First-Trimester Vaginal Bleeding and Complications Later in Pregnancy

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OBJECTIVE: To evaluate the association of first-trimester bleeding without miscarriage and complications later in the first pregnancy as well as in the next pregnancy.

METHODS: In a retrospective, registry-based cohort study, we identified women delivering in Denmark from 1978 to 2007 with a first singleton pregnancy (n=782,287) and first and second singleton pregnancies (n=536,419). First-trimester bleeding is defined as vaginal bleeding before 12 full weeks of gestation. We employed multivariate logistic regression with adjustment for maternal age and calendar year.

RESULTS: First-trimester bleeding increased the risk of delivery in weeks 32–36 from 3.6% to 6.1% (odds ratio [OR], 1.65; 95% confidence interval [CI], 1.57–1.77) and in weeks 28–31 from 0.3% to 0.9% (OR 2.98; 95% CI 2.50–3.54) and increased the risk of placental abruption from 1.0% to 1.4% (OR 1.48; 95% CI 1.30–1.68).

First-trimester bleeding in the first pregnancy increased the risk of recurrence in the second pregnancy from 2.2% to 8.2% (OR 4.05; 95% CI 3.78–4.34), preterm delivery from 2.7% to 4.8% (OR 1.83; 95% CI 1.67–2.00), and placental abruption from 0.9% to 1.0% (OR 1.29; 95% CI 1.07–1.56) in the second pregnancy.

CONCLUSION: Women with first-trimester bleeding in the first pregnancy have an increased risk of complications later in the first pregnancy and of recurrence of first-trimester bleeding and other complications in the second pregnancy.

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LEVEL OF EVIDENCE: II

A list of diagnoses and International Classification of Diseases (ICD)-8 and ICD-10 codes pertaining to this article is available in the Appendix online at http://links.lww.com/AOG/A171.

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First-trimester vaginal bleeding is one of the most common complications in pregnancy with an incidence of 15–25%. About half of these will end in miscarriage within 20 weeks of gestation,[1,2] and those women who remain pregnant have an increased risk of developing other complications later in pregnancy.[3–13]

Local hemostatic factors in the uterus during implantation, decidualization, and early pregnancy, for example, tissue factor expressed in cytotrophoblasts,[14] and systemic factors in the women during the ongoing pregnancy[15] seem to play distinct roles in a successful pregnancy; dysfunction of any of these factors could lead to an adverse outcome[16]; for example, local formation of thrombin and soluble fms-like tyrosine kinase-1. Both of these seem to be involved in development of placental abruption and preeclampsia.[14]

We hypothesize that first-trimester bleeding is a marker of a general proclivity to other pregnancy complications surfacing later in the pregnancy. Also, this proclivity will resurface in the next pregnancy as either first-trimester bleeding or other pregnancy complications or both.

Several studies have investigated the consequences of bleeding on the risk of complications later in the same pregnancy but not the association between two pregnancies. Therefore, we have designed a registry-based, retrospective cohort study investigating 1) the association between first-trimester bleeding and complications later in the first pregnancy and 2) the association between first-trimester bleeding in the first pregnancy and later pregnancy complications in the second pregnancy as well as the opposite association.

MATERIALS AND METHODS

The National Patient Registry has collected information on all discharge diagnoses and complications during pregnancy and delivery in Denmark since 1978.[17] We extracted information on all singleton deliveries in Denmark from January 1, 1978, to October 1, 2007, which

accrued 1,795,806 deliveries of 965,475 women. From this population, we defined two cohorts free of cardiovascular morbidity, such as chronic hypertension and previous ischemic heart disease. Cohort 1 was defined as women aged 15 to 50 years with a first delivery (n=796,915), excluding those with a preceding cardiovascular diagnosis (n=11,605; 1.5%) or insulin-dependent and non–insulin-dependent diabetes (n=2,387; 0.3%) and women who died or emigrated within 3 months of delivery (n=65 and n=571, respectively). Cohort 1 consists of 782,287 women. Cohort 2 (a subpopulation of cohort 1) was defined as women with a second singleton delivery. Cohort 2 consists of 536,419 women.

The primary exposure was first-trimester bleeding defined as vaginal bleeding verified by a physician, that is, women referred to a clinic and diagnosed by a physician after having vaginal bleeding before 12 completed weeks of gestation. Gestational age was calculated from date of bleeding, date of delivery, and the reported gestational age at delivery. Of note, women with subsequent miscarriage or induced abortion before 20 completed weeks were not included in the study population. Women with bleeding and unknown gestational age were considered controls because we could not classify them as first-trimester bleedings. Likewise, many women with missing values of fetal growth were considered controls because of missing values in gestational age.

The outcomes (and secondary exposures) were preterm delivery, premature rupture of membranes (PROM), hypertensive pregnancy disorders, fetal growth, placental abruption, and stillbirth after 20 weeks of gestation. At delivery, gestational age and birth weight were recorded routinely. Initially, gestational age was assessed by the last menstruation period; gradually from 1978 to 2007, gestational age was determined by early second-trimester ultrasonography. A priori, we stratified preterm delivery into four groups by gestational age: 20–27, 28–31, and 32–37 completed weeks; we used deliveries after 37 completed weeks as the reference group. Fetal growth was measured by the birth weight standardized for sex and gestational age.[18] Small for gestational age (SGA) and large for gestational age (LGA) were defined as fetal growth 2 standard deviations (SDs) below and above the mean, respectively. Of note, we did not standardize for parity, which produces a higher proportion of SGA in the first pregnancy compared with the second pregnancy.

Analyzing preterm delivery and PROM, we excluded pregnancies complicated by hypertensive pregnancy disorders, SGA, placental abruption, and stillbirth to accrue a surrogate for spontaneous delivery.

Implausible values of birth weight, gestational age, fetal growth, and the combination of these were reassigned as missing values (n=963). Missing values were analyzed as a separate group. These occurred more frequently in the earlier years of the Registry.

The presence of vaginal bleeding, PROM, hypertensive pregnancy disorders, placental abruption, stillbirth, and cardiovascular diseases were assessed by the specific International Classification of Diseases-8 and -10 codes for these diagnoses (see the Appendix, available online at http://links.lww.com/A171). Given the binomial nature of these variables in the Registry, no missing values were recorded. The hypertensive pregnancy disorders were stratified into gestational hypertension, mild preeclampsia, and severe preeclampsia (including eclampsia and HELLP syndrome). The definition of preeclampsia has changed little during the 30-year study period,[19] and the frequency of preeclampsia in the Registry has remained almost stable. The accuracy of the diagnoses of the hypertensive pregnancy disorders in the Registry has in subpopulations been manually validated several times, accruing specificities above 99% for all types, but sensitivities at 10% for gestational hypertension and 69% for preeclampsia or positive predictive values of 56% for gestational hypertension, 100% for severe preeclampsia, and 74% for mild and severe preeclampsia combined.[19]

We used multivariable logistic regression to calculate the associations. We included maternal age and year of delivery in all models and years between pregnancies in associations across two pregnancies. Initially we calculated stratified results, some of which are presented in the article. All odds ratios (ORs) are presented with 95% confidence intervals (CIs). SPSS 16.0 for Macintosh (SPSS Inc., Chicago, IL) was used for all calculations. The study was approved by the Danish Data Protection Agency (2005–41–5262 and 2007–41–1544).

RESULTS

The mean age at delivery was 26.8 (SD 4.6) years in cohort 1, and 25.9 (SD 4.0) and 29.5 (SD 4.2) years in cohort 2, the first and second deliveries, respectively. In cohort 1, 18,311 (2.3%) women had bleeding; in cohort 2, 11,563 (2.2%) and 12,262 (2.3%) women had first-trimester bleeding in the first and second deliveries, respectively.

In cohort one, women with first-trimester bleeding had an increased risk of delivering preterm later in the same pregnancy. The proportion of women

Table 1. Pregnancy Complications After First-Trimester Bleeding

Outcome	First-Trimester Bleeding	Control	Model	*P*
Preterm delivery (wk)*				
37 or more	14,827 (92.6)	626,550 (92.3)	1 (Reference)	
32–36	970 (6.1)	24,270 (3.6)	1.65 (1.55–1.77)	<.001
28–31	138 (0.9)	1,928 (0.3)	2.98 (2.50–3.54)	<.001
20–27	78 (0.5)	944 (0.1)	3.32 (2.63–4.19)	<.001
Missing values	0 (0.0)	25,212 (3.7)	N/A	
PROM*				
37 wk or more				
No PROM	13,934 (94.0)	595,193 (95.0)	1 (Reference)	
PROM	893 (6.0)	31,357 (5.0)	1.19 (1.11–1.28)	<.001
Preterm				
No PROM	960 (80.9)	22,798 (84.0)	1 (Reference)	
PROM	226 (19.1)	4,344 (16.0)	1.18 (1.01–1.37)	.036
Missing values				
No PROM	0	24,215 (96.0)		
PROM	0	997 (4.0)	N/A	
Fetal growth				
SGA	1,107 (6.0)	42,002 (5.5)	1.12 (1.05–1.19)	<.001
AGA	16,701 (91.2)	674,566 (88.3)	1 (Reference)	
LGA	334 (1.8)	11,312 (1.5)	1.11 (0.99–1.23)	.075
Missing values	169 (0.9)	36,096 (4.7)	0.27 (0.23–0.32)	<.001
Hypertensive pregnancy disorders				
None	17,194 (93.9)	723,818 (94.7)	1 (Reference)	
Gestational hypertension	171 (0.9)	7,278 (1.0)	0.97 (0.84–1.13)	.72
Mild preeclampsia	731 (4.0)	26,079 (3.4)	1.21 (1.12–1.30)	<.001
Severe preeclampsia	215 (1.2)	6,801 (0.9)	1.25 (1.09–1.43)	<.001
Placental abruption				
No	18,061 (98.6)	756,542 (99.0)	1 (Reference)	
Yes	250 (1.4)	7,434 (1.0)	1.48 (1.30–1.68)	<.001
Stillbirth				
No	18,198 (99.4)	760,050 (99.5)	1 (Reference)	
Yes	113 (0.6)	3,926 (0.5)	1.19 (0.99–1.44)	.066

N/A, not applicable; PROM, premature rupture of membranes; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age.
Data are n (%) or odds ratio (95% confidence interval).
Adjusted for maternal age and year of delivery (n=782,287).
* Exclusion of pregnancies complicated by hypertensive pregnancy disorders, SGA, placental abruption, and stillbirth (n=694,917).

experiencing first-trimester bleeding increased by decreasing gestational age at delivery (Table 1). First-trimester bleeding increased the risk of preterm delivery in weeks 32–36 from 3.6% to 6.1% (OR 1.65; 95% CI 1.57–1.77) and in weeks 28–31 from 0.3% to 0.9% (OR 2.98; 95% CI 2.50–3.54). In addition, women with first-trimester bleeding had a 1.19-fold (95% CI 1.11–1.28) increased risk of PROM and 1.18-fold (95% CI 1.01–1.37) increased risk of preterm PROM, thus illustrating no effect modification by gestational age of PROM. Also, women with first-trimester bleeding had a 1.48-fold (95% CI 1.30–1.68) increased risk of placental abruption (Table 1).

In cohort 2, first-trimester bleeding in the first pregnancy increased the risk from 2.2% to 8.2% (OR 4.05; 95% CI 3.78–4.34) of first-trimester bleeding in the second pregnancy (Table 2). Also, first-trimester bleeding in the first pregnancy increased the risk of preterm delivery in the second pregnancy from 2.7% to 4.8% (OR 1.83; 95% CI 1.67–2.00), PROM from 3.1% to 4.1% (OR 1.40; 95% CI 1.27–1.54), placental abruption from 0.9% to 1.0% (OR 1.29; 95% CI 1.07–1.56), and stillbirth from 0.4% to 0.5% (OR 1.34; 95% CI 1.02–1.76) (Table 3). Only in the association with preterm delivery did we detect an effect modification by first-trimester bleeding in the second pregnancy and by preterm delivery in the first pregnancy (Tables 4 and 5); these factors diminished the effect of first-trimester bleeding in the first pregnancy. We also investigated the reverse association: women delivering preterm at gestational ages of 32–36 weeks in the first pregnancy had a 1.41-fold (95% CI 1.29–1.55) increased risk of first-trimester bleeding in the second pregnancy. Women delivering in gestational age

Table 2. First-Trimester Bleeding in First Pregnancy and Risk of Recurrence in Second Pregnancy

Outcome in First Pregnancy	First-Trimester Bleeding in Second Pregnancy			*P*
No bleeding	524,856 (97.8)	11,310 (2.2)	1 (Reference)	
Bleeding	11,563 (2.2)	952 (8.2)	4.05 (3.78–4.34)	<.001
Total	536,419 (100)	12,262 (2.3)		

Data are n (%) or odds ratio (95% confidence interval) unless otherwise specified.
Adjusted for maternal age at first delivery, year of delivery, and time between pregnancies.

28–31 weeks had a 2.57-fold (95% CI 2.02–3.28) increased risk (Table 6). No effect modification by bleeding in the first pregnancy was observed in the stratified analyzes (Table 7).

DISCUSSION

Previous studies have linked first-trimester vaginal bleeding to preterm delivery,[7–12] PROM,[9,10,20] and placental abruption[8,10,21] in the same pregnancy. We found that first-trimester bleeding in the first pregnancy tends to recur and also carries a risk of complications over to the second pregnancy. Also, preterm delivery, PROM, and placental abruption in the first pregnancy carry a risk over to the second pregnancy of first-trimester bleeding.

The association between SGA and first-trimester bleeding–in the first pregnancy and across first and second pregnancies–was small and inconsistent, and previous studies have had difficulty in demonstrating the association[9–11]; in our study, first-trimester bleeding did not increase the risk of LGA. Also, preeclampsia was weakly associated with first-trimester bleeding in the first pregnancy; Weiss et al previously have reported an increased risk of preeclampsia after "light bleeding," but strangely not after "heavy bleeding," and, in contrast, Eskild and Vatten found a protective effect of early bleeding on the risk of developing preeclampsia.[10,22] Stillbirth was not associated with first-trimester bleeding in the first pregnancy; however, stillbirth in the first pregnancy increased the risk

Table 3. First-Trimester Bleeding in First Pregnancy and Risk of Complications in Second Pregnancy

Outcome in First Pregnancy		Outcome in Second Pregnancy*		*P*
Preterm delivery				
No bleeding	492,719 (97.8)	13,280 (2.7)	1 (Reference)	
Bleeding	10,827 (2.2)	520 (4.8)	1.83 (1.67–2.00)	<.001
Total	503,546 (100)	13,800 (2.7)		
PROM				
No bleeding	492,719 (97.8)	15,053 (3.1)	1 (Reference)	
Bleeding	10,827 (2.2)	442 (4.1)	1.40 (1.27–1.53)	<.001
Total	503,546 (100)	15,495 (3.1)		
Fetal growth SGA†				
No bleeding	524,856 (97.8)	15,125 (2.9)	1 (Reference)	
Bleeding	11,563 (2.2)	323 (2.8)	1.08 (0.97–1.21)	.16
Total	536,419 (100)	15,448 (2.9)		
Preeclampsia				
No bleeding	524,856 (97.8)	9,910 (1.9)	1 (Reference)	
Bleeding	11,563 (2.2)	249 (2.2)	1.20 (1.06–1.36)	.005
Total	536,419 (100)	10,159 (1.9)		
Placental abruption				
No bleeding	524,856 (97.8)	4,499 (0.9)	1 (Reference)	
Bleeding	11,563 (2.2)	114 (1.0)	1.29 (1.07–1.56)	.007
Total	536,419 (100)	4,613 (0.9)		
Stillbirth				
No bleeding	524,856 (97.8)	1,885 (0.4)	1 (Reference)	
Bleeding	11,563 (2.2)	53 (0.5)	1.34 (1.02–1.76)	.037
Total	536,419 (100)	1,938 (0.4)		

PROM, premature rupture of membranes; SGA, small for gestational age.
Data are n (%) or odds ratio (95% confidence interval) unless otherwise specified.
All models are adjusted for maternal age at first delivery, year of delivery, and time between pregnancies.
* For preterm delivery and PROM in second pregnancy, exclusions were women with hypertensive pregnancy disorders, SGA, placental abruption, and stillbirth in second pregnancy (n=503,546).
† Fetal growth outcome SGA in second pregnancy.

Table 4. First-Trimester Bleeding in First Pregnancy and Risk of Complications in Second Pregnancy: Stratification by Bleeding in Second Pregnancy

Outcome in First Pregnancy		Outcome in Second Pregnancy*		*P*
Preterm delivery				
No bleeding in second pregnancy				
No bleeding in first pregnancy	482,287 (98.0)	12,660 (2.6)	1 (Reference)	
Bleeding in first pregnancy	9,946 (2.0)	457 (4.6)	1.80 (1.63–1.98)	<.001
Bleeding in second pregnancy				
No bleeding in first pregnancy	10,432 (92.2)	620 (5.9)	1 (Reference)	
Bleeding in first pregnancy	881 (7.8)	63 (7.2)	1.26 (0.96–1.65)	.098
Total	503,546 (100.0)	13,800 (2.7)		
PROM				
No bleeding in second pregnancy				
No bleeding in first pregnancy	482,287 (98.0)	12,473 (2.6)	1 (Reference)	
Bleeding in first pregnancy	9,946 (2.0)	313 (3.1)	1.37 (1.24–1.52)	<.001
Bleeding in second pregnancy				
No bleeding in first pregnancy	10,432 (92.2)	353 (3.4)	1 (Reference)	
Bleeding in first pregnancy	881 (7.8)	37 (4.2)	1.29 (0.95–1.75)	.11
Total	503,546 (100)	13,176 (2.6)		
Fetal growth SGA†				
No bleeding in second pregnancy				
No bleeding in first pregnancy	513,546 (98.0)	14,728 (2.9)	1 (Reference)	
Bleeding in first pregnancy	10,611 (2.0)	299 (2.8)	1.10 (0.98–1.24)	0.11
Bleeding in second pregnancy				
No bleeding in first pregnancy	11,310 (92.2)	397 (3.5)	1 (Reference)	
Bleeding in first pregnancy	952 (7.8)	24 (2.5)	0.81 (0.53–1.23)	0.31
Total	536,419 (100)	15,448 (2.9)		
Preeclampsia				
No bleeding in second pregnancy				
No bleeding in first pregnancy	513,546 (98.0)	9,629 (1.9)	1 (Reference)	
Bleeding in first pregnancy	10,611 (2.0)	225 (2.1)	1.19 (1.04–1.37)	0.010
Bleeding in second pregnancy				
No bleeding in first pregnancy	11,310 (92.2)	281 (2.5)	1 (Reference)	
Bleeding in first pregnancy	952 (7.8)	24 (2.5)	1.04 (0.68–1.60)	0.84
Total	536,419 (100)	10,159 (1.9)		
Placental abruption				
No bleeding in second pregnancy				
No bleeding in first pregnancy	513,546 (98.0)	4,352 (0.8)	1 (Reference)	
Bleeding in first pregnancy	10,611 (2.0)	97 (0.9)	1.21 (0.99–1.48)	.066
Bleeding in second pregnancy				
No bleeding in first pregnancy	11,310 (92.2)	147 (1.3)	1 (Reference)	
Bleeding in first pregnancy	952 (7.8)	17 (1.8)	1.56 (0.93–2.60)	.090
Total	536,419 (100)	4,613 (0.9)		
Stillbirth				
No bleeding in second pregnancy				
No bleeding in first pregnancy	513,546 (98.0)	1,832 (0.4)	1 (Reference)	
Bleeding in first pregnancy	10,611 (2.0)	49 (0.5)	1.36 (1.02–1.81	.034
Bleeding in second pregnancy				
No bleeding in first pregnancy	11,310 (92.2)	53 (0.5)	1 (Reference)	
Bleeding in first pregnancy	952 (7.8)	4 (0.4)	0.95 (0.34–2.63	.91
Total	536,419 (100)	1,938 (0.4)		

PROM, premature rupture of membranes; SGA, small for gestational age.
Data are n (%) or odds ratio (95% confidence interval).
All models are adjusted for maternal age at first delivery, year of delivery, and time between pregnancies.
* For preterm delivery and PROM in second pregnancy, exclusions were women with hypertensive pregnancy disorders, SGA, placental abruption, and stillbirth in second pregnancy (n=503,546).
† Fetal growth SGA in second pregnancy .

of first-trimester bleeding in the second pregnancy, although this could be ascribed to bias; Johns and Jauniaux[9] and Williams et al[7] did not find an association in their studies.

Impaired invasion of cytotrophoblasts and remodeling of the spiral arteries in early placentation have been demonstrated in pregnancies ending in miscarriage[23] and also those pregnancies complicated

Table 5. First-Trimester Bleeding in First Pregnancy and Risk of Complications in Second Pregnancy: Stratification by Outcome in First Pregnancy

Outcome in First Pregnancy		Outcome in Second Pregnancy*		*P*
Preterm delivery (wk)				
37 or more in first pregnancy				
No bleeding in first pregnancy	452,420 (97.8)	9,875 (2.2)	1 (Reference)	
Bleeding in first pregnancy	10,016 (2.2)	376 (3.8)	1.77 (1.60–1.97)	<.001
Preterm delivery in first pregnancy				
No bleeding in first pregnancy	21,444 (96.4)	2,949 (13.8)	1 (Reference)	
Bleeding in first pregnancy	811 (3.6)	144 (17.8)	1.34 (1.12–1.61)	.002
Missing values				
No bleeding in first pregnancy	18,855 (100)	456 (2.4)	N/A	
Bleeding in first pregnancy	0 (0.0)	0		
Total	503,546 (100)	13,800 (2.7)		
PROM				
No PROM in first pregnancy				
No bleeding in first pregnancy	468,523 (97.9)	13,322 (2.8)	1 (Reference)	
Bleeding in first pregnancy	10,170 (2.1)	388 (3.8)	1.41 (1.27–1.56)	<.001
PROM in first pregnancy				
No bleeding in first pregnancy	24,196 (97.4)	1,731 (7.2)	1 (Reference)	
Bleeding in first pregnancy	657 (2.6)	54 (8.2)	1.21 (0.91–1.61)	.19
Total	503,546 (100)	15,495 (3.1)		
Fetal growth†				
AGA in first pregnancy				
No bleeding in first pregnancy	462,634 (97.8)	9,871 (2.1)	1 (Reference)	
Bleeding in first pregnancy	10,579 (2.2)	221 (2.1)	1.08 (0.94–1.24)	.27
SGA in first pregnancy				
No bleeding in first pregnancy	27,991 (97.6)	4,225 (15.1)	1 (Reference)	
Bleeding in first pregnancy	680 (2.4)	101 (14.9)	1.01 (0.81–1.25)	.96
LGA in first pregnancy				
No bleeding in first pregnancy	7,015 (97.3)	22 (0.3)	N/A	
Bleeding in first pregnancy	193 (2.7)	0 (0.0)		
Missing values				
No bleeding in first pregnancy	27,216 (99.6)	1,007 (3.7)	1 (Reference)	
Bleeding in first pregnancy	111 (0.4)	1 (0.9)	0.38 (0.05–2.75)	.34
Total	536,419 (100)	15,448 (2.9)		
Preeclampsia				
No preeclampsia in first pregnancy				
No bleeding in first pregnancy	503,221 (97.9)	6,482 (1.3)	1 (Reference)	
Bleeding in first pregnancy	11,000 (2.1)	158 (1.4)	1.19 (1.01–1.39)	.035
Preeclampsia in first pregnancy				
No bleeding in first pregnancy	21,635 (97.5)	3,428 (15.8)	1 (Reference)	
Bleeding in first pregnancy	563 (2.5)	91 (16.2)	1.04 (0.83–1.30)	.75
Total	536,419 (100)	10,159 (1.9)		
Placental abruption				
No abruption in first pregnancy				
No bleeding in first pregnancy	519,819 (97.9)	4,140 (0.8)	1 (Reference)	
Bleeding in first pregnancy	11,407 (2.1)	103 (0.9)	1.28 (1.05–1.56)	.013
Abruption in first pregnancy				
No bleeding in first pregnancy	5,037 (97.0)	359 (7.1)	1 (Reference)	
Bleeding in first pregnancy	156 (3.0)	11 (7.1)	0.95 (0.49–1.82)	.87
Total	536,419 (100)	4,613 (0.9)		
Stillbirth				
No stillbirth in first pregnancy				
No bleeding in first pregnancy	521,780 (97.8)	1,782 (0.3)	1 (Reference)	
Bleeding in first pregnancy	11,478 (2.2)	50 (0.4)	1.34 (1.01–1.78)	.041
Stillbirth in first pregnancy				
No bleeding in first pregnancy	3,076 (97.3)	103 (3.3)	1 (Reference)	
Bleeding in first pregnancy	85 (2.7)	3 (3.5)	1.00 (0.31–3.23)	.997
Total	536,419 (100)	1,938 (0.4)		

N/A, not applicable; PROM, premature rupture of membranes; AGA, appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age.

Data are n (%) or odds ratio (95% confidence interval).

All models are adjusted for maternal age at first delivery, year of delivery, and time between pregnancies.

* For preterm delivery and PROM in second pregnancy, exclusions were women with hypertensive pregnancy disorders, SGA, placental abruption, and stillbirth in second pregnancy (n=503,546).

† Fetal growth SGA in second pregnancy.

Table 6. Complications in First Pregnancy and Risk of First-Trimester Bleeding in Second Pregnancy

Outcome in First Pregnancy		First-Trimester Bleeding in Second Pregnancy		*P*
Preterm delivery (wk)*				
37 or more	441,561 (92.3)	9,870 (2.2)	1 (Reference)	
32–36	15,683 (3.3)	502 (3.2)	1.41 (1.29–1.55)	<.001
28–31	1,222 (0.3)	70 (5.7)	2.57 (2.02–3.28)	<.001
20–27	580 (0.1)	26 (4.5)	2.15 (1.45–3.20)	<.001
Missing values	19,258 (4.0)	335 (1.7)	0.95 (0.84–1.07)	.39
Total	478,304 (100)	10,803 (2.3)		
PROM*				
None	454,110 (94.9)	10,171 (2.2)	1 (Reference)	
PROM	24,194 (5.1)	632 (2.6)	1.20 (1.11–1.30)	<.001
Total	478,304 (100)	10,803 (2.3)		
Fetal growth				
SGA	28,671 (5.3)	715 (2.5)	1.10 (1.02–1.19)	.014
AGA	473,213 (88.2)	10,863 (2.3)	1 (Reference)	
LGA	7,208 (1.3)	192 (2.7)	1.15 (0.99–1.33)	.062
Missing values	27,327 (5.1)	492 (1.8)	0.92 (0.84–1.01)	.095
Total	536,419 (100)	12,262 (2.3)		
Preeclampsia				
None	514,221 (95.9)	11,737 (2.3)	1 (Reference)	
Preeclampsia	22,198 (4.1)	525 (2.4)	1.03 (0.95–1.13)	.48
Total	536,419 (100)	12,262 (2.3)		
Placental abruption				
None	531,226 (99.0)	12,088 (2.3)	1 (Reference)	
Placental abruption	5,193 (1.0)	174 (3.4)	1.51 (1.30–1.76)	<.001
Total	536,419 (100)	12,262 (2.3)		
Stillbirth				
Live offspring	533,258 (99.4)	12,139 (2.3)	1 (Reference)	
Stillbirth	3,161 (0.6)	123 (3.9)	2.15 (1.79–2.58)	<.001
Total	536,419 (100)	12,262 (2.3)		

PROM, premature rupture of membranes; SGA, small for gestational age; LGA, large for gestational age; AGA, appropriate for gestational age.
Data are n (%) or odds ratio (95% confidence interval).
All models are adjusted for maternal age at first delivery, year of delivery, and time between pregnancies.
* For preterm delivery and PROM in first pregnancy, exclusions were women with hypertensive pregnancy disorders, SGA, placental abruption, or stillbirth in first delivery (n=478,304).

by preterm delivery, PROM, and placental abruption[24–26] and preeclampsia.[27] The same impaired placentation could be the link between first-trimester bleeding and complications later in pregnancy.[13] Another model, coined by Johns et al,[13] centers on the actual bleeding in the placental bed: An iron deposit may provoke a production of excessive oxidative stress, which has been linked to preterm delivery and PROM[28] and to preeclampsia.[15] A nidus will make an infection more likely, which also has been linked to preterm delivery.[28–30] Also, decidual bleeding will generate excess amount of thrombin from decidual-cell expressed tissue factor, which again could impede the ongoing implantation.[14] These models are not mutually exclusive; we found that first-trimester bleeding in the first pregnancy carries the risk of complications over into the second pregnancy and vice versa. This suggests a common proclivity of first-trimester bleeding and preterm delivery, PROM, and placental abruption.

The strengths and weaknesses of the study are based on the nature of the employed National Patient Registry, a large population-based cohort representing a census of delivering women. An incidence of 2.3% of first-trimester bleeding seems low in comparison with previous studies[1]; for example, Mulik et al reported a 7.1% incidence.[8] Although there was underreporting, this difference may be ascribed to the inclusion of only viable pregnancies beyond 20 weeks of gestation.[2] Furthermore, the registry will include information only on women who sought medical assistance and were referred to a physician. In consequence, the woman herself could act as a bias: If a woman had serious complications in her first preg-

Table 7. Complications in First Pregnancy and Risk of First-Trimester Bleeding in Second Pregnancy: Stratification by Bleeding in First Pregnancy

Outcome in First Pregnancy		First-Trimester Bleeding in Second Pregnancy		*P*
Preterm delivery (wk)*				
No bleeding in first pregnancy				
37 or more	432,040 (92.3)	9,123 (2.1)	1 (Reference)	<.001
32–36	15,162 (3.2)	442 (2.9)	1.36 (1.24–1.50)	
28–31	1,148 (0.2)	59 (5.1)	2.41 (1.85–3.14)	
20–27	539 (0.1)	19 (3.5)	1.78 (1.13–2.82)	
Missing values	19,258 (4.1)	335 (1.7)	0.98 (0.87–1.10)	
Bleeding in first pregnancy				
37 or more	9,521 (93.7)	747 (7.8)	1 (Reference)	<.001
32–36	521 (5.1)	60 (11.5)	1.51 (1.14–2.00)	
28–31	74 (0.7)	11 (14.9)	2.13 (1.12–4.07)	
20–27	41 (0.4)	7 (17.1)	2.58 (1.13–5.89)	
Missing values	0 (0.0)		N/A	
Total	478,304 (100)	10,803 (2.3)		
PROM*				
No bleeding in first pregnancy				
None	444,588 (95.0)	9,412 (2.1)	1 (Reference)	
PROM	23,559 (5.0)	566 (2.4)	1.17 (1.08–1.28)	<.001
Bleeding in first pregnancy				
None	9,522 (93.7)	759 (8.0)	1 (Reference)	
PROM	635 (6.3)	66 (10.4)	1.35 (1.03–1.76)	.029
Total	478,304 (100)	10,803 (2.3)		
Fetal growth				
No bleeding in first pregnancy				
SGA	27,991 (5.3)	656 (2.3)	1.10 (1.01–1.19)	.026
AGA	462,634 (88.1)	9,991 (2.2)	1 (Reference)	
LGA	7,015 (1.3)	176 (2.5)	1.15 (0.99–1.34)	.063
Missing values	27,216 (5.2)	487 (1.8)	0.96 (0.87–1.06)	.38
Bleeding in first pregnancy				
SGA	680 (5.9)	59 (8.7)	1.07 (0.81–1.42)	.62
AGA	10,579 (91.5)	872 (8.2)	1 (Reference)	
LGA	193 (1.7)	16 (8.3)	1.00 (0.60–1.68)	>.999
Missing values	111 (1.0)	5 (4.5)	0.55 (0.22–1.35)	.19
Total	536,419 (100)	12,262 (2.3)		
Preeclampsia				
No bleeding in first pregnancy				
None	503,221 (95.9)	10,834 (2.2)	1 (Reference)	
Preeclampsia	21,635 (4.1)	476 (2.2)	1.02 (0.93–1.12)	.71
Bleeding in first pregnancy				
None	11,000 (95.1)	903 (8.2)	1 (Reference)	
Preeclampsia	563 (4.9)	49 (8.7)	1.05 (0.77–1.42)	.77
Total	536,419 (100)	12,262 (2.3)		
Placental abruption				
No bleeding in first pregnancy				
None	519,819 (99.0)	11,155 (2.1)	1 (Reference)	
Placental abruption	5,037 (1.0)	155 (3.1)	1.47 (1.25–1.72)	<.001
Bleeding in first pregnancy				
None	11,407 (98.7)	933 (8.2)	1 (Reference)	
Placental abruption	156 (1.3)	19 (12.2)	1.58 (0.97–2.57)	.067
Total	536,419 (100)	12,262 (2.3)		
Stillbirth				
No bleeding in first pregnancy				
Live offspring	521,780 (99.4)	11,195 (2.1)	1 (Reference)	
Stillbirth	3,076 (0.6)	115 (3.7)	2.21 (1.83–2.67)	<.001
Bleeding in first pregnancy				
Live offspring	11,478 (99.3)	944 (8.2)	1 (Reference)	
Stillbirth	85 (0.7)	8 (9.4)	1.28 (0.61–2.67)	.51
Total	536,419 (100)	12,262 (2.3)		

PROM, premature rupture of membranes; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age.

Data are n (%) or odds ratio (95% confidence interval).

All models are adjusted for maternal age at first delivery, year of delivery, and time between pregnancies.

* For preterm delivery and PROM in first pregnancy, exclusions were women with hypertensive pregnancy disorders, SGA, placental abruption, and stillbirth in first pregnancy (n=478,304).

nancy, this experience could lower her threshold for seeking medical attention in second pregnancy. However, because of the prospective registration of the data, recall bias is not present.

The validity of the hypertensive diagnoses in the National Patient Registry, demonstrating positive predictive values of 56% of gestational hypertension and 74% for preeclampsia,[19] warrants caution when interpreting the associations to these complications: The low-to-moderate predictive values will tend to underestimate the associations. Validation of PROM, placental abruption, and stillbirth remains to be performed.

Potential confounders such as socioeconomic status, assisted reproductive technology or fecundability, smoking, and body mass index could not be assessed in the present study. These could be risk factors for both vaginal bleeding and later pregnancy complications. Also, we could not distinguish between light and heavy bleeding,[10,20] the presence of ultrasound-verified hematomas,[13] or inflammation,[28,30] all of which have been associated with adverse pregnancy outcomes. Thus, the weaker associations should be interpreted with caution. However, the potential bias affects the biological interpretation of the associations, not the statistical predictive value of first-trimester vaginal bleeding for later pregnancy complications.

In conclusion, first-trimester vaginal bleeding is a clinical, relevant event for the obstetrician as a marker for preterm delivery, PROM, and placental abruption in the index pregnancy as well as in the subsequent pregnancy; these findings add to the evidence of the linkage and recurrence of pregnancy complications.[31] The linkage to these pregnancy complications may provide a basis for selective increased pregnancy surveillance as well as insight into the etiology of miscarriage, vaginal bleeding, and other pregnancy complications.

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