HHS Public Access

Author manuscript

Obstet Gynecol. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

Obstet Gynecol. 2018 June ; 131(6): 1021–1030. doi:10.1097/AOG.0000000000002616.

Fetal Growth Patterns in Pregnancies With First-Trimester Bleeding

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Abstract

Objective: To assess the relationship between first-trimester vaginal bleeding and fetal growth patterns.

Methods: We conducted a secondary analysis of the NICHD Fetal Growth Studies–Singletons, a prospective cohort study of low-risk, non-obese women with healthy lifestyles. Duration of bleeding was self-reported at enrollment (10w0d to 13w6d) and categorized as 0, 1, or >1 day. Longitudinal measures of fetal biometrics were obtained in up to six study visits, and estimated fetal weight was computed. Growth trajectories were created for biometrics and estimated fetal weight. When global test among groups was significant ($p<0.05$), week-specific global and pairwise differences were tested. Birthweight and risk of small-for-gestational-age neonate were secondary outcomes. All analyses were adjusted for maternal age, weight, height, parity, and racial ethnic group, and infant sex in a sensitivity analysis.

Results: In 2,307 eligible women, 410 (17.8%) reported first-trimester bleeding, of whom 176 bled for 1 day, and 234 bled for >1 day. Women with >1 day of bleeding demonstrated decreased fetal abdominal circumference from 34 to 39 weeks compared to women without bleeding. For women with >1 day bleeding, compared to women without bleeding, estimated fetal weight was 68–107 grams smaller from 35 to 39 weeks. Mean birthweight at term was 88 g smaller,

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Each author has indicated that he or she has met the journal's requirements for authorship.

Presented as at the Society of Pediatric and Perinatal Epidemiologic Research Annual Meeting, June 19–20, 2017; Seattle, WA

Financial Disclosure

Deborah A. Wing has been a consultant for Parsagen, for which she received no compensation. She has provided expert opinion to the company on a few clinical questions raised by the U.S. Food and Drug Administration (FDA) in the company's ongoing discussions with the FDA. The other authors did not report any potential conflicts of interest.

Clinical Trial Registration: ClinicalTrials.gov, NCT00912132.

confirming differences in calculated fetal weight, and small-for-gestational-age neonates were delivered to 148 (8.5%), 9 (5.7%), and 33 (15.7%) women in the no bleeding, 1 day, and >1 day of bleeding groups, respectively.

Conclusion: More than one day of first-trimester vaginal bleeding was associated with smaller estimated fetal weight late in pregnancy driven by smaller abdominal circumference. The magnitude of decrease in birthweight was small, albeit comparable to observed decreases associated with maternal smoking. It remains unknown whether early pregnancy bleeding is associated with short-term or long-term morbidity and if additional intervention would be of benefit.

Précis:

More than one day of first-trimester vaginal bleeding is associated with smaller estimated fetal weight and abdominal circumference measurements beginning in the third trimester.

Introduction

First trimester bleeding is frequent, occurring in 16–25% of pregnancies,[1] and has been shown to be associated with increased risk of adverse pregnancy outcomes including preterm delivery, pre-labor premature rupture of membranes, small-for-gestational-age (SGA) fetal measurements, low birthweight, and fetal death, though evidence is equivocal[2–11] In a 2010 meta-analysis, first-trimester bleeding was associated with intrauterine growth restriction in only four of eight cohort studies, with significant heterogeneity among studies[1] Furthermore, fetal growth restriction is typically defined as estimated fetal weight less than 10th percentile, which does not discriminate between pathologic and constitutional growth restriction, as some fetuses are constitutionally small but normally grown, and low birthweight is more indicative of preterm delivery[7,12,13] Limitations in sample size, recall bias, and potential confounding due to pre-existing maternal conditions contribute to these mixed results. Additionally, little is known about the relation between first-trimester bleeding and individual fetal biometrics or the gestational timing of altered growth in association with early bleeding, which have the potential to inform the pathology of decreased estimated fetal weight or birthweight. The objective of the present study was to determine if the presence and duration of first-trimester bleeding in non-obese, healthy women was associated with differences in fetal growth in a prospective cohort study.

Materials and Methods

This study was a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies–Singletons[14] The study recruited 2,334 non-obese women with healthy lifestyles (e.g. non-smokers, no illicit drug use) and low-risk medical and obstetrical histories (e.g. no chronic diseases) from 2009 to 2013 at 12 centers across the United States. Details of recruitment, inclusion and exclusion criteria, and data collection have been previously reported[14] Of relevance, baseline maternal characteristics and lifestyle were assessed during the enrollment interview between 10 weeks 0 days (10w0d) and 13w6d. Women were included if they were between 18–40 years of age with pre-pregnancy body mass index (BMI) 19.0–29.9 kg/m^2 and were planning to deliver at one of the participating hospitals. Gestational age was determined based on last menstrual period and confirmed by first-trimester ultrasound. Approval was received from the institutional review board for each of the participating sites, the data coordinating center, and the NICHD; participants provided informed consent.

At enrollment, information on demographics, obstetrical and medical histories, and lifestyle and health leading up to and during the first trimester of pregnancy was collected via in-person interview. Information included self-reported duration (cumulative number of days) and severity (mild, moderate, severe) of bleeding since the beginning of pregnancy. In-person interviews were conducted by research nurses at up to five follow-up study visits, and bleeding since the last visit was assessed using the same metrics. After an enrollment sonogram, women were randomly assigned to one of four ultrasound schedules with five planned, regularly spaced visits. Ultrasounds were conducted by trained experts using standard operating procedures and identical equipment (Voluson E8 GE Healthcare; Milwaukee, WI)[15] Fetal ultrasound measurements obtained at each visit included biparietal diameter (calipers placed on outer edge of proximal skull edge and inner edge of distal edge), head circumference, abdominal circumference, humerus length, and femur length. Estimated fetal weight was computed using a Hadlock formula and fetal head circumference, abdominal circumference, and femur length[16] head–abdominal circumference ratio was calculated to assess symmetry of fetal growth. Neonatal and maternal outcomes were assessed by abstraction of medical records. Hypertensive disorders were identified using postpartum diagnoses abstracted from the medical record.

The primary outcome assessed in this secondary analysis was the fetal growth pattern derived from calculated fetal weight and individual fetal biometrics across gestation. Secondary outcomes included mean birthweight and prevalence of SGA infants defined as <10th percentile for neonatal sex and gestational age at delivery using the Duryea birthweight reference[17]

Women were grouped into one of three categories by number of cumulative days of first trimester (<14 weeks of gestation) bleeding: 0, 1, >1 day. These categories were selected in order to distinguish the effects of prolonged bleeding from a single incidence (one day), and because number of days provides a more objective measure than self-reported severity. Distribution of self-reported number of days of bleeding is shown in Figure 1. Maternal characteristics were compared among groups using chi-square or one-way analysis of variance for categorical or continuous data, respectively. Fetal biometric measurements and estimated fetal weight were log-transformed to stabilize variances across gestational age and to improve normal approximations for the error structures. For each biometric measurement (biparietal diameter, head circumference, abdominal circumference, humerus length, femur length and head circumference–abdominal circumference ratio) and estimated fetal weight, fetal growth trajectories were created by fitting a linear mixed model with cubic splines for the fixed and a cubic polynomial for the random effects for each of the bleeding groups[18] Three-knot points (25th, 50th, 75th percentiles) were chosen at gestational ages that evenly divided the distributions. Percentiles were estimated based on assumed normal distribution of the random effects and error structure. Estimated trajectories (10th, 50th, and 90th percentiles) were determined across gestational age for each bleeding group. For estimated fetal weight and biometric measures, we tested for overall differences in the bleeding group trajectories using a likelihood-ratio test. When the global test was significant ($p<0.05$), we tested for week-specific differences among groups using Wald tests at each week of gestation. Significant differences were evaluated after adjustment for the following maternal characteristics, selected a priori based on causal diagrams and a review of confounders previously reported in the literature: maternal age, weight, height, parity, and self-identified racial ethnic group[7–9,19] An additional model added infant sex as a covariate in the main analysis due to the difference in proportion of female to male infants among groups. The Multivariate Imputation by Chained Equations software for R was used to impute (m=10) missing covariates when performing adjusted tests for week-specific differences in fetal growth trajectories.

Several sensitivity analyses were performed. First, the analysis was repeated by self-reported bleeding severity (mild, moderate-severe) compared with no bleeding. Moderate and severe bleeding were grouped due to the low frequency of severe bleeding, and association with number of days of bleeding was evaluated using a chi-square test. Next, fetal growth was evaluated among women with bleeding in the first trimester only, first and subsequent trimesters, or subsequent trimesters only, compared with no bleeding. The final sensitivity analysis assessed the effects of first-trimester bleeding (stratified by number of days) on fetal growth among women who did not develop any complications, and excluded pregnancies which resulted in stillbirth, preterm delivery < 37 weeks' gestation, hypertensive diseases, gestational diabetes, or neonatal conditions (e.g. aneuploidy, anomalies, death). Poisson regression with robust estimator of variance for standard error and adjustment for maternal age, height, weight, parity and racial ethnic group was used to evaluate the relative risk of delivering an SGA neonate in the 2,307 women included in the primary analysis and in the subset of 1,730 who delivered at term without complications. In these same groups, analysis of covariance was used to evaluate the association between categorical number of days of first-trimester bleeding and birthweight, to confirm the differences in estimated fetal weight that were observed among the groups. The analysis of covariance was adjusted for the same covariates as the fetal growth analyses, as well as gestational age at delivery, to account for the effects of preterm and early term (37–38 weeks) delivery on birthweight.

All analyses were completed with the use of SAS software (version 9.4, SAS Institute, Inc., Cary, NC) or R (version 3.3.1, available at http://www.R-project.org).

Results

Of 2,334 women enrolled, 14 were found to be ineligible after enrollment. Three had no first-trimester bleeding data, two were missing information on number of days of bleeding, and eight had no ultrasound data; thus, a total of 2,307 women were included in the main analysis. In total, 410 women (17.8%) reported first-trimester bleeding. Of those, 176 (42.9%) bled for 1 day, and 234 (57.1%) bled for more than 1 day. Distribution of maternal characteristics is presented in Table 1. Bleeding was more likely for slightly older and heavier women, and for those born outside the United States. Imputation was used for women missing data on height (n=15; 11 with no bleeding, 3 with 1 day, 1 with >1 day) and weight (n=4; all with no bleeding).

Figure 2 presents estimated fetal weight trajectories for the three groups, including 10^{th}, 50^{th}, and 90^{th} percentiles. Estimated fetal weight for pregnancies with >1 day of bleeding differed significantly from no bleeding from 14 to 16 weeks and 35 to 39 weeks gestation (global test p<0.001). Magnitudes of difference in estimated fetal weight are presented in Table 2. The median estimated fetal weight for women with >1 day of bleeding was 2–3 grams larger from 14 to 16 weeks than that of women with no bleeding, but became progressively smaller in the third trimester compared to women with no bleeding, with estimated fetal weight 68–107 grams smaller from 35 weeks through 39 weeks of gestation. There were no statistically significant differences in estimated fetal weight for 1 day of bleeding compared with no bleeding. The addition of infant sex as a covariate resulted in non-significant differences in estimated fetal weight from weeks 14–16; the significant differences from weeks 35–39 remained unchanged, indicating that different proportions of females to males among the bleeding groups did not explain the observed decreases in fetal growth.

Differences in mean birthweight and prevalence of small or large-for-gestational-age neonates by number of days of bleeding are presented in Table 3. In addition to differences in estimated fetal weight during the third trimester, there were differences in the rate of SGA births among groups, with 148 (8.5%), 9 (5.7%), and 33 (15.7%) SGA neonates delivered in the no bleeding, 1 day, and >1 day of bleeding groups, respectively. Relative risk of delivering an SGA infant for women with >1 day of bleeding compared to no bleeding was 2.14 (95% CI: 1.51–3.02) in the full cohort and 2.06 (95% CI: 1.38–3.08) in the subset of uncomplicated pregnancies. The association between first-trimester bleeding and mean birthweight followed the same pattern as estimated fetal weight, with overall mean birthweight 153 grams smaller and mean birthweight at term 88 grams smaller in the >1 day of bleeding group compared to no bleeding. Figure 3 presents the growth trajectories for individual fetal biometric parameters in the main analysis. Biparietal diameter did not differ significantly among the groups (global p=0.433). Head circumference differed significantly only at 14 weeks gestation, with slightly larger (1.4 mm) head circumference for women with >1 day of bleeding compared to no bleeding (global p=0.047). Abdominal circumference for women with >1 day of bleeding was slightly larger than no bleeding at 14 and 15 weeks and became significantly smaller beginning at week 34 (global p<0.001). Femur and humerus length trajectories differed significantly among groups early in second trimester (14 to 16 weeks) only (global p<0.001 for both), with slight increases in femur and humerus length for women with >1 day of bleeding compared to no bleeding. Head–abdominal circumference ratio differed significantly among the groups, with smaller head–abdominal circumference ratio from 14 to 16 weeks, and larger head–abdominal circumference ratio from 35 to 39 weeks for >1 day of bleeding compared to no bleeding (global p=0.006).

Two previously excluded women with data on bleeding severity, but who were missing number of days, were included in the severity sensitivity analysis (n=2,309). Of 412 (17.8%) women who reported first-trimester bleeding, 367 (89.1%) described bleeding as mild and 45 (10.9%) described bleeding as moderate or severe. Estimated fetal weight trajectories differed significantly among groups from 34 to 36 weeks (global p=0.003) and are shown in Figure 4A. Estimated fetal weight was lower from weeks 34–36 for women with mild bleeding compared to no bleeding. At 38 weeks gestation, estimated fetal weight was 3157 g for no bleeding, 3092 g for mild bleeding, and 3078 for moderate or severe bleeding. Bleeding severity was correlated with number of days of bleeding (p=0.01, Chi-square analysis), with 6.3% of 1 day and 14.1% of >1 day bleeding cases reported as moderate or severe.

For the analysis evaluating the effects of whether bleeding continued or resolved after the first trimester, 2,032 women were included after excluding 277 women who were without complete information on bleeding throughout pregnancy. Of women whose data were analyzed, 538 (26.5%) bled at any time during pregnancy. Of those, 276 (51.3%) bled in the first trimester only, 186 (34.6%) in subsequent trimesters only, and 76 (14.1%) in both the first and subsequent trimesters. Differences in estimated fetal weight or biometric parameters among groups did not reach statistical significance in this sensitivity analysis (Figure 4B).

In the analysis limited to 1,730 women with pregnancies that did not develop complications (e.g. gestational diabetes or hypertensive diseases) and delivered at term, the incidence of first-trimester bleeding was 16.5%. The pattern of decreased estimated fetal weight in association with first-trimester bleeding was greater in this group, with significant differences beginning at 33 weeks for >1 day of bleeding (global p<0.001) and estimated fetal weight 128 grams smaller than the no bleeding group at 39 weeks compared to 106 grams smaller in the full cohort (Figure 4C). Differences in individual fetal biometrics in this cohort followed the same pattern as the full cohort.

Discussion

In our prospective cohort study of healthy, low-risk, singleton pregnancies, first-trimester bleeding was common. More than 1 day of bleeding was associated with asymmetric, decreased fetal growth beginning in the third trimester and an increased risk of SGA at birth. Our finding that the association between first-trimester bleeding and decreased fetal growth was even stronger in the subset of women with uncomplicated pregnancies who delivered at term suggests that this mechanism of impaired fetal growth acts independently of potentially confounding obstetric complications. One day of bleeding was not associated with significant differences in fetal growth. Bleeding that continued into subsequent trimesters was also not associated with a greater magnitude of decreased growth which may suggest that bleeding later in pregnancy is due to a different mechanism.[20]

Our findings are consistent with previous studies that found an association between first-trimester bleeding and low birthweight (<2500 g) or estimated fetal weight <10th percentile for gestational age[10,21,22] Most previous studies investigated bleeding by severity and found an association between severe bleeding and low birthweight[4,5,7] Conversely, our study found that even mild bleeding was significantly associated with decreased fetal growth. These differences may be due to lack of power, or the subjective nature of reported severity. A novel contribution of our study is the assessment of the effects of bleeding based on duration, which is more objective and therefore potentially more clinically useful. Our finding that duration and severity of bleeding did not fully correlate suggests that the two measures are not interchangeable. The finding that 1 day of bleeding was associated with small, not statistically significant decreases in fetal growth, and accounts for nearly half of all incidents of first-trimester bleeding, provides an explanation for the numerous previous studies which did not stratify by duration and found no significant association between bleeding and fetal growth[4,11,13,23]

The increased head–abdominal circumference ratio observed in the >1 day of bleeding group supports previous hypotheses that first-trimester bleeding may be an early sign of placental dysfunction[7] Increased levels of hemoglobin and red blood cells were observed in the cord blood at birth for pregnancies with first-trimester bleeding but not bleeding associated with placenta previa[24,25] The authors hypothesized that increased red blood cell levels were an attempt to compensate for oxygen deficiency Other theories postulating the mechanism explaining early bleeding as a sign of placental insufficiency include the finding that bleeding peaks at 5–8 weeks gestation, coinciding with the luteal-placental shift and potentially indicating suboptimal placental development resulting in decreased levels of progesterone which might be insufficient to prevent an episode of bleeding similar to menses.[19]

Limitations of this study include potential recall error due to the retrospective nature of data collection and the subjectivity of self-reported bleeding. However, there is no other established method of measuring vaginal bleeding in clinical practice, and bleeding was self-reported before the outcome was established, limiting its potential to bias the results of the study. An assessment of the accuracy of prospective diary or retrospective interview (end of first trimester) to assess first-trimester bleeding demonstrated significant agreement between the two methods[26] Our study was limited by lack of information on the gestational week of bleeding, and whether number of days was consecutive. Women in the study reported a wide range of number of days of bleeding, and there is potentially a biologic difference between 2 or 3 days of bleeding compared to more, but this study lacked power to distinguish any difference based on number of days beyond one day of bleeding. Finally, because first-trimester bleeding was assessed at a gestational age ranging from 10w0d to 13w7d, there is potential to have missed some incidents of first-trimester bleeding that occurred after 10w0d. However, 79.5% of enrollment interviews in this study occurred during weeks 12 or 13, reducing some of this potential error.

In conclusion, more than 1 day of first-trimester vaginal bleeding was associated with asymmetric, decreased fetal growth independent of associated complications. Although the magnitude of this observed decrease in estimated fetal weight and birthweight was small, the difference in mean birthweight is comparable to differences in birthweight observed in pregnancies with maternal smoking, which range from about 50 to 200 grams depending on maternal characteristics[27–29] It remains unknown whether bleeding is associated with short-term or long-term morbidity and if additional intervention, such as third trimester sonography, would be of benefit. It is clinically relevant that bleeding that resolved by the second or third trimester is not necessarily exempt from decreased fetal growth. It is, however, reassuring that 1 day of first-trimester bleeding, which was the most common duration reported, was not associated with statistically significant patterns of decreased fetal growth.

Acknowledgements

The authors thank the clinical centers involved in data collection for the NICHD Fetal Growth Studies (in alphabetical order): Christina Care Health Systems, Columbia University, Fountain Valley Hospital, California, Long Beach Memorial Medical Center, New York Hospital, Queens, Northwestern University, University of Alabama at Birmingham, University of California, Irvine, Medical University of South Carolina, Saint Peters University Hospital, Tufts University, and Women and Infants Hospital of Rhode Island. C-TASC and The Emmes Corporation were the data coordinating centers that provided data and imaging support for this multi-site study.

Supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health (Contract Numbers: HHSN275200800013C; HHSN275200800002I; HHSN27500006; HHSN275200800003IC; HHSN275200800014C; HHSN275200800012C; HHSN275200800028C; HHSN275201000009C). Intramural investigators designed the study that was implemented by clinical site investigators.

References

1. Saraswat L, Bhattacharya S, Maheshwari A, Bhattacharya S. Maternal and perinatal outcome in women with threatened miscarriage in the first trimester: a systematic review. BJOG : an international journal of obstetrics and gynaecology 2010;117:245–57. [PubMed: 19943827]
2. Berkowitz GS, Harlap S, Beck GJ, Freeman DH, Baras M. Early gestational bleeding and pregnancy outcome: a multivariable analysis. International Journal of Epidemiology 1983;12:165–73. [PubMed: 6874211]
3. Funderburk SJ, Guthrie D, Meldrum D. Outcome of pregnancies complicated by early vaginal bleeding. British J Obstet Gynecol 1980;87:100–5.
4. Sipila P, Sorri-Hartikainen A-L, Oja H, Von Wendt L. Perinatal outcome of pregnancies complicated by vaginal bleeding. British J Obstet Gynecol 1992;99:959–63.
5. Strobino B, Pantel-Silverman J. Gestational vaginal bleeding and pregnancy outcome. Am J Epidemiolgoy 1989;129:806–15.
6. Sun L, Tao F, Hao J, Su P, Liu F, Xu R. First trimester vaginal bleeding and adverse pregnancy outcomes among Chinese women: from a large cohort study in China. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2012;25:1297–301.
7. Weiss JL, Malone FD, Vidaver J, et al. Threatened abortion: A risk factor for poor pregnancy outcome, a population-based screening study. American journal of obstetrics and gynecology 2004;190:745–50. [PubMed: 15042008]
8. Williams MA, Mittendorf R, Lieberman E, Monson RR. Adverse infant outcomes associated with first-trimester vaginal bleeding. Obstet Gynecol 1991;78:14–8. [PubMed: 2047055]
9. Yang JY, Savitz DA. The effect of vaginal bleeding during pregnancy on preterm and small-for-gestational-age births: US National maternal and infant health survey, 1988. Pediatric and Perinatal Epidemiology 2001;15:34–9. [PubMed: 11237112]
10. Mulik V, Bethel J, Bhal K. A retrospective population-based study of primigravid women on the potential effect of threatened miscarriage on obstetric outcome. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 2004;24:249–53. [PubMed: 15203618]
11. Johns J, Jauniaux E. Threatened miscarriage as a predictor of obstetric outcome. Obstetrics and Gynecology 2006;107:845–50. [PubMed: 16582121]
12. Wilcox A Intrauterine growth retardation: beyond birthweight criteria. Elsevier 1983;8:189–93.
13. Davari-Tanha F, Shariat M, Kaveh M, Ebrahimi M, Jalalvand S. Threatened abortion: A risk factor for poor pregnacy outcome. Acta Medica Iranica 2008;46:314–20.
14. Buck Louis GM, Grewal J, Albert PS, et al. Racial/ethnic standards for fetal growth: the NICHD Fetal Growth Studies. American journal of obstetrics and gynecology 2015;213:449 e1–e41. [PubMed: 26410205]

15. Hediger ML, Fuchs KM, Grantz KL, et al. Ultrasound Quality Assurance for Singletons in the National Institute of Child Health and Human Development Fetal Growth Studies. J Ultrasound Med 2016;35:1725–33. [PubMed: 27353072]

16. Hadlock F, Harrist R, Sharman R, Deter R, Park S. Estimation of fetal weight with use of head, body, and femur measurements - a prospective study. American journal of obstetrics and gynecology 1985;151:333–7. [PubMed: 3881966]

17. Duryea EL, Hawkins JS, McIntire DD, Casey BM, Leveno KJ. A revised birth weight reference for the United States. Obstet Gynecol 2014;124:16–22. [PubMed: 24901276]

18. Pinheiro J, Bate D. Mixed Effects Models in S and S-Plus (Statistics and Computing) Springer 2000.

19. Hasan R, Baird DD, Herring AH, Olshan AF, Jonsson Funk ML, Hartmann KE. Patterns and predictors of vaginal bleeding in the first trimester of pregnancy. Annals of epidemiology 2010;20:524–31. [PubMed: 20538195]

20. Creasy RK, Resnik R, Green MF, Iams JD, Lockwood CJ, Moore TR. Creasy and Resnik's Maternal-Fetal Medicine, (pp. 732, Seventh ed.) Philidelphia, PA: Elsevier; 2014.

21. Arafa M, Abdel-Fataah M, Abou Zeid H, El-Khouly A. Outcomes of pregnancies complicated by early vaginal bleeding. Eastern Mediterranean Health Journal 2000;6:457–64. [PubMed: 11556037]

22. Williams MA, Hickok DE, Zingheim RW, Mittendorf R, Kimelman J, Mahony BS. Low birth weight and preterm delivery in relation to early-gestation vaginal bleeding and elevated maternal serum alpha-fetoprotein. Obstet Gynecol 1992;80:745–9. [PubMed: 1383900]

23. Tongsong T, Srisomboon J, Wanapirak C, Sirichotiyakul S, Pongsatha S, Polsrisuthikul T. Pregnancy outcome of threatened abortion with demonstrable fetal cardiac activity: a cohort study. J Obstet Gynecol 1995;21:331–5.

24. Walker J, Turnbull E. Hemoglobin and red cells in the human fetus and their relation to the oxygen content of the blood in the vessels of the umbilical cord. Lancet 1953:312–8.

25. Turnbull E, Walker J. The outcome of pregnancy complicated by threatened abortion. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 1956:553–9.

26. Hasan R, Funk ML, Herring AH, Olshan AF, Hartmann KE, Baird DD. Accuracy of reporting bleeding during pregnancy. Paediatric and perinatal epidemiology 2010;24:31–4. [PubMed: 20078827]

27. Butler NR, Goldstein H, Ross EM. Cigarette Smoking in Pregnancy: Its Influence on Birth Weight and Perinatal Mortality. British Medical Journal 1972;2:127–30. [PubMed: 5017304]

28. Conter V, Cortinovis I, Rogari P, Riva L. Weight growth in infants born to mothers who smoked during pregnancy. British Medical Journal 1995;310:768–71. [PubMed: 7711580]

29. Zheng W, Suzuki K, Tanaka T, Kohama M, Yamagata Z, Okinawa Child Health Study G. Association between Maternal Smoking during Pregnancy and Low Birthweight: Effects by Maternal Age. PLoS One 2016;11:e0146241. [PubMed: 26795494]

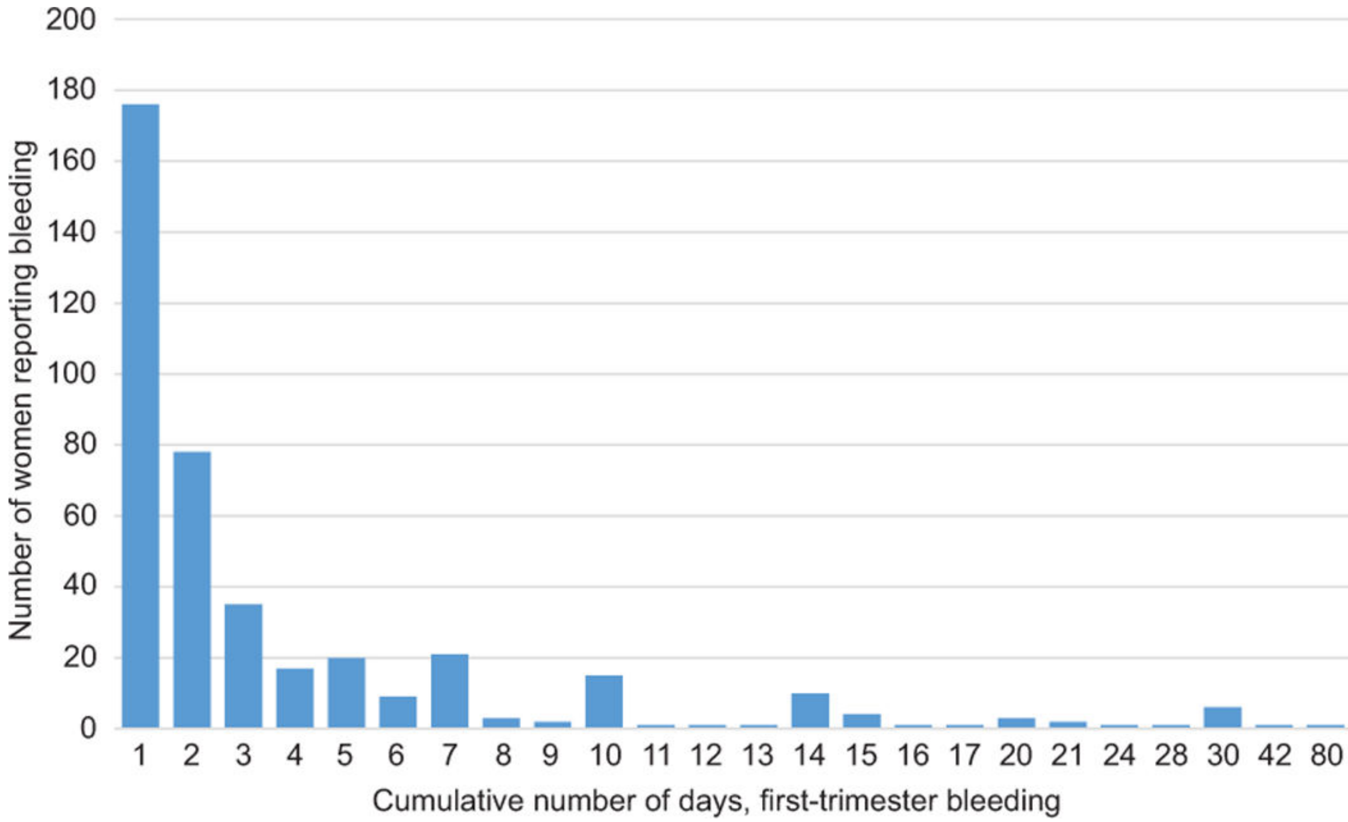

Figure 1.
Distribution of self-reported, cumulative number of days of first-trimester bleeding, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies–Singletons.

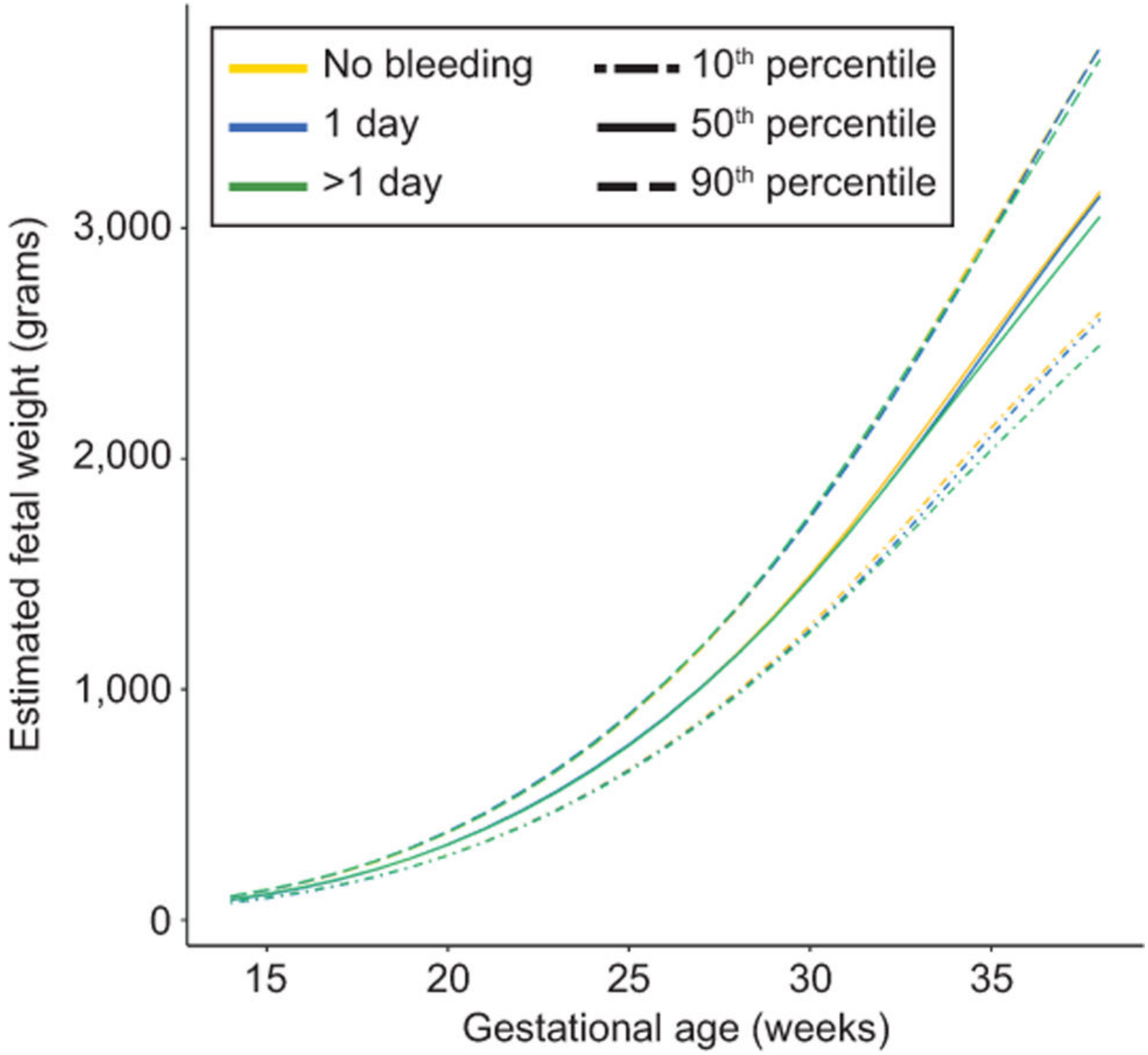

Figure 2.

Estimated fetal weight by days of first trimester (<14 weeks of gestation) bleeding and gestation, reference, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies–Singletons. Estimated 10th, 50th, and 90th percentiles for fetal weight by self-reported number of days of first-trimester (<14 weeks of gestation) bleeding, as estimated from linear mixed models with log-transformed outcomes and cubic splines.

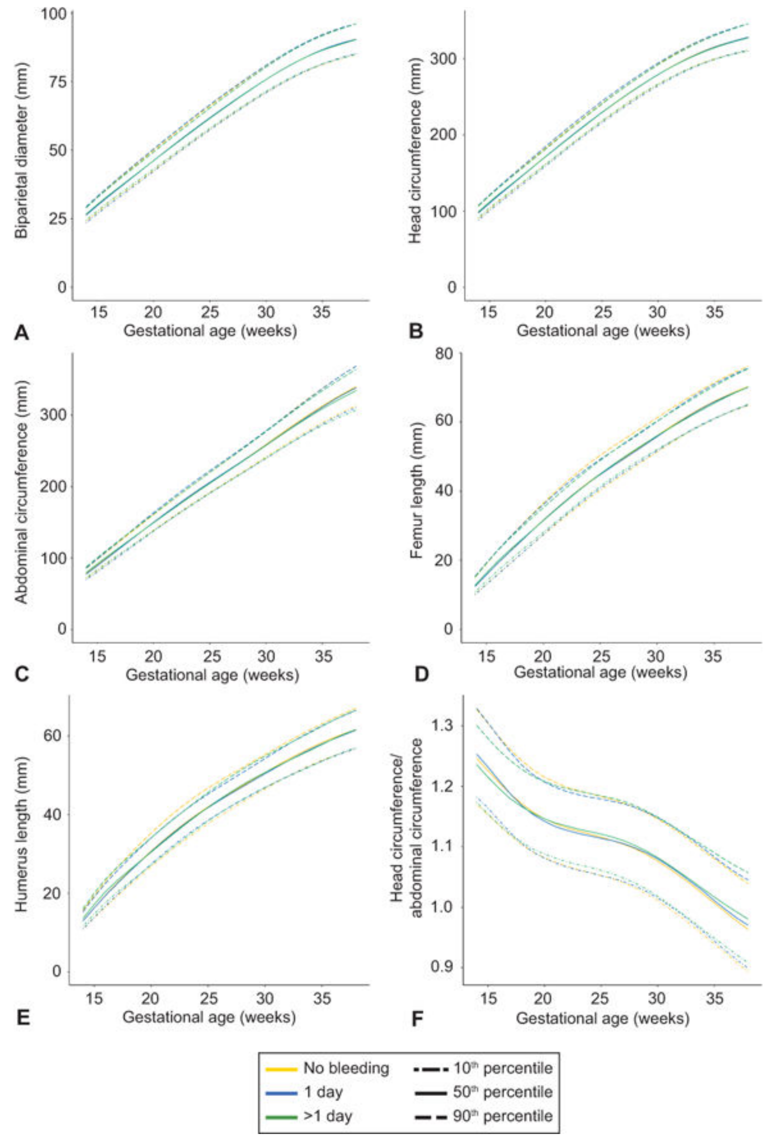

Figure 3.

Fetal anthropometric measurements by days of first-trimester (<14 weeks of gestation) bleeding and gestation, reference, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies–Singletons. Estimated 10th, 50th, and 90th percentiles for fetal anthropometric parameters by self-reported number of days of first-trimester (<14 weeks of gestation) bleeding, as estimated from linear mixed models with log-transformed outcomes and cubic splines. Biparietal diameter (**A**), head circumference (**B**), abdominal circumference (**C**), femur length (**D**), humerus length (**E**), and head circumference/abdominal circumference ratio (**F**).

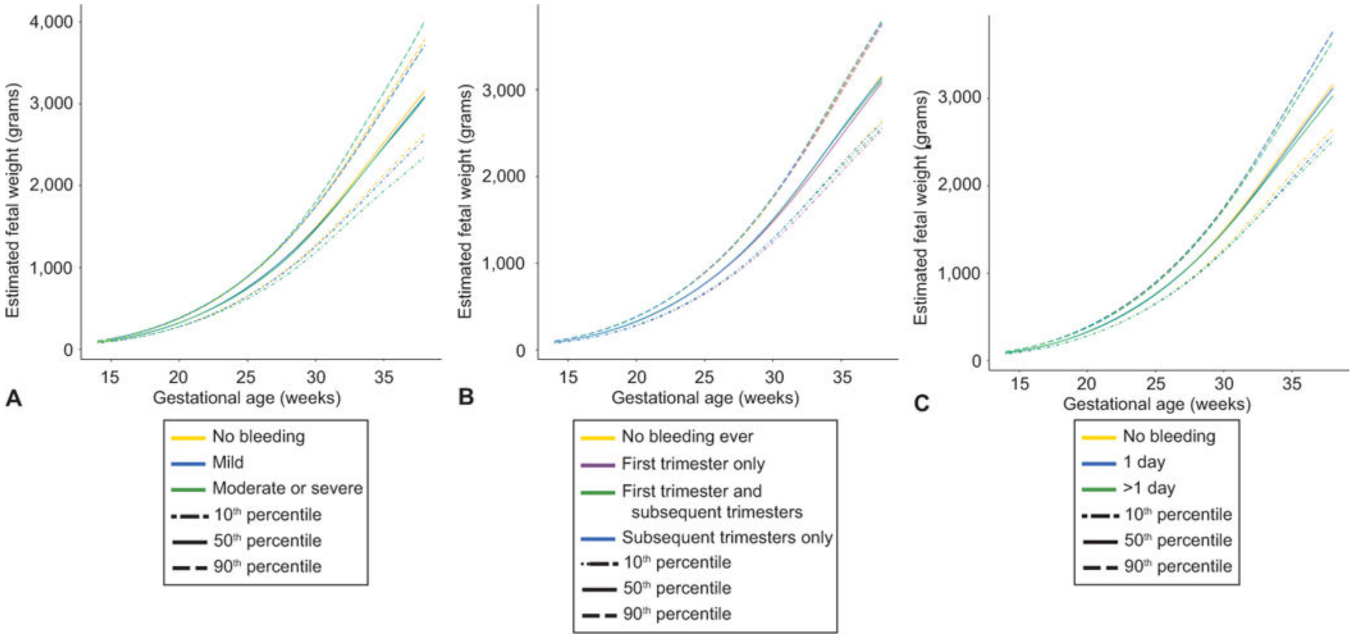

Figure 4.

Estimated fetal weight by bleeding characteristics and gestation, sensitivity analyses, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies–Singletons. Estimated 10th, 50th, and 90th percentiles for fetal weight by bleeding severity (**A**), trimester of bleeding (**B**), and number of days of bleeding in the sunset limited to uncomplicated pregnancies (**C**). Uncomplicated pregnancies exclude pregnancies which resulted in stillbirth, preterm delivery (<37 weeks of gestation), hypertensive diseases, gestational diabetes, or neonatal conditions (eg, aneuploidy, anomalies, death).

Table 1.

Maternal characteristics at enrollment by number of days of self-reported first trimester (< 14 weeks of gestation) bleeding (n=2,307; NICHD Fetal Growth Studies – Singletons)

Maternal Characteristic	No bleeding (n=1897)	1 day of bleeding (n=176)	>1 day bleeding (n=234)	*P*
Racial ethnic group, No. (%)				0.474
White, non-Hispanic	511 (26.9)	37 (21.0)	61 (26.1)	
Black, non−Hispanic	500 (26.4)	47 (26.7)	53 (22.7)	
Hispanic	523 (27.6)	51 (29.0)	70 (29.9)	
Asian, Pacific Islander	363 (19.1)	41 (23.3)	50 (21.4)	
Native born United States, No. (%) *,†				0.007
Yes	1272 (67.1)	107 (60.8)	143 (61.1)	
No	624 (32.9)	68 (38.6)	91 (38.9)	
Age, years *				0.008
Mean ± SD	28.0 ± 5.5	28.4 ± 4.8	29.2 ± 5.4	
Self−reported height, cm				0.164
Mean ± SD	162.3 ± 6.9	162.6 ± 7.2	163.2 ± 7.1	
Self−reported weight, kg *				0.030
Mean ± SD	62.2 ± 9.4	64.0 ± 10.8	63.2 ± 10.1	
BMI, kg/m^2				0.089
Mean ± SD	23.6 ± 3.1	24.1 ± 3.1	23.7 ± 3.0	
Parity, No. (%)				0.719
0	942 (49.7)	85 (48.3)	110 (47.0)	
1+	955 (50.3)	91 (51.7)	124 (53.0)	

Maternal Characteristic	No bleeding (n=1897)	1 day of bleeding (n=176)	>1 day bleeding (n=234)	*P*
Marital status, No. (%)				0.545
Married or living with partner	1431 (75.5)	134 (76.1)	185 (79.1)	
Divorced, separated, or widowed	48 (2.5)	7 (4.0)	6 (2.6)	
Not married	416 (22.0)	35 (19.9)	43 (18.4)	
Education, No. (%)				0.286
< High school	207 (10.9)	18 (10.2)	24 (10.3)	
High school	337 (17.8)	30 (17.1)	34 (14.5)	
Some college or associate degree	555 (29.3)	60 (34.1)	58 (24.8)	
Bachelor's degree	456 (24.0)	40 (22.7)	62 (26.5)	
Master's or advanced degree	342 (18.0)	28 (15.9)	56 (23.9)	
Family income, No. (%)				0.275
≤$29,999	461 (28.3)	51 (34.0)	38 (19.6)	
$30,000−39,999	152 (9.3)	12 (8.0)	17 (8.8)	
$40,000−$49,999	126 (7.7)	14 (9.3)	17 (8.8)	
$50,000−$74,999	196 (12.1)	15 (10.0)	31 (16.0)	
$75,000−$99,999	216 (13.3)	19 (12.7)	29 (15.0)	
≥$100,000	476 (29.3)	39 (26.0)	62 (32.0)	
Health insurance, No. (%)[†]				
Private or managed care	1023 (57.8%)	82 (50.6%)	133 (62.7%)	0.063
Medicaid, self−pay, other	748 (42.2%)	80 (49.4%)	79 (37.3%)	
Current paid jobs, No. (%)				0.378
0	644 (34.0)	67 (38.1)	88 (37.6)	
1	1163 (61.3)	104 (59.1)	139 (59.4)	
≥2	90 (4.7)	5 (2.8)	7 (3.0)	

Maternal Characteristic	No bleeding (n=1897)	1 day of bleeding (n=176)	>1 day bleeding (n=234)	*P*
Current student, No. (%)				0.280
Yes	337 (17.8)	37 (21.0)	35 (15.0)	
No	1559 (82.2)	139 (79.0)	199 (85.0)	
Infant sex, No. (%)				0.562
Male	918 (52.4)	82 (51.3)	103 (48.6)	
Female	833 (47.6)	78 (48.8)	109 (51.4)	

Abbreviations: No., number; SD, standard deviation

*Chi Square Test or analysis of covariance *P* value <0.05 for differences in demographic characteristics across bleeding groups

†Not included in the totals are missing data: United States Native-born status (n=2), height (n=15), weight (n=4), BMI (n=19), marital status (n=2), family income (n=336; 270 with no bleeding, 26 with 1 day, 40 with >1 day), insurance (n=162; 126 with no bleeding, 14 with 1 day, 22 with >1 day), current student status (n=1)

Table 2.

Estimated fetal weight by number of days of self-reported first-trimester bleeding (<14 weeks gestation), primary analysis, full cohort (n=2,307; NICHD Fetal Growth Studies–Singletons)

	Median Estimated Fetal Weight,[*] grams		
Gestational age, weeks	**No bleeding (n=1897)**	**1 day (n=176)**	**>1 day (n=234)**
14	87	87	89[†]
15	110	110	113[†]
16	139	139	142[†]
17	175	175	177
18	217	218	219
19	268	269	268
20	326	327	326
21	393	395	392
22	469	471	467
23	555	557	552
24	651	654	648
25	759	761	755
26	878	879	874
27	1010	1010	1006
28	1156	1153	1151
29	1318	1310	1310
30	1494	1480	1482
31	1684	1664	1665
32	1886	1859	1858
33	2096	2065	2058
34	2312	2280	2260
35	2528	2499	2460[†]
36	2742	2720	2658[†]

	Median Estimated Fetal Weight,* grams		
Gestational age, weeks	No bleeding (n=1897)	1 day (n=176)	>1 day (n=234)
37	2952	2935	2854†
38	3157	3138	3050†
39	3355	3320	3249†

*Computed from head circumference, abdominal circumference, and femur length[16]

†Value differed significantly from the no bleeding group (global and weekly pairwise $p<0.05$, obtained by the Wald test with adjustment for maternal age, height, weight, parity, and racial ethnic group)

Table 3.

Distribution of small for gestational age (SGA) or large for gestational age (LGA) newborns and mean birthweight by days of bleeding, (n=2,116; NICHD Fetal Growth Studies–Singletons).

	No bleeding (n=1747)	1 day (n=159)	>1 day (n=210)
SGA or LGA, n (%)			
SGA <10th percentile *	148 (8.5%)	9 (5.7%)	33 (15.7%)
LGA >90th percentile	148 (8.5%)	12 (7.6%)	15 (7.1%)
Mean birthweight (+/−SD), g	3334 ± 494	3326 ± 446	3181 † ± 602
Full term only (39/0 – 40/6 weeks)	3450 ± 393	3421 ± 410	3362 † ± 456

* Chi Square Test P value < 0.05 for differences across bleeding groups

† Mean birthweight differed significantly from no bleeding (global and pairwise P value <0.05, obtained by analysis of covariance with adjustment for maternal age, height, weight, parity, racial ethnic group, and gestational age at delivery)