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Patterns of vaginal bleeding during the first 20 weeks of pregnancy and risk of pre-eclampsia in nulliparous women: results from the SCOPE study

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Key words
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Conflict of interest
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Abstract

Objective. To describe patterns of vaginal bleeding in the first 20 weeks of pregnancy and evaluate the association between patterns of bleeding and risk of subsequent pre-eclampsia in nulliparous women. *Design.* Cohort study. *Setting.* Participating centres of the Screening for Pregnancy Endpoints (SCOPE) study in Auckland (New Zealand), Adelaide (Australia), Manchester and London (UK) and Cork (Ireland). *Population.* Healthy nulliparous women ($n = 3431$). *Methods.* Logistic regression was used to assess the association between bleeding characteristics and pre-eclampsia while controlling for known determinants of pre-eclampsia. *Main outcome measures.* Preeclampsia, defined as gestational hypertension with proteinuria or any multi-system complication of preeclampsia. Four bleeding variables were evaluated: any bleeding during the first 20 weeks; maximal bleeding intensity; duration of bleeding; and number of bleeding episodes. *Results.* Of the 3431 women enrolled, 780 (23%) experienced vaginal bleeding during the first 20 weeks of pregnancy. Risk of pre-eclampsia was not associated with the presence or absence of bleeding (adjusted odds ratio (ORa) 0.96, 95% confidence interval (95% CI) 0.67–1.38). Analyses confined to women with vaginal bleeding showed that any bleeding episode of five or more consecutive days, compared with shorter episodes, increased risk of pre-eclampsia approximately twofold (ORa 2.15, 95% CI 1.01–4.57), as did multiple compared with single episodes of bleeding (ORa 2.33, 95% CI 1.16–4.67). *Conclusions.* Bleeding is a common complication during the first 20 weeks of nulliparous pregnancy, and the presence or absence of vaginal bleeding is not a determinant of subsequent pre-eclampsia. Among women with vaginal bleeding, consideration of the bleeding pattern, in terms of intensity, duration and frequency, appears to be informative with respect to pre-eclampsia risk.

Abbreviations: CI, confidence interval; OR, odds ratio; ORa, adjusted odds ratio; SCOPE, Screening for Pregnancy Endpoints.

Introduction

Bleeding in the first 20 weeks of pregnancy is a common complication affecting about one in five pregnant women (1) and is of clinical relevance as these women have increased risks of adverse outcomes, particularly placental abruption, low birthweight and preterm delivery (2–4). Furthermore, some authors have reported that the risk of pregnancy complications is related to bleeding characteristics, with heavier bleeding, multiple as opposed to single episodes and prolonged bleeding being associated with higher risks (5,6).

Key Message

Vaginal bleeding is a common complication during the first 20 weeks of nulliparous pregnancy. Although the presence or absence of bleeding is not a determinant of subsequent pre-eclampsia, certain bleeding patterns are associated with risk of pre-eclampsia.

As bleeding may be an early marker of placental dysfunction, a few studies have evaluated the association between bleeding and development of later pre-eclampsia, but the results have been conflicting. Weiss et al. (7) found a 40% increased risk of pre-eclampsia in women with light bleeding during the first trimester of pregnancy in comparison to women without bleeding, whereas women with heavy bleeding did not have elevated risk. Dadkhah et al. (8) found a 35% increased risk for women bleeding during the first half of pregnancy, but the association was not statistically significant. In contrast, others have reported decreased risks of pre-eclampsia after first trimester bleeding or bleeding of unknown origin during the second half of pregnancy (9,10).

A limitation of the currently available evidence is that, except for one study (7), no distinction has been made between different patterns of bleeding. Furthermore, some of the studies (8,9) presented only unadjusted association estimates, even though baseline characteristics may differ between women with and without bleeding (7,8). Lack of adjustment for potential confounders hampers comparability of studies.

In the present study, we analysed patterns of vaginal bleeding in the first 20 weeks of pregnancy and evaluated the association between vaginal bleeding and development of pre-eclampsia in a population-based cohort of 3431 nulliparous women. Our aims were as follows: (i) to describe the patterns of vaginal bleeding; and (ii) to assess the associations between patterns of bleeding and pre-eclampsia, adjusting for baseline differences in determinants of pre-eclampsia.

Material and methods

The participants were healthy nulliparous women with singleton pregnancies recruited to the SCOPE (Screening for Pregnancy Endpoints) study between November 2004 and August 2008 in Auckland (New Zealand), Adelaide (Australia), Manchester and London (UK) and Cork (Ireland). SCOPE is a prospective, multicenter cohort study with the main aim of developing screening tests to predict pre-eclampsia, small-for-gestational age infants and spontaneous preterm birth. Ethical approval was gained from local ethics committees, and all women provided written informed consent.

Women were recruited to the SCOPE study at 14–16 weeks of gestation. Gestational age was calculated from the first day of the last menstrual period. If information about the date of the last menstrual period was uncertain, then scan dates were used to calculate gestational age (11). Women considered at high risk of pre-eclampsia, small-for-gestational age babies or spontaneous preterm birth because of underlying medical conditions (including known pre-existing chronic hypertension on antihypertensive medication or a blood pressure greater than 160/100 mmHg at 14–16 weeks of gestation), obstetrical history, three or more previous miscarriages or terminations of pregnancy or who received interventions that may modify pregnancy outcome were excluded. Women with no previous history of chronic hypertension, who had mild elevation of blood pressure at the 14–16 weeks SCOPE interview, were included in the study.

Women who agreed to participate were interviewed and examined by a research midwife at 14–16 and 19–21 weeks of gestation, and data were entered into an Internet-accessible auditable database developed by Medscinet AB (Stockholm, Sweden). Details of the data collected have previously been described (11) and included demographic information, current pregnancy history and medical and gynecological history. Detailed data were also collected about any episode of vaginal bleeding, including the gestation at onset of bleeding, duration (in days) and intensity. Intensity of bleeding was categorized as spotting, light, like a period or heavy with clots. The definitions of bleeding intensity in the standard operating procedures used by the research midwives were as follows: spotting is a few spots of blood after toilet or on pants; light bleeding is bleeding heavier than spotting but lighter than an average period; 'like a period' is bleeding requiring pads that need to be changed one to five times per day; and heavy bleeding with clots is soaking pads every couple of hours with or without passing of clots.

Four additional bleeding variables were also constructed, as follows: any bleed during the first 20 weeks (yes/no); maximal bleeding intensity of any bleeding episode (no bleeding/spotting/light to heavy bleeding); maximal duration of bleeding (no bleeding/one- to four-day bleeds/any bleeds of duration five or more days); and number of episodes of bleeding (none/one/two or more). Maternal physical measurements included blood pressure, height and weight. Participants were followed prospectively, with pregnancy outcome data and infant measurements recorded by research midwives, usually within 72 h of birth.

Outcome measures

The primary outcome was pre-eclampsia, defined as gestational hypertension with proteinuria (24 h urinary protein $\geq$300 mg or spot urine protein:creatinine ratio $\geq$30 mg/mmol creatinine or urine dipstick protein $\geq$2+)

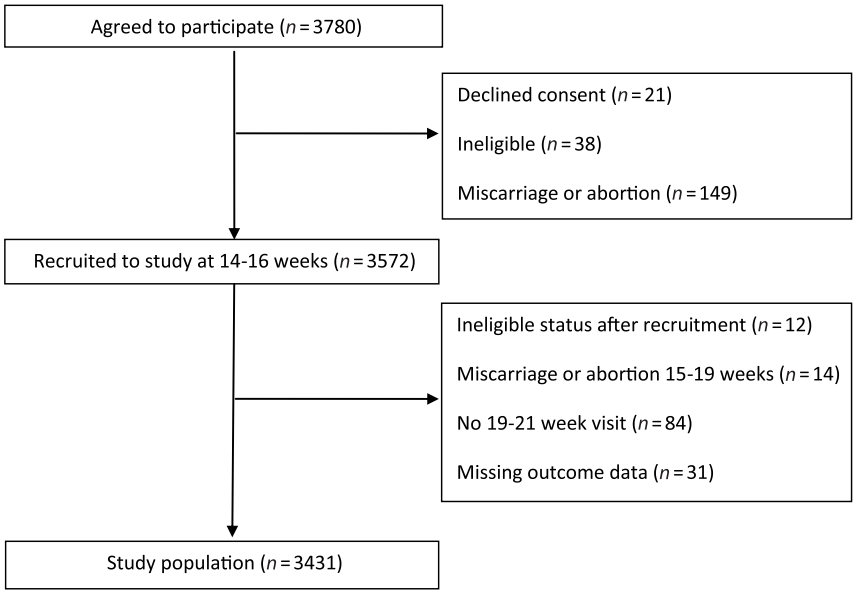

Figure 1. Recruitment and selection of study population.

or any multisystem complication of pre-eclampsia (12). Gestational hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least two occasions four hours apart after 20 weeks of gestation, but before the onset of labor, or postpartum systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least two occasions four hours apart.

Statistical methods

Data were available for >99% of the variables included in the database. Missing data were imputed for multivariate analyses using expected maximization (13). Uni- and multivariate logistic regression was used to evaluate the association between vaginal bleeding characteristics and the occurrence of pre-eclampsia. The following variables were considered potential confounders: maternal age; ethnicity; gravidity; smoking during first trimester; body mass index at 14–16 weeks; systolic blood pressure and diastolic blood pressure at 14–16 weeks; and months of sexual relationship with the biological father. Confounding was evaluated by adding one potential confounder at a time to the model, starting the model with only the bleeding variable of interest; if the odds ratio (OR) or one of the ORs for the bleeding variable changed by 10% or more, the variable was considered a confounder and was retained in the model.

Analyses were performed in the whole cohort and also in the subgroup of women with bleeding at <20 weeks. In order to avoid multicollinearity, analyses comparing women with and without pre-eclampsia in the total cohort were carried out for each bleeding variable separately (meaning four unadjusted and four adjusted models). Analyses restricted to women with bleeding allowed evaluation of the influence of each individual bleeding characteristic, while simultaneously adjusting for the others (meaning three unadjusted models, one adjusted for bleeding variables, and one adjusted for bleeding variables and confounders). All statistical calculations were carried out by use of the SAS system (version 9.2).

Results

Three thousand seven hundred and eighty nulliparous women agreed to participate in the SCOPE study, 208 of whom were excluded before or at the 14–16 week interview (Figure 1). A further 141 women were excluded from the study population, in most cases because women did not attend the second study visit at 19–21 weeks. The total study population comprised 3431 women (Figure 1).

Mean age at recruitment was 28 years; 87% of the women were of European descent and 74% were primigravid. Twenty-two per cent of all participants smoked during the first trimester and 45% were overweight or obese. Twenty-three per cent ($n = 780$) had vaginal bleeding during the first 20 weeks of their pregnancy; 19% bled during the first trimester and 6% between 13 and 20 weeks of pregnancy. Maternal characteristics in relation to bleeding are detailed in Table 1.

Among the 780 women with vaginal bleeding during the first 20 weeks of pregnancy, 72% bled during the first trimester only, 17% after the first trimester only and 11% during both periods. Nearly three-quarters of the women (73%) had only one bleeding episode, 19% had two and

Table 1. Maternal characteristics in relation to vaginal bleeding during the first 20 weeks of pregnancy; SCOPE study.

			Any vaginal bleeding during:		
Variable	*n*	No vaginal bleeding (%)	weeks 1–20 (%)	weeks 1–12 (%)	weeks 13–20 (%)
All	3431	77.3	22.7	18.9	6.4
Age at recruitment (years)					
<25	934	28.1	24.1	21.8	30.3
25–29	955	27.1	30.3	30.8	30.7
30–34	1115	32.1	33.7	34.6	28.0
35 and over	427	12.6	11.9	12.8	11.0
Ethnicity					
Caucasian	2989	86.8	88.3	88.5	86.7
Asian	147	4.3	4.2	3.8	5.5
Maori/Pacific Islander	106	3.4	1.9	2.0	1.4
Indian	94	2.6	3.1	3.1	3.2
Other ethnicities	95	2.9	2.4	2.6	3.2
Gravidity					
1	2549	74.3	70.1	70.8	67.4
2 or higher	882	25.7	29.9	29.2	32.6
Smoking during first trimester					
Yes	749	22.4	19.7	18.8	21.6
No	2682	77.6	80.3	81.2	78.4
Body mass index (kg m^{-2})					
<18.5	57	1.7	1.7	1.5	2.3
18.5 to <25	1843	53.7	53.9	52.9	51.8
25 to <30	967	28.6	26.8	27.2	26.6
30 and over	564	16.1	17.7	18.3	19.3
Systolic blood pressure at 14–16 weeks					
≤120	3053	89.3	88.0	87.5	89.0
>120	378	10.7	12.0	12.5	11.0
Diastolic blood pressure at 14–16 weeks					
≥80	3342	97.8	96.2	95.7	95.9
>80	89	2.2	3.8	4.3	4.1
Months of sexual relationship*					
Up to six months	290	8.5	8.2	7.5	10.7
More than six months	3136	91.5	91.8	92.5	89.3

*Five missing values.

8% had three episodes or more. For 69% of the women, spotting was the heaviest bleeding experienced, 21% had light bleeding and 10% had one or more episodes of moderate-to-heavy bleeding. About half of the women (54%) bled for one day, 17% of the women had at least one episode of bleeding of five or more consecutive days, while the remainder (29%) had one or more bleeding episodes of two to a maximum of four days. The mean total number of bleeding days was two (interquartile range, 1–4 days). Figure 2 displays the percentage of women who started bleeding at each week of gestation. Onset of new bleeding peaked in the sixth week of gestation (5.6%), and <1% of women had new onset of bleeding from 16 to 20 weeks. Neither bleeding intensity nor duration (not displayed) showed any trends across gestational age. In comparison to women with light-to-heavy episodes of bleeding, those with spotting only were less likely to have multiple bleeds [14.9 vs. 22.7%, relative risk 0.65, 95% confidence interval (CI) 0.48–0.89].

Mean gestational age at delivery was 39.5 weeks and mean birthweight 3390 g. Spontaneous preterm birth occurred in 165 (4.8%) of the women, and 363 children (10.6%) were small for gestational age (below 10th percentile). Twenty-three women (0.7%) had placental abruptions. One hundred and eighty-three women (5.3%) developed pre-eclampsia. Crude associations between vaginal bleeding and pregnancy outcomes are shown in Table 2.

The risk of pre-eclampsia was similar for women with and without an episode of vaginal bleeding at ≤20 weeks of gestation (5.5 vs. 5.3%, respectively, $p = 0.80$). Neither bleeding during the first trimester nor between 13 and 20 weeks of gestation was significantly associated with pre-eclampsia ($p = 0.89$ and $p = 0.46$, respectively). In Table 3, crude and adjusted odds ratios are shown for the risk of pre-eclampsia

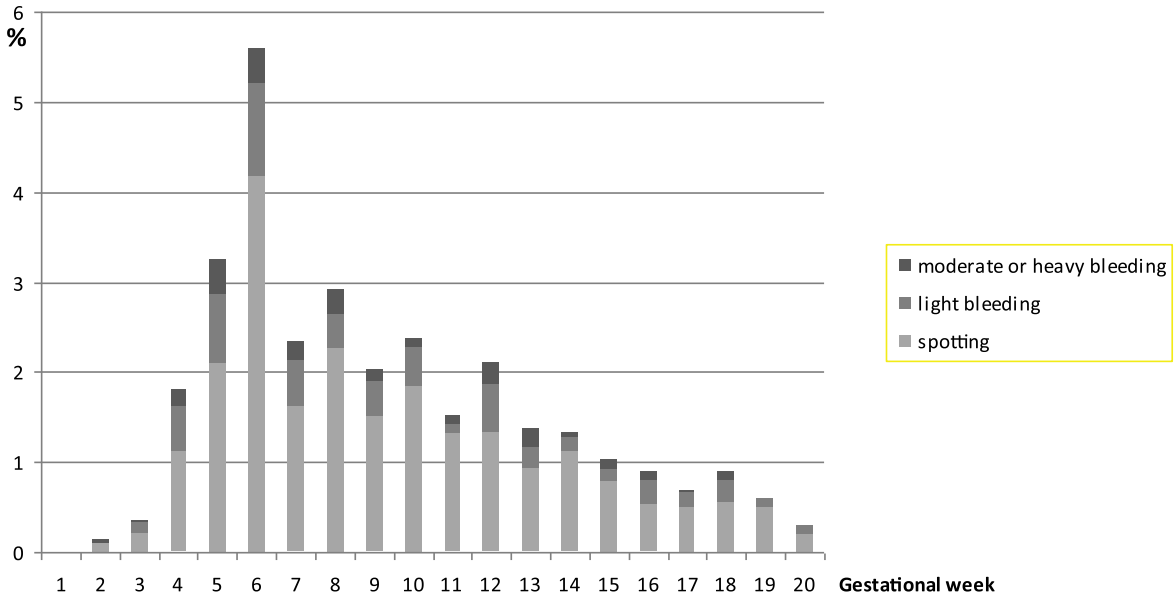

Figure 2. Percentage of women who started bleeding at each week of gestation.

Table 2. Pregnancy outcomes in relation to maternal vaginal bleeding during the first 20 weeks of pregnancy; SCOPE study.

	Vaginal bleeding during first 20 weeks of pregnancy		
Pregnancy outcome	No vaginal bleeding $n = 2651$	Any vaginal bleeding $n = 780$	*p*-Value
Spontaneous preterm delivery	4.4%	6.2%	0.04
Small for gestational age	10.5%	10.9%	0.74
Placental abruption	0.7%	0.6%	0.91
Pre-eclampsia	5.3%	5.5%	0.80

in relation to any bleeding episode, maximal bleeding intensity, duration of bleeding and number of bleeding episodes. Analyses were carried out for each bleeding characteristic separately, with no bleeding as the reference category. The risk of pre-eclampsia was not associated with the presence or absence of any bleeding (adjusted OR 0.96, 95% CI 0.67–1.38). None of the individual bleeding characteristics was significantly associated with the risk of pre-eclampsia.

Because of the inter-relations between bleeding characteristics, we performed a multivariate analysis that evaluated several bleeding characteristics simultaneously among women with bleeding (Table 4). Any bleeding with a duration of five or more consecutive days, in comparison to shorter episodes, increased the risk of pre-eclampsia more than twofold [adjusted odds ratio (ORa) 2.15, 95% CI 1.01–4.57], and so did having multiple episodes of bleeding in comparison to a single bleed (ORa 2.33, 95% CI 1.16–4.67). Spotting only, in comparison to any episode of light-to-heavy bleeding, was also associated with a more than doubled risk of pre-eclampsia (ORa 2.38, 95% CI 1.06–5.26).

On the basis of the results of the logistic regression analysis, we created subgroups of women with specific combinations of bleeding characteristics, in order to consider the potential utility of these bleeding patterns for identifying women with either high or low risk of pre-eclampsia. As shown in Table 5, pre-eclampsia rates were very low for women with a single episode of light-to-heavy bleeding lasting up to four days (0.9%, vs. 5.3% for women with no bleeding). Women with various combinations of any bleeding lasting five or more days, multiple episodes of bleeding and spotting only were associated with risks of pre-eclampsia ranging from 7.2 to 14.3%, but confidence intervals around the point estimates were broad.

Discussion

In this prospective study of healthy nulliparous women, we report that one in four (23%) bled during the first 20 weeks of pregnancy, with a peak during the sixth week. These data are consistent with findings from earlier studies which reported

Table 3. Characteristics of vaginal bleeding during first 20 weeks of pregnancy and risk of pre-eclampsia in nulliparous women ($n = 3431$); SCOPE study.

Characterisitics of bleeding	No pre-eclampsia 3248	Pre-eclampsia 183	Crude OR	95% CI	Adjusted OR*	95% CI
Any bleed†						
No	2511	140	1	Reference	1	Reference
Yes	737	43	1.05	0.74–1.49	0.96	0.67–1.38
Maximal bleeding intensity†						
No bleeding	2511	140	1	Reference	1	Reference
Spotting	505	33	1.17	0.79–1.73	1.14	0.76–1.70
Light to heavy	232	10	0.77	0.40–1.49	0.67	0.34–1.32
Duration of bleeding†						
No bleeding	2511	140	1	Reference	1	Reference
One- to four-day bleeds	614	31	0.90	0.61–1.35	0.85	0.57–1.28
Any bleed five or more days	123	12	1.77	0.95–3.27	1.59	0.85–3.00
Number of bleeds†						
None	2511	140	1	Reference	1	Reference
One	543	26	0.87	0.57–1.34	0.81	0.52–1.25
Two or more	194	17	1.51	0.90–2.55	1.46	0.85–2.50

Abbreviations: CI, confidence interval; and OR, odds ratio.
*Confounding factors were age, ethnicity, gravidity, smoking during first trimester, body mass index, mean systolic blood pressure at 14–16 weeks, diastolic blood pressure at 14–16 weeks, and months of sexual relationship with biological father.
†Each bleeding variable was analysed separately.

Table 4. Bleeding characteristics in the first 20 weeks of pregnancy and risk of pre-eclampsia (women with bleeding, $n = 780$).

	Unadjusted			Adjusted for other bleeding variables		Adjusted for other bleeding variables and confounders*	
Bleeding variable	*n*	OR	95% CI	OR	95% CI	OR	95% CI
Any bleed with duration five or more days							
No	645	1	Reference	1	Reference	1	Reference
Yes	135	1.96	0.98–3.91	2.06	1.02–4.16	2.15	1.01–4.57
Number of bleeds							
One	569	1	Reference	1	Reference	1	Reference
More than one	211	1.83	0.97–3.45	2.09	1.08–4.01	2.33	1.16–4.67
Most severe bleeding intensity							
Light-to-heavy bleeding	242	1	Reference	1	Reference	1	Reference
Spotting	538	1.52	0.74–3.13	1.96	0.92–4.17	2.38	1.06–5.26

*Evaluated for confounding were age, ethnicity, gravidity, smoking during first trimester, body mass index, mean systolic blood pressure at 14–16 weeks, diastolic blood pressure at 14–16 weeks, and months of sexual relationship with biological father.

Table 5. Risk of pre-eclampsia in nulliparous women with various vaginal bleeding patterns; SCOPE study.

Bleeding pattern	Pre-eclampsia/all	Risk of pre-eclampsia (%)	95% CI (%)
Single light-to-heavy bleeding episode of fewer than five days	1/114	0.9	0.0–4.2
No vaginal bleeding	140/2651	5.3	4.5–6.2
Any bleeding episode	43/780	5.5	4.1–7.3
Spotting only	33/538	6.1	4.3–8.4
Multiple bleeding + spotting only	8/111	7.2	3.4–13.2
Multiple bleeding episodes	17/211	8.1	4.9–12.3
Any bleeding with duration five or more days	12/135	8.9	4.9–14.6
Any bleeding with duration five or more days + multiple bleeding	4/41	9.8	3.2–21.9
Any bleeding with duration five or more days + spotting only	10/80	12.5	6.5–21.2
Any bleeding with duration five or more days + multiple bleeding + spotting only	2/14	14.3	2.5–39.7

cumulative incidences between 19 and 27% (1,14–16), with a peak at six weeks (14,16) or the second gestational month (15). Most women who bled did so during the first trimester only (three-quarters), had only one bleeding episode (three-quarters), and for two-thirds of the women the maximal intensity was spotting. About half the women had bleeding episodes lasting no more than one day. These distributions are comparable to those found in other studies, although spotting only has been observed to occur in up to 79% of women with bleeding (15,16). Women with spotting only were less likely to have multiple bleeds or a longer duration of bleeding than those with light to heavy bleeding, consistent with earlier observations (16). Our data confirm that vaginal bleeding during the first half of pregnancy is a common phenomenon in women with ongoing pregnancies, which will assist clinicians to counsel women.

Pre-eclampsia occurred in 5.3% of our cohort. We found no increased risk of pre-eclampsia among women who bled during pregnancy compared with those who did not (ORa 0.96; 95% CI 0.67–1.28). Previous studies evaluating the association between bleeding in early pregnancy and pre-eclampsia have attained mixed results, but generally point to the absence of any strong association when all types of bleeding are aggregated (7–10).

We found that, when evaluated among the total population, none of the bleeding characteristics was significantly associated with risk of pre-eclampsia. This is in contrast to an earlier report from the SCOPE study (11), where women who bled for five days or more had a 1.9-fold increased risk of pre-eclampsia (95% CI 1.0–3.7). In the present study, the ORa for bleeding of duration five days or more was 1.59 (95% CI 0.85–3.00). The differences between these point estimates can be explained firstly, by differences in the study populations, with the present study excluding women who missed the 19–21 week visit ($n = 84$) and including women without ultrasound data, secondly, by use of a different referent category (no bleeding in the present study, no bleeding or bleeding up to four days in the previous study compared with women who bled for five days or more), and thirdly, by a different set of co-variables employed in the two studies. As the previous study was focused on development of a prediction model for pre-eclampsia, variables were selected on the basis of a stepwise regression procedure, whereas in the present study, co-variables for the prediction model were included on the basis of their confounding effect on the association between bleeding factors and pre-eclampsia.

When we confined our analysis to women who bled, which enabled us to evaluate the influence of different bleeding characteristics simultaneously while adjusting for confounders, statistically significant associations emerged. We observed that any bleeding of duration five consecutive days or more, in comparison to shorter episodes, increased the risk of pre-eclampsia more than twofold (ORa 2.15, 95% CI 1.01–4.57), and so did having multiple compared with single episodes of bleeding (ORa 2.33, 95% CI 1.16–4.67). Interestingly, spotting only was associated with a higher risk of pre-eclampsia compared with any light-to-heavy bleeding (ORa 2.38, 95% CI 1.06–5.26). Weiss et al. (7) found that women with light but not heavier bleeding were at increased risk of pre-eclampsia, but they did not control for (or evaluate) other bleeding characteristics. No other previous studies have analysed different bleeding characteristics either separately or simultaneously.

These results indicate that, although bleeding in itself is not a risk factor for pre-eclampsia, the existence of certain characteristics among women who bleed is still informative with respect to the probability of developing pre-eclampsia. When either favorable or unfavorable characteristics cluster within one woman, the risk of pre-eclampsia may be considerably decreased or increased. For example, while baseline risk is 5.3% for all low-risk nulliparous women, those with a single light-to-heavy bleeding episode of less than five days during the first 20 weeks of pregnancy face a low probability of pre-eclampsia. Women with any episode of five days or more of spotting only, however, may experience two to three times the baseline risk. However, the majority of the women with bleeding in the first 20 weeks of pregnancy, i.e. those with spotting only, experience a risk of pre-eclampsia similar to baseline risk.

A major strength of this study is its large multicenter prospective design with excellent follow-up. We obtained high-quality data for all known risk factors of pre-eclampsia from questionnaires administered at interviews, along with detailed standard operating procedures. Principal investigators reviewed outcome data for cases, ensuring accurate diagnosis. One of the challenges when focusing on rare events in prospective cohort studies, such as SCOPE, is the relatively low numbers of cases compared with studies based on huge epidemiological databases. While the latter might have a substantially greater number of events, their interpretation is restrained by less accurate diagnosis.

A possible limitation of our study is that we included only women with ongoing pregnancies at 20 weeks of gestation. This is unlikely to have had a major effect on bleeding characteristics, because the large majority of women with bleeding in early pregnancy go on to have viable babies (7,17). Furthermore, exclusion of women with pregnancy loss at <20 weeks is unlikely to have influenced pre-eclampsia rates, because this disorder is extremely rare before 20 weeks of gestation. As a consequence, it is unlikely that the association between gestational bleeding and pre-eclampsia was affected by the restriction to viable pregnancies.

Our study population comprised relatively healthy nulliparous pregnant women, and our findings may therefore not be applicable to high-risk nulliparous women or to populations of mixed parity. Due to exclusion of high-risk women, the pre-eclampsia rate was relatively low (5.3%). The risk

estimations for women with different combinations of bleeding characteristics (Table 5) should be interpreted in the light of restriction to low-risk pregnancies. A risk prediction model for pre-eclampsia has recently been developed for the SCOPE population, containing multiple known risk factors (11).

Our study is the first to evaluate in detail the association of different bleeding characteristics with risk of pre-eclampsia. The study population was confined to nulliparous women; therefore, our results need replication in independent populations, including women of higher parities.

In conclusion, although we found no association between the occurrence of any bleeding and pre-eclampsia in low-risk nulliparous women, our results indicate that when bleeding occurs, the characteristics (in terms of intensity, duration and number of episodes) may be informative with respect to the risk of pre-eclampsia.

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