated reduced heterogeneity.

In order to further explore the heterogeneity within studies that utilized population samples, meta-regression was performed with $\log(\text{OR})$ as the dependent variable and the incidence of vaginal bleeding within the cohort and NOS scores as the independent variables. Figure 5 demonstrated the association between the incidence of vaginal bleeding and subsequent odds of preterm delivery. The association between a study's incidence of vaginal bleeding and subsequent OR for preterm birth was highly significant ($p<0.001$) with an adjusted R^2 of 91%, suggesting that differences in the incidence of bleeding account for 91% of the total variation in effect sizes between studies. Meta-regression also demonstrated a significant association with the NOS score ($p=0.036$), in that studies higher quality demonstrated lower odds of preterm birth. Of note, high quality studies also demonstrated a higher mean incidence of vaginal bleeding, though these differences did not achieve statistical significance (data not shown). In univariate regression of other study characteristics, there was no significant association between a study's OR a year of publication ($p=0.19$), total sample size ($p=0.95$) or incidence of preterm birth ($p=0.84$).

The subgroup analysis for 1st versus 2nd trimester and light versus heavy vaginal bleeding are presented in Table V. The results from all groups were limited by modest to severe heterogeneity. The odds of preterm birth were higher with heavy versus light and second versus first trimester bleeding, though the significant degree of heterogeneity within each group limits the meaningfulness of these comparisons.

The results of the analyses of preterm birth subtypes are presented in Table VI. Though eight studies reported on rates of preterm births at earlier gestational ages than 37 weeks, the

exact gestational age cut-offs for their “early” subgroups ranged from 30–34 weeks. Thus the five studies which utilized a cut-off of 34 weeks were analyzed separately from the three studies that used even lower gestational age limits. In studies that reported on the total number of preterm births and the number of preterm births that occurred at an earlier gestational age, simple subtraction was used to determine the number of subjects with “late” preterm births, defined variably as 30–34 to 37 weeks. Of note, 37 weeks was used as the upper limit of gestational age for the “preterm birth” subgroup, with the exception of two publications[7, 9] which did not explicitly state a gestational age limit. An analysis of the primary outcomes was repeated with the exclusion of these two publications and did not demonstrate a meaningful difference (pooled OR=1.84, $I^2=48.8\%$). With regards to other preterm birth subtypes, only three studies reported specific information on “spontaneous”, as opposed to “indicated” preterm birth, with “spontaneous” being defined as preterm births which occur after preterm premature rupture of membranes or after preterm labor.

Discussion

The presence of vaginal bleeding prior to 24 weeks gestation is associated with an increased risk of preterm birth, however significant heterogeneity exists among the published studies limiting the extent to which a single pooled Odds Ratio could be meaningfully interpreted. Additionally the Odds Ratios, while statistically significant, were also not particularly strong, as most of the pooled results were < 2.0 . In an analysis of heterogeneity, the between study variation appears to arise primarily from differences in the incidence of bleeding in studies that utilize population samples and study quality. In fact, differences in the incidence of vaginal bleeding accounted for 91% of the total variability in ORs between studies utilizing population samples in meta-regression. By contrast, heterogeneity was actually minimal in studies that utilized samples of convenience, which is probably a reflection of the bleeding incidence being fixed by the constraints of the study design.

Presumably cohort studies with a higher incidence of vaginal bleeding are either more thorough in seeking cases of bleeding or have more lenient case definitions, both of which may weaken the association with preterm birth through the inclusion of subjects who are not at true risk of adverse outcomes. Of note, the relationship between clinical vaginal bleeding and preterm birth was also analyzed in the Preterm Prediction study [32], though not included in this analysis secondary to the requirement that bleeding and preterm birth be the primary analysis of the paper. It is interesting to note, however, that the incidence of first or second trimester vaginal bleeding in the Preterm Prediction Study is higher than that of any of our other included studies (25.9%) and did not have a statistically significant association with preterm birth ($p=0.86$) in the overall analysis (though significant associations were identified in subgroups, such as multiparous patients). Likewise there was a trend towards a higher incidence of vaginal bleeding in studies that had higher scores of methodological quality on the Newcastle-Ottawa scale, and increasing study quality was significantly associated with a decreased odds of preterm birth secondary to vaginal bleeding in metaregression. Thus overall there is a suggestion that higher quality studies that identify all subjects with bleeding in a more complete manner, resulting in a higher reported incidence of bleeding, demonstrate a decreased association with preterm birth relative to studies that identify fewer subjects with bleeding. The implications for the practicing clinician is that the

true association between early pregnancy bleeding events and preterm birth, while still statistically significant, may be of a smaller magnitude than previously believed.

Of note, some studies that utilized samples of convenience incorrectly identified themselves as “case control” studies [29, 31]. In a study in which subjects with vaginal bleeding are identified and then followed to determine whether or not they experience obstetrical complications, the bleeding event constitutes an “exposure” and the obstetrical complication constitutes an “outcome”. Thus “cases” should be individuals with preterm birth, as opposed to vaginal bleeding, and a true “case control study” of vaginal bleeding and preterm birth would identify subjects with and without preterm birth and then compare their incidence of prior vaginal bleeding, as opposed to the other way around. Although it is possible to perform a case control study with vaginal bleeding constituting the “case”, such a study would be one that identified risk factors for the outcome of bleeding [23]. Studies that identified subjects with vaginal bleeding, matched them to subjects without bleeding and then determined the subsequent obstetrical outcomes would be better described as utilizing a “sample of convenience”.

The primary result in our meta-analysis is similar to that from two prior meta-analyses by Ananth et al[33] and Saraswat et al[34] both of which also found a statistically significant association with preterm birth, though neither of which explored the high degree of underlying heterogeneity or analyzed preterm birth subgroups. Included studies differed between our study and the prior analyses in that Ananth et al included studies from 1950 to 1992, and Saraswat et al was limited to studies of “threatened miscarriage” in the first trimester, and also excluded publications on the basis of quality. Rather than exclude studies on the basis of quality, we had elected *a priori* to include all studies and then evaluate the association between study quality and odds ratios. Additionally not all studies of “threatened miscarriage” included only subjects with vaginal bleeding, as some included subjects with either bleeding or pain [31], and were thus excluded from our study though included in Sawaswat et al.

Two potential limitations of our study include the exclusion of studies that did not have an available English language translation and studies that were either unpublished abstracts or not published in peer-reviewed journals (the “grey literature”). Though we had elected to exclude studies that were not available in English, no publications ultimately were excluded for this indication, and the recent meta-analysis by Sawaswat et al[34] which did not excluded non-English publications also did not identify any publications on bleeding and preterm birth that were not available in English. With regards to the “grey literature”, this is often excluded in order to avoid publications that may be of suspect quality, though excluding them raises the potential for publication bias. However, there was no evidence of publication bias in our study in either the visual analysis of a funnel plot or in the more formal Egger’s test. Thus we do not believe that either of these exclusions ultimately impacted our results.

It had been anticipated that bleeding subtypes could be identified in which either heterogeneity was reduced or the association between bleeding or preterm birth would be found to be particularly strong. Such information would have potentially been clinically

useful with regards to patient counseling after a bleeding event. Unfortunately this did not prove to be the case. For example, it was anticipated that subgroups in which the bleeding events shared a similar trimester or relative intensity would demonstrate a more homogenous association than in the total collection of publications. However in all such subgroups the I^2 remained greater than 50%, and in fact was extremely elevated in the “light bleeding” subgroup. This probably reflects the fact that different studies that included subgroups with “light” versus “heavy” bleeding utilized different definitions for them, as is outlined in Table II.

Likewise it had been anticipated that preterm birth subtypes, for example indicated versus spontaneous deliveries or early versus late preterm births, could be identified that had either reduced heterogeneity or a clearly increased magnitude of risk. However, this also essentially did not prove to be the case. The one potential exception is that the pooled OR of preterm births at less than 30–33 weeks gestation was quite high (3.62), however the heterogeneity was also quite significant and this subgroup only included three studies. Thus one hesitates to conclude that bleeding specifically increases the risk of “early” preterm births, especially since there were no meaningful differences between the odds of delivery at <34 weeks and between 34–37 weeks. Likewise, the heterogeneity among subgroups of “spontaneous” and “indicated” preterm births was minimal (~0%), however this was also only based upon three studies. The relatively small number of studies that included specific data on “spontaneous” versus “indicated” preterm births as well as different gestational age cut-offs also serves to highlight a relative deficiency that exists in the current literature. Other important sources of heterogeneity in the current literature included different lower limits of gestational age cut-offs, which ranged from 20 to 28 weeks, and different underlying etiologies of the vaginal bleeding. Unfortunately none of the included publications provided either information on the underlying etiology of the bleeding event or etiology-specific risks of preterm birth with the exception of French et al [21], which evaluated the combined effect of both vaginal bleeding and vaginitis. Additionally, two studies that did not meet our inclusion criteria [10, 11] evaluated the association between clinical bleeding and elevated MSAFP or IgM with regards to preterm birth, thus indirectly evaluating potential placental or inflammatory etiologies.

Of note, vaginal bleeding is often cited as being a specific risk factor for PPROM. This is due in part to the fact that thrombin activation has been associated with the production of matrix metalloproteinases [35] and other enzymes involved in the degradation of fetal membranes. However, the pooled relative risk of PPROM (1.61) in this analysis, while statistically significant, also did not differ in a meaningful way from the aggregate risk of preterm birth, as was also demonstrated by Saraswat et al[34]. Thus, while an association does exist, it does not appear to clearly be stronger than that of other preterm birth subtypes.

In conclusion, clinical vaginal bleeding is significantly associated with an increased risk of preterm birth, though that magnitude of the risk varies between different studies. The primary source of this variation is differences in the incidence of vaginal bleeding within population samples and study quality. Thus future studies in this area should strive to ensure that all episodes of vaginal bleeding within the study population are accounted for, so as to not potentially inflate the association with preterm birth. Additionally, relatively few studies

were encountered in this review that provided risks of “spontaneous” versus “indicated” preterm deliveries or the risk of preterm delivery in association with vaginal bleeding of different etiologies, and thus strong consideration should be given to providing these subdivisions in future publications. Perhaps a more difficult problem for both researchers and clinicians who are attempting to interpret this literature is the range of different definitions for bleeding which are utilized by different studies, both overall and in “light” and “heavy” subgroups. Since these definitions are both not standardized and inherently subjective, one potential solution would be the utilization of quantifiable markers, such as thrombin-antithrombin complexes[36–37].

Acknowledgments

Funding: Women’s Reproductive Health Research K-12: HD001332-09

We would like to acknowledge reference librarian Margaret Chretien for her assistance with the development of the search strategy and Carol Lin, MD, for her assistance with the manuscript.

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(exp Uterine Hemorrhage) or (vaginal bleed\$) or (abruption) or
(exp Abruptio Placentae) or (Abortion, Threatened) or
(threatened miscarriage) or (bleed\$)

And

(exp Pregnancy Trimester, First) or
(exp Pregnancy Trimester, Second)

And

(Fetal Membranes, Premature Rupture) or
(premature rupture of membrane\$) or
(preterm rupture of membrane\$) or
(exp Obstetric Labor, Premature) or (exp Pregnancy Outcome)

Figure 1.
Search strategy

Figure 2.
Forest Plot of studies of preterm birth after vaginal bleeding. The y-axis is Log (Odds Ratio). Individual studies are demonstrated graphically with 95% confidence intervals.

Figure 3. Funnel Plot of studies of preterm birth after vaginal bleeding. The y-axis is Log (Odds Ratio) and the x-axis is standard error of the Log (Odds Ratio).

Figure 4.

Stratified forest plot of cohort studies of preterm birth after vaginal bleeding stratified according to study design. The y-axis is Log (Odds Ratio). Individual studies are demonstrated graphically with 95% confidence intervals.

Figure 5. Scatter plot of the incidence of vaginal bleeding within cohort studies and the Log (Odds Ratio) of preterm birth. Black circles represent individual studies with a diameter that is proportional to their sample size. Only studies that used a population sample were included.

Table I

Reasons for study exclusion

No subjects without vaginal bleeding (case series): 23
Preterm birth not reported as outcome: 10
Vaginal bleeding not the primary or sole exposure: 6
Limited to previa, infertility patients or other subgroups: 2

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Table II

Characteristics of included studies

Year	First Author	Total population	Total w/ bleeding (%) [*]	Study design	Definition of Bleeding
1980	Funderburk[16]	25,377	259 (1.0%)	Population sample. Record review, not otherwise specified, presumed retrospective	At least one episode of spotting
1983	Berkowitz[6]	16,305	2,385 (14.6%)	Population sample. Retrospective review of post-partum questionnaire	Greater or less than menses
1984	Batzofin[17]	7,229	523 (7.2%)	Population sample. Record review, not otherwise specified, presumed retrospective	Deemed significant by provider
1985	Hertz[5]	375	93	Convenience sample Presumed prospective, though unclear	“Threatened abortion” defined as vaginal bleeding with or without cramps
1989	Strobino[8]	3,346	744 (22.2%)	Population sample Prospective after second trimester interview	At least “spotting or slight” for “Light” and “characterized as moderate or heavy” for “Heavy”
1992	Sipila[19]	8,718	807 (9.3%)	Population sample Questionnaire at 24 wks then prospective collection of delivery data	“Light” subgroup did not require hospital care
1991	Williams[18]	11,444	1,174 (12%)	Population sample Retrospective review of post-partum questionnaire	“Heavy” subgroup had been admitted.
1993	Verma[9]	113	63	Convenience sample Unclear if retrospective or prospective	Present or absent only
1995	Tongsong[26]	520	255	Convenience sample Prospective with subjects enrolled at the time of bleeding	Clinically diagnosed with “threatened abortion”
1996	Das[7]	110	55	Convenience sample Presumed prospective	Vaginal bleeding sufficient for an ultrasound to have been ordered
1998	Karim[27]	268	95	Convenience sample retrospective medical record review	Vaginal bleeding sufficient for ultrasound examination
1998	Signore[28]	334	167	Convenience sample retrospective chart review	Present or absent only
1999	French[20]	1,169	190 (15.8%)	Population sample Secondary analysis of prospective trial	Vaginal bleeding sufficient for ultrasound examination
2000	Arafa[21]	1,503	159 (10.6%)	Population sample Interviewed postpartum	Not defined
2001	Yang[15]	8671	308 (4.3%)	Population sample Retrospective review of questionnaire	“Light”: one episode of spotting; “Heavy”: > 1 teaspoon
2003	Harville[23]	136	14 (8.8%)	Population sample Prospective patient log	Sufficient for Bed rest
2004	Mulik[13]	6,903	458 (6.6%)	Population sample Retrospective analysis of database	Requires a pad for at least a day
2004	Yang[14]	2,802	683 (24.3%)	Population sample Questionnaire at 24–29 Weeks, prospective	Not defined
2004	Weiss[24]	16,506	2,346 (14.2%)	Population sample Secondary analysis of prospective study. 1 st trimester questionnaire	Any bleeding or spotting
2006	Wijesiriwardana[12]	39,260	7,627 (19.4%)	Population sample. “Retrospective cohort”	“Light”: Spotting only “Heavy”: Similar to menses
2006	Johns[29]	214	214	Convenience sample Prospective	Sufficient for subjects to seek hospital assessment prior to 12 weeks
					Vaginal bleeding sufficient for referral, “spotting” was excluded

Year	First Author	Total population	Total w/ bleeding (%) [*]	Study design	Definition of Bleeding
2007	Hossain[25]	2,678	622 (26.2%)	Population sample. Interview prior to 20 wks, then data collected prospectively	Present or absent only
2008	Davari-Tanha[30]	600	150	Convenience sample Prospective	Not defined

* The percent incidence of vaginal bleeding is only provided for studies that utilized a population sample.

**[†] 1st half of pregnancy” and “more severe” subgroups were selected from many different available subgroups for meta-analysis as this was most similar to other included studies

Table III

Analysis of vaginal bleeding and preterm birth in study design subgroups

Subgroup	# of studies [ref]	OR [95% CI]	I ²
Prospective	10 [8, 14, 19–20, 23–26, 29–30]	1.58 [1.37–1.83]	41.9%
Retrospective	8 [6, 12–13, 15, 18, 21, 27–28]	1.98 [1.73–1.25]	61.6%
NOS = 9	11 [6,8,12,13,15,19,21,22,25,26,29]	1.76 [1.54–1.93]	63.5%
NOS<9	12 [5,7,9,16–18,20,24,27,28,30,31]	2.12 [1.89–2.38]	0.0%

Legend: OR=Pooled Odds ratio for preterm birth, presented with 95% confidence intervals. NOS=Newcastle Ottawa quality assessment scale of cohort studies.

Table IV

Analysis of vaginal bleeding subgroups

Subgroup	# of studies [ref]	OR [95% CI]	<i>I</i> ²
1st tri bleeding	13 [8, 12, 14, 18–21, 24–27, 29–30]	1.54 [1.36–1.73]	52.8%
2 nd tri bleeding	7 [14, 19–21, 25, 27–28]	2.1 [1.45–3.04]	63.8%
“Light” [*] bleeding	5 [6, 8, 14, 19, 24]	1.5 [1.17–1.93]	80.2%
“Heavy” [*] bleeding	6 [6, 8, 14, 19, 22, 24]	2.15 [1.69–2.75]	55.8%

Legend: OR=Pooled Odds ratio for preterm birth, present with 95% confidence intervals.

^{*} Defined variably between studies, see Table II.

Table V

Analysis of preterm birth subgroups

Subgroup	# of studies [ref]	OR [95% CI]	<i>I</i> ²
Delivery < 34 wks	5 [5, 12, 14, 25, 29]	1.63 [1.24–2.15]	39.8%
Delivery <30–33 wks	3 [13, 15, 18]	3.62 [2.68–4.9]	61.7%
Late PTB	8 [5, 12–15, 18, 25, 29]	1.53 [1.27–1.84]	64.2%
PPROM	10 [5, 9, 12, 14, 20, 24–26, 29–30]	1.61 [1.29–2.01]	33.7%
SPTB	3 [14, 20, 25]	1.62 [1.29–2.02]	0%
Indicated PTB	3 [14, 20, 25]	1.33 [1.06–1.7]	0%

Legend: OR=Pooled Odds ratio for preterm birth, present with 95% confidence intervals, PTB = Preterm Birth, PPRM = preterm premature rupture of membranes, SPTB = spontaneous preterm birth secondary to preterm labor or PPRM. Late preterm births are those at occur at 34+0 to 36+6 weeks.