Adverse Pregnancy Outcomes among Women with Prior Spontaneous or Induced Abortions

Michel A. Makhlouf, MD, PhD[1] Rebecca G. Clifton, PhD[2] James M. Roberts, MD[3] Leslie Myatt, PhD[4] John C. Hauth, MD[5] Kenneth J. Leveno, MD[6] Michael W. Varner, MD[7] John M. Thorp, Jr., MD[8] Brian M. Mercer, MD[9] Alan M. Peaceman, MD[10] Susan M. Ramin, MD[11] Jay D. Iams, MD[12] Anthony Sciscione, DO[13] Jorge E. Tolosa, MD, MSCE[14] Yoram Sorokin, MD[15] for the Eunice Kennedy Shriver National Institute of Child Health Human Development Maternal-Fetal Medicine Units Network

[1] Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, Texas
[2] The George Washington University Biostatistics Center, Washington, DC
[3] Department of Obstetrics and Gynecology University of Pittsburgh, Pittsburgh, Pennsylvania
[4] Department of Obstetrics and Gynecology, University of Cincinnati, Cincinnati, Ohio
[5] Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, Alabama
[6] Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, Texas
[7] Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, Utah
[8] Department of Obstetrics and Gynecology University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
[9] Department of Obstetrics and Gynecology, Case Western Reserve University-MetroHealth Medical Center, Cleveland, Ohio
[10] Department of Obstetrics and Gynecology, Northwestern University, Chicago, Illinois
[11] Department of Obstetrics and Gynecology University of Texas Health Science Center at Houston, Houston, Texas
[12] Department of Obstetrics and Gynecology, The Ohio State University, Columbus, Ohio
[13] Department of Obstetrics and Gynecology, Drexel University, Philadelphia, Pennsylvania
[14] Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, Oregon
[15] Department of Obstetrics and Gynecology, Wayne State University, Detroit, Michigan

Address for correspondence Michel Makhlouf, MD, PhD, Department of Obstetrics and Gynecology, The University of Texas Medical Branch, Galveston, TX 77555-0587 (e-mail: mimakhlo@utmb.edu).

Am J Perinatol 2014;31:765–772.

Abstract

Objective The aim of the article is to determine whether prior spontaneous abortion (SAB) or induced abortion (IAB), or the interpregnancy interval are associated with subsequent adverse pregnancy outcomes in nulliparous women.

Methods We performed a secondary analysis of data collected from nulliparous women enrolled in a completed trial of vitamins C and E or placebo for preeclampsia prevention. Adjusted odds ratios (ORs) for maternal and fetal outcomes were determined for nulliparous women with prior SABs and IABs as compared with primigravid participants.

Keywords
- spontaneous abortion
- induced abortion
- maternal outcomes
- neonatal outcomes

received
September 5, 2013
accepted after revision
September 19, 2013
published online
December 17, 2013

DOI http://dx.doi.org/10.1055/s-0033-1358771.
ISSN 0735-1631.

Results Compared with primigravidas, women with one prior SAB were at increased risk for perinatal death (adj. OR, 1.5; 95% CI, 1.1–2.3) in subsequent pregnancies. Two or more SABs were associated with an increased risk for spontaneous preterm birth (PTB) (adj. OR, 2.6, 95% CI, 1.7–4.0), preterm premature rupture of membranes (PROM) (adj. OR, 2.9; 95% CI, 1.6–5.3), and perinatal death (adj. OR, 2.8; 95% CI, 1.5–5.3). Women with one previous IAB had higher rates of spontaneous PTB (adj. OR, 1.4; 95% CI, 1.0–1.9) and preterm PROM (OR, 2.0; 95% CI, 1.4–3.0). An interpregnancy interval less than 6 months after SAB was not associated with adverse outcomes.

Conclusion Nulliparous women with a history of SAB or IAB, especially multiple SABs, are at increased risk for adverse pregnancy outcomes.

Spontaneous pregnancy loss before 20 weeks gestation is known to affect 12 to14% of the pregnant women.[1,2] About 1.2 million pregnancies in the United States are medically or surgically terminated each year, corresponding to 22.4% of the pregnancies,[3] with 40% performed in nulliparous women. Both spontaneous abortion (SAB) and induced abortion (IAB) have been associated with adverse pregnancy outcome in a subsequent pregnancy,[4–10] including preterm birth (PTB), pre-eclampsia, low-birth weight, and operative delivery. The relation of future pregnancy outcomes to the duration of the conception-free interval following a spontaneous or IAB is uncertain.[11] Improved outcomes with longer intervals were observed in a retrospective study,[7] but SABs and IABs were not separately analyzed. Some studies showed no effect of the interpregnancy interval,[12,13] while others found more favorable outcomes with shorter intervals.[14,15] Our hypotheses were that a history of spontaneous or IAB is associated with adverse pregnancy outcomes in a subsequent pregnancy, and that among women with history of abortion, a shorter interpregnancy interval is also associated with adverse outcomes.

Patients and Methods

Study Population

We analyzed outcome data of low-risk nulliparous women enrolled in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network randomized controlled trial of vitamins C and E versus placebo daily from 9 to 16 weeks' gestation until delivery.[16] Recruitment was conducted from July 2003 through February 2008 at 16 clinical centers. Briefly, pregnant women with a viable singleton fetus between 9 weeks 0 days and 16 weeks 6 days gestation were eligible for the primary study. Women with a previous pregnancy that lasted beyond 19 weeks 6 days were ineligible. Women with a systolic blood pressure 135 mm Hg or higher, diastolic blood pressure 85 mm Hg or higher, proteinuria, or those who were taking or had taken antihypertensive medication were also excluded. Women were also excluded if they had pregestational diabetes, were taking antiplatelet drugs or non steroidal anti-inflammatory agents, had uterine bleeding within the week before recruitment, uterine malformation, serious medical condition, known fetal anomaly or aneuploidy, in vitro fertilization resulting in the current pregnancy, or abuse of illicit drugs or alcohol. Participants were followed until delivery and their outcomes were determined prospectively.

Study Groups

As part of the primary study enrollment, women were asked about past pregnancies in detail including, month, year, and outcome. Participants were specifically asked whether the pregnancy ended as a result of spontaneous miscarriage, IAB, ectopic, or molar pregnancy. Patients who were not fluent in English were enrolled by someone fluent in their language and signed a consent form in their language.

For this secondary analysis, participants were categorized to one of three groups: those with no prior pregnancy (primigravid), those with one or more SABs, and those with one or more IABs. Women with a prior ectopic pregnancy, molar pregnancy, or with history of both SAB and IAB were excluded. Outcomes were analyzed based on the number of prior abortions (one vs. more than one).

The effect of interpregnancy interval on pregnancy outcomes was analyzed in women with a history of one SAB or one IAB. The interpregnancy interval was defined as the time elapsed from date of abortion to last menstrual period of the index pregnancy. Three interpregnancy intervals were analyzed: less than 6 months (<183 days), 6 to 12 months (range, 183–364 days) and greater than 12 months (≥ 365 days). These intervals were chosen based on those reported in prior studies.[7,15]

Study Outcomes

Study outcomes were collected by trained research staff following prespecified definitions. Data were collected in a uniform manner across all the study sites on prespecified forms. Maternal outcomes analyzed were spontaneous PTB, indicated PTB, preterm premature rupture of membranes (PROM) and preeclampsia. Spontaneous PTB was defined as a birth occurring at less than 37 weeks 0 days gestation as a result of spontaneous onset of labor or preterm PROM, excluding pregnancies that were lost as a result of SAB or IAB before 20 weeks 0 days. PTBs occurring secondary to maternal or fetal indications (i.e., indicated preterm deliveries) were reported separately from spontaneous PTBs. Fetal

and neonatal outcomes included fetal or neonatal death, birthweight less than the fifth percentile for gestational age adjusted by sex and race,[17] and admission to the neonatal intensive care unit.

Statistical Analyses

Categorical variables were compared using the χ^2 test and continuous variables using the Kruskal–Wallis test. Multivariable logistic regression analysis was used to calculate odds ratios (OR) and included maternal age, race, education, smoking, marital status, body mass index at enrollment, and whether they received placebo or vitamins C and E in the randomized trial. A nominal *p* value less than 0.05 was considered to indicate statistical significance and no adjustments were made for multiple comparisons. Analyses were performed using SAS software (Cary, NC). The original trial had been approved by the institutional review board (IRB) at each clinical site and the data coordinating center.

Results

Study Participants

In the original study,[16] 10,154 women underwent randomization and 183 were lost to follow-up. One subject had data removed at her request and another had data removed at the IRB's request. Therefore, outcomes were available for 9,969 nulliparas enrolled in the randomized trial. We excluded 231 women: 3 women were multiparous and erroneously enrolled, 1 died before delivery, 88 had a history of ectopic pregnancy, and 139 women had a history of both SAB and IAB. The analyzed groups consisted of 7,681 primigravid women, 1,060 women with a history of 1 SAB and 180 women with a history of 2 or more SABs. There were 642 women with a history of 1 IAB and 175 subjects with a history of 2 or more IABs. The demographics are listed in ►**Table 1**.

Women with Prior SAB

Compared with primigravid women, women with a history of one SAB were at increased risk for fetal or neonatal death (adj. OR, 1.5; 95% CI, 1.1–2.3) (►**Table 2**). Women with two or more SABs were at increased risk for spontaneous PTB (adj. OR, 2.6; 95% CI, 1.7–4.0), preterm PROM (adj. OR, 2.9; 95% CI, 1.6–5.3), perinatal death (adj. OR, 2.8; 95% CI, 1.5–5.3), and birthweight less than the fifth percentile (adj. OR, 2.2; 95% CI, 1.3–3.7). The risk for preeclampsia and neonatal intensive care admissions were not different in women with a history of one SAB or two or more SABs compared with primigravid women.

Women with Prior IAB

Compared with primigravidas, women with a history of one IAB were at increased risk for spontaneous PTB (adj. OR, 1.4; 95% CI, 1.0–1.9) and preterm PROM (adj. OR, 2.0; 95% CI, 1.4–3.0). These risks were not significantly increased in women with two or more IABs. Women with a history of two or more IABs had a lower risk of neonatal birthweight less than the fifth percentile (adj. OR, 0.2; 95% CI, 0.1–1.0). There was no significant difference in the risk for pre-eclampsia, fetal or neonatal death, or neonatal intensive care admissions compared with primigravid women (►**Table 3**).

Effect of Interpregnancy Interval

Of the 1,060 women with a history of one SAB, the interpregnancy interval could be determined in 1,040 women. There were 395 women with a SAB-to-pregnancy interval of less than 6 months, 216 with an interval of 6 to 12 months, and 429 with an interval greater than 12 months. Women in the 6 to 12 months group were at higher risk for preterm PROM (adj. OR, 3.7; 95% CI, 1.3–10.3) compared with women with an interval less than 6 months. There was no statistically significant difference in any of the other outcomes compared with women with an interval less than 6 months (►**Table 4**).

Table 1 Demographics and baseline characteristics

	Primigravid (*N* = 7,681)	One or more SABs (*N* = 1,240)	One or more IABs (*N* = 817)	*p*
Treatment group				0.60
Placebo, *n* (%)	3,827 (49.8)	610 (49.2)	420 (51.4)	
Vitamins, *n* (%)	3,854 (50.2)	630 (50.8)	397 (48.6)	
Tobacco use, *n* (%)	1,057 (13.8)	225 (18.1)	211 (25.8)	< 0.0001
Married, *n* (%)	3,370 (43.9)	556 (44.8)	233 (28.5)	< 0.0001
Race				< 0.0001
African American, *n* (%)	1,839 (23.9)	321 (25.9)	288 (35.3)	
Hispanic, *n* (%)	2,475 (32.2)	377 (30.4)	174 (21.3)	
Caucasian/Other, *n* (%)	3,367 (43.8)	542 (43.7)	355 (43.5)	
Maternal age, mean ± SD	23.1 ± 5.0	24.5 ± 5.5	25.0 ± 5.6	< 0.0001
Total years of schooling, mean ± SD	12.7 ± 2.8	12.7 ± 2.7	13.5 ± 2.1	< 0.0001
BMI at enrollment, mean ± SD	26.1 ± 6.0	27.0 ± 6.6	26.4 ± 5.9	< 0.0001
GA at enrollment (weeks) , mean ± SD	13.4 ± 2.1	13.3 ± 2.1	13.3 ± 2.2	0.07

Abbreviations: BMI, body mass index; GA, gestational age; IAB, induced abortion; SAB, spontaneous abortion; SD, standard deviation.

Table 2 Multivariable analysis of maternal and fetal outcomes in subjects with history of one or multiple SABs

Outcome	Primigravid ($N = 7{,}681$), *n* (%)	One SAB ($N = 1{,}060$), *n* (%), (95% CI)	Two or more SABs ($N = 180$), *n* (%), (95% CI)
Spontaneous preterm birth[a]	438 (5.8)	58 (5.6), 1.0 (0.7–1.3)	**25 (14.4), 2.6 (1.7–4.0)**
Indicated preterm birth[a]	231 (3.0)	35 (3.4), 1.1 (0.7–1.5)	6 (3.4), 1.0 (0.4–2.4)
Preterm PROM	172 (2.3)	23 (2.2), 0.9 (0.6–1.4)	**13 (7.3), 2.9 (1.6–5.3)**
Pre-eclampsia	539 (7.0)	74 (7.0), 1.0 (0.7–1.2)	9 (5.0), 0.6 (0.3–1.2)
Fetal/Neonatal death	157 (2.1)	**35 (3.3), 1.5 (1.1–2.3)**	**12 (6.7), 2.8 (1.5–5.3)**
Birthweight < 5th percentile	371 (4.9)	48 (4.7), 1.0 (0.7–1.3)	**17 (9.9), 2.2 (1.3–3.7)**
Neonatal intensive care admission	861 (11.2)	110 (10.4), 0.9 (0.7–1.1)	27 (15.1), 1.2 (0.8–1.8)

Abbreviations: BMI, body mass index; CI, confidence interval; PROM, premature rupture of membranes; SAB, spontaneous abortion.
[a]Excludes 110 women whose current pregnancy resulted in SAB or IAB (87 primigravid, 17 one SAB, 6 two or more SABs).
Note: Odds ratio compared with the primigravid group (95% confidence interval) were calculated after adjusting for maternal age, race, education, smoking, marital status, BMI at enrollment, and study drug (placebo or vitamins C and E). Odds ratio in bold typeface are statistically significant.

In women with a history of a single IAB, interpregnancy interval could be determined in 631 women; 61 women had an IAB-to-pregnancy interval of less than 6 months, 64 women had an interval of 6 to 12 months, and 506 women had an interval greater than 12 months. There was no statistically significant difference in any of the other outcomes between the groups (data not shown).

Comment

Our secondary analysis identified an increased risk of adverse pregnancy outcomes in low-risk women with a history of either SAB or IAB. A history of one SAB is associated with an increased risk of perinatal death in a subsequent pregnancy. A history of two or more SABs was associated with an increased

Table 3 Multivariable analysis of maternal and fetal outcomes in subjects with history of one or multiple IABs

Outcome	Primigravid ($N = 7{,}681$), *n* (%)	One IAB ($N = 642$), *n* (%), (95% CI)	Two or more IABs ($N = 175$), *n* (%), (95% CI)
Spontaneous preterm birth[a]	438 (5.8)	**52 (8.2), 1.4 (1.0–1.9)**	16 (9.3), 1.6 (1.0–2.8)
Indicated preterm birth[a]	231 (3.0)	22 (3.5), 1.1 (0.7–1.7)	5 (2.9), 0.9 (0.3–2.1)
Preterm PROM	172 (2.3)	**31 (4.9), 2.0 (1.4–3.0)**	8 (4.7), 1.8 (0.9–3.8)
Pre-eclampsia	539 (7.0)	41 (6.4), 0.9 (0.7–1.3)	13 (7.4), 1.1 (0.6–1.9)
Fetal/Neonatal death	157 (2.1)	17 (2.7), 1.2 (0.7–2.0)	7 (4.0), 1.7 (0.8–3.8)
Birthweight < 5th percentile	371 (4.9)	22 (3.5), 0.7 (0.5–1.1)	**2 (1.2), 0.2 (0.1–1.0)**
Neonatal intensive care admission	861 (11.2)	79 (12.3), 1.1 (0.8–1.4)	22 (12.6), 1.1 (0.7–1.7)

Abbreviations: BMI, body mass index; CI, confidence interval; IAB, induced abortion; PROM, premature rupture of membranes; SAB, spontaneous abortion.
[a]Excludes 97 women whose current pregnancy resulted in SAB or IAB (87 primigravid, 7 one IAB, 3 two or more IABs).
Note: Odds ratio compared with the primigravid group (95% confidence interval) were calculated after adjusting for maternal age, race, education, smoking, marital status, BMI at enrollment, and study drug (placebo or vitamins C and E). Odds ratio in bold typeface are statistically significant.

Table 4 Multivariable analysis of maternal and fetal outcomes in subjects with history of one SAB based on interpregnancy interval

Outcome	Less than 6 mo ($N = 395$) , *n* (%)	6–12 mo($N = 216$), *n* (%), (95% CI)	Greater than 12 mo ($N = 429$), *n* (%), (95% CI)
Spontaneous preterm birth[a]	17 (4.4)	15 (7.0) 1.6 (0.8–3.4)	24 (5.7) 1.2 (0.6–2.3)
Indicated preterm birth[a]	14 (3.6)	4 (1.9) 0.5 (0.2–1.5)	17 (4.0) 0.9 (0.4–2.0)
Preterm PROM	6 (1.5)	**11 (5.2)** **3.7 (1.3–10.3)**	5 (1.2) 0.8 (0.2–2.8)
Pre-eclampsia	31 (7.8)	11 (5.1) 0.6 (0.3–1.2)	31 (7.2) 0.8 (0.4–1.3)
Fetal/Neonatal death	13 (3.3)	6 (2.8) 0.7 (0.3–2.0)	16 (3.7) 0.8 (0.3–1.7)
Birthweight $<$ 5th percentile	20 (5.2)	6 (2.8) 0.5 (0.2–1.2)	22 (5.3) 0.9 (0.5–1.7)
Neonatal intensive care admission	43 (10.9)	16 (7.5) 0.6 (0.3–1.1)	50 (11.7) 0.9 (0.6–1.4)

Abbreviations: CI, confidence interval; BMI, body mass index; IAB, induced abortion; PROM, premature rupture of membranes; SAB, spontaneous abortion.

[a]Excludes 17 women whose current pregnancy resulted in SAB or IAB.

Note: Odds ratio compared with the less than 6 months group (95% confidence interval) were calculated after adjusting for maternal age, race, education, smoking, marital status, BMI at enrollment, and study drug (placebo or vitamin C and E). Odds ratio in bold typeface are statistically significant.

risk of spontaneous PTB, perinatal death, and birthweight less than the fifth percentile compared with primigravid women. These findings are consistent with previous reports, and raise new questions about pathways that might explain the observed associations.

Bhattacharya and Bhattacharya[5] found an increased risk of pregnancy complications in women with one prior miscarriage compared with nulliparous women. Hammoud et al[18] also noted a small increased risk (OR of 1.13) of PTB and preterm premature rupture of membranes (PPROM) in women with a history of one miscarriage. Our findings are consistent with other studies showing adverse outcomes with increasing number of miscarriages.[18–20] The association between SAB and subsequent PTB was also confirmed in a recent meta-analysis.[10]

Moreover, the results of our study are consistent with the findings of others reporting an increased risk of adverse outcomes in women with a prior IAB.[4,10,21–24] Chen et al found lower odds for preterm delivery in women with one mifepristone abortion compared with women with no abortion.[25] Reasons for the association between both SAB and IAB and subsequent PTB are unclear. Women experiencing SAB and IAB may share risk factors for PTB that are currently unknown, or may acquire risk for subsequent PTB via the medical care they received that might alter endometrial environment, for example, antibiotic prophylaxis, duration of cervical dilation, or uterine curettage.

If uterine instrumentation is the common exposure, it is interesting to note that women exposed to fertility evaluation have also been reported to have an increased risk of subsequent PTB.[26] In our study, we do not have data on medical versus surgical terminations. Unlike multiple SABs, we did not find a statistically significant association between multiple IABs and PTBs or PPROM, although our ability to detect this association may have been limited by our sample size.

Studies examining the association of SAB or IAB with hypertension and pre-eclampsia in a subsequent pregnancy have reported conflicting results.[27–31] SAB and IAB were found to be associated with reduced pre-eclampsia risk in some studies,[27,28,30] but not others.[30,32] Certain studies have shown this association to be dependent on timing of abortion[33] or the woman's parity.[28] We did not find an association between prior SAB or IAB and pre-eclampsia. However, our study analyzed women who had no history of hypertension or proteinuria, factors known to be related to subsequent pre-eclampsia. Although this may create a selection bias, the advantage to this exclusion is determining the association of prior SAB or IAB with pre-eclampsia without the confounding effects of hypertensive disorders.

Women with two or more IABs had a reduced risk of SGA infants. Chen et al[25] reported slightly higher birth weight following mifepristone IAB. Nulliparity is a risk factor for SGA[34] compared with multiparous women. It is possible that the reduced risk for SGA in women with multiple IABs is related to their multigravid status.

The effect of interpregnancy interval on pregnancy outcomes following a miscarriage has been controversial.[11] A large retrospective study[7] from South America showed improved outcomes with longer intervals, however, SABs and IABs were not separately analyzed and the study included multiparous women. In another study evaluating interpregnancy interval after SAB, Goldstein et al found no significant differences in outcomes between the immediate or delayed

conception groups, however their study population consisted of 64 participants.[12] In contrast, a large population-based retrospective study examining pregnancy records in Scotland from 1981 to 2000 found better pregnancy outcomes in nulliparous women who conceived within 6 months of a SAB.[15] The SAB sample size for our study yields a power of 0.75 for two-sided α of 0.05 to detect the PTB rate difference reported previously.[7] In the SAB group, our study found higher risk for preterm PROM in women whose interpregnancy interval was 6 to 12 months as compared with those with an interval of less than 6 months but the potential biological mechanisms of this observation are unknown. Otherwise, there was no statistically significant association between interpregnancy interval and adverse outcomes. Our results do not support recommending a waiting period following miscarriage. One limitation of our study and all other studies addressing interpregnancy interval following miscarriage is lack of knowledge whether the women had intentionally waited beyond 6 months or had decreased fertility or other factors compared with those that conceived sooner. Our findings, along those of other investigations, underscore the need for a prospective study to address this question.

Data on the previous type and number of abortions were collected by research personnel in an interview with the study participant, and the medical records of the prior pregnancies were not reviewed. Although abstracting data from medical records is more accurate, our data were obtained specifically on each past pregnancy and by research personnel fluent in the patient's language. While under-reporting of IAB is a known limitation of surveys,[35] the net effect of under-reporting would be an apparent decrease in the risk of adverse outcomes in the IAB group. Therefore, the risk of adverse outcomes could be potentially higher than what our data have shown.

The strengths of our study include a large cohort, low-risk population and well-documented maternal and perinatal outcomes. In addition, because SAB and IAB data were collected and analyzed in an identical fashion, our findings suggest that the adverse outcomes following multiple SABs are more frequent and more severe than after IAB; in agreement with a recent cohort study from Scotland.[36] The discrepancy in outcomes following multiple SABs versus multiple IABs suggests that adverse outcomes following multiple SABs are not solely related to pregnancy evacuation.

A possible limitation of our study is the lack of information on gestational age at the time of abortion or of the surgical or medical techniques used in the termination. Higher gestational age at the time of an SAB is associated with worse outcomes in a subsequent pregnancy.[37,38] Similarly, dilation and evacuation may be associated with worse complications than medically IAB.[4–25] Finally, it is possible that the multiple comparisons performed could have resulted in spurious findings and apparent associations because of chance. The last of these is made unlikely by the similarity of our observations to previous observational reports.

Our findings suggest that adverse outcomes in future pregnancies are increased in women with a history of SAB or IAB even in the absence of medical risk factors. These risks are higher in women with a history of two prior SABs. In contrast, there was no clear association between interpregnancy interval and subsequent pregnancy outcome. Large prospective studies specifically intended to discover linkages between SAB and IAB with preterm parturition and other adverse outcomes are needed to better identify risk factors for subsequent pregnancies in women with prior abortion(s). Nonetheless, our findings may be helpful in the counseling of women with previous spontaneous or IABs.

Acknowledgments/Appendix

The authors thank Elizabeth Thom, PhD, for protocol development, data management, and statistical analysis, Sabine Bousleiman, RNC, MSN, and Margaret Cotroneo, RN, for protocol development, and coordination between clinical research centers, Gail D. Pearson, MD, ScD, for protocol development and oversight, and George Saade, MD for manuscript oversight.

In addition to the authors, other members of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network are as follows:

G. Saade, J. Moss, B. Stratton, G. Hankins, J. Brandon, C. Nelson-Becker, G. Olson, and L. Pacheco from University of Texas Medical Branch, Galveston, TX.

S. Caritis, T. Kamon, M. Cotroneo, and D. Fischer from University of Pittsburgh, Pittsburgh, PA.

P. Reed, R. Silver, K. Hill (University of Utah), S. Quinn, F. Porter (LDS Hospital), V. Morby (McKay-Dee Hospital), J. Miller (Utah Valley Regional Medical Center) from University of Utah, Salt Lake City, UT

D.J. Rouse, A. Northen, P. Files, J. Grant, M. Wallace, and K. Bailey from University of Alabama at Birmingham, Birmingham, AL

R. Wapner, S. Bousleiman, R. Alcon, K. Saravia, F. Loffredo, A. Bayless (Christiana), C. Perez (St. Peter's University Hospital), M. Lake (St. Peter's University Hospital), and M. Talucci from Columbia University, New York, NY.

K. Boggess, K. Dorman, J. Mitchell, K. Clark, and S. Timlin from University of North Carolina at Chapel Hill, Chapel Hill, NC.

J. Bailit, C. Milluzzi, W. Dalton, C. Brezine, and D. Bazzo from Case Western Reserve University-MetroHealth Medical Center, Cleveland, OH.

J. Sheffield, L. Moseley, M. Santillan, K. Buentipo, J. Price, L. Sherman, C. Melton, Y. Gloria-McCutchen, and B. Espino from University of Texas Southwestern Medical Center, Dallas, TX.

M. Dinsmoor (NorthShore University HealthSystem), T. Matson-Manning, and G. Mallett from Northwestern University, Chicago, IL.

S. Blackwell, K. Cannon, S. Lege-Humbert, and Z. Spears from University of Texas Health Science Center at Houston, Houston, TX.

M. Carpenter, J. Tillinghast, and M. Seebeck from Brown University, Providence, RI.

P. Samuels, F. Johnson, S. Fyffe, C. Latimer, S. Frantz, S. Wylie from The Ohio State University, Columbus, OH.

M. Talucci, M. Hoffman (Christiana), J. Benson (Christiana), Z. Reid, C. Tocci from Drexel University, Philadelphia, PA.

M. Harper, P. Meis, and M. Swain from Wake Forest University Health Sciences, Winston-Salem, NC.

W. Smith, L. Davis, E. Lairson, S. Butcher, S. Maxwell, and D. Fisher from Oregon Health & Science University, Portland, OR.

G. Norman, S. Blackwell, P. Lockhart, D. Driscoll, and M. Dombrowski from Wayne State University, Detroit, MI.

E. Thom, T. Boekhoudt, L. Leuchtenburg from The George Washington University Biostatistics Center, Washington, DC.

G. Pearson, V. Pemberton, J. Cutler, and W. Barouch from National Heart, Lung, and Blood Institute, Bethesda, MD.

S. Tolivaisa from *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD.

G.D. Anderson from MFMU Steering Committee Chair (University of Texas Medical Center, Galveston, TX).

Note

The project described was supported by grants from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (HD34208, HD27869, HD40485, HD40560, HD40544, HD34116, HD40512, HD21410, HD40545, HD40500, HD27915, HD34136, HD27860, HD53118, HD53097, HD27917, and HD36801); the National Heart, Lung, and Blood Institute; and the National Center for Research Resources (M01 RR00080, UL1 RR024153, UL1 RR024989) and its contents do not necessarily represent the official view of NICHD, NHLBI, NCRR, or NIH.

References

1 Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M; ANDERSEN A-MN. Maternal age and fetal loss: population based register linkage study. BMJ 2000;320(7251):1708–1712
2 Wilcox AJ, Weinberg CR, O'Connor JF, et al. Incidence of early loss of pregnancy. N Engl J Med 1988;319(4):189–194
3 Jones RK, Kost K, Singh S, Henshaw SK, Finer LB. Trends in abortion in the United States. Clin Obstet Gynecol 2009;52(2):119–129
4 Atrash HK, Hogue CJ. The effect of pregnancy termination on future reproduction. Baillieres Clin Obstet Gynaecol 1990;4(2): 391–405
5 Bhattacharya S, Bhattacharya S. Effect of miscarriage on future pregnancies. Womens Health (Lond Engl) 2009;5(1):5–8
6 Bhattacharya S, Townend J, Shetty A, Campbell D, Bhattacharya S. Does miscarriage in an initial pregnancy lead to adverse obstetric and perinatal outcomes in the next continuing pregnancy? BJOG 2008;115(13):1623–1629
7 Conde-Agudelo A, Belizán JM, Breman R, Brockman SC, Rosas-Bermudez A. Effect of the interpregnancy interval after an abortion on maternal and perinatal health in Latin America. Int J Gynaecol Obstet 2005;89(Suppl 1):S34–S40
8 Martius JA, Steck T, Oehler MK, Wulf KH. Risk factors associated with preterm (<37+0 weeks) and early preterm birth (<32+0 weeks): univariate and multivariate analysis of 106 345 singleton births from the 1994 statewide perinatal survey of Bavaria. Eur J Obstet Gynecol Reprod Biol 1998;80(2):183–189
9 Moreau C, Kaminski M, Ancel PY, et al; EPIPAGE Group. Previous induced abortions and the risk of very preterm delivery: results of the EPIPAGE study. BJOG 2005;112(4):430–437
10 Swingle HM, Colaizy TT, Zimmerman MB, Morriss FH Jr. Abortion and the risk of subsequent preterm birth: a systematic review with meta-analyses. J Reprod Med 2009;54(2):95–108
11 Bhattacharya S, Smith N. Pregnancy following miscarriage: what is the optimum interpregnancy interval? Womens Health (Lond Engl) 2011;7(2):139–141
12 Goldstein RR, Croughan MS, Robertson PA. Neonatal outcomes in immediate versus delayed conceptions after spontaneous abortion: a retrospective case series. Am J Obstet Gynecol 2002;186(6): 1230–1234, discussion 1234–1236
13 Wyss P, Biedermann K, Huch A. Relevance of the miscarriage-new pregnancy interval. J Perinat Med 1994;22(3):235–241
14 Basso O, Olsen J, Christensen K. Risk of preterm delivery, low birthweight and growth retardation following spontaneous abortion: a registry-based study in Denmark. Int J Epidemiol 1998; 27(4):642–646
15 Love ER, Bhattacharya S, Smith NC, Bhattacharya S. Effect of interpregnancy interval on outcomes of pregnancy after miscarriage: retrospective analysis of hospital episode statistics in Scotland. BMJ 2010;341:c3967
16 Roberts JM, Myatt L, Spong CY, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Vitamins C and E to prevent complications of pregnancy-associated hypertension. N Engl J Med 2010;362(14):1282–1291
17 Alexander GR, Kogan MD, Himes JH. 1994-1996 U.S. singleton birth weight percentiles for gestational age by race, Hispanic origin, and gender. Matern Child Health J 1999;3(4):225–231
18 Hammoud AO, Merhi ZO, Diamond M, Baumann P. Recurrent pregnancy loss and obstetric outcome. Int J Gynaecol Obstet 2007;96(1):28–29
19 Jivraj S, Anstie B, Cheong YC, Fairlie FM, Laird SM, Li TC. Obstetric and neonatal outcome in women with a history of recurrent miscarriage: a cohort study. Hum Reprod 2001;16(1):102–106
20 Reginald PW, Beard RW, Chapple J, et al. Outcome of pregnancies progressing beyond 28 weeks gestation in women with a history of recurrent miscarriage. Br J Obstet Gynaecol 1987;94(7):643–648
21 Ancel P-Y, Lelong N, Papiernik E, Saurel-Cubizolles M-J, Kaminski M; EUROPOP. History of induced abortion as a risk factor for preterm birth in European countries: results of the EUROPOP survey. Hum Reprod 2004;19(3):734–740
22 Freak-Poli R, Chan A, Tucker G, Street J. Previous abortion and risk of pre-term birth: a population study. J Matern Fetal Neonatal Med 2009;22(1):1–7
23 Lowit A, Bhattacharya S, Bhattacharya S. Obstetric performance following an induced abortion. Best Pract Res Clin Obstet Gynaecol 2010;24(5):667–682
24 Voigt M, Henrich W, Zygmunt M, Friese K, Straube S, Briese V. Is induced abortion a risk factor in subsequent pregnancy? J Perinat Med 2009;37(2):144–149
25 Chen A, Yuan W, Meirik O, et al. Mifepristone-induced early abortion and outcome of subsequent wanted pregnancy. Am J Epidemiol 2004;160(2):110–117
26 Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol 2004;103(3):551–563
27 Beck I. Incidence of pre-eclampsia in first full-term pregnancies preceded by abortion. J Obstet Gynaecol (Lahore) 1985;6(2):82–84
28 Eskenazi B, Fenster L, Sidney S. A multivariate analysis of risk factors for preeclampsia. JAMA 1991;266(2):237–241

29 Koifman A, Levy A, Zaulan Y, et al. The clinical significance of bleeding during the second trimester of pregnancy. Arch Gynecol Obstet 2008;278(1):47–51
30 Seidman DS, Ever-Hadani P, Stevenson DK, Gale R. The effect of abortion on the incidence of pre-eclampsia. Eur J Obstet Gynecol Reprod Biol 1989;33(2):109–114
31 Zhu Q-X, Gao E-S, Chen A-M, Luo L, Cheng Y-M, Yuan W. Mifepristone-induced abortion and placental complications in subsequent pregnancy. Hum Reprod 2009;24(2): 315–319
32 Stone JL, Lockwood CJ, Berkowitz GS, Alvarez M, Lapinski R, Berkowitz RL. Risk factors for severe preeclampsia. Obstet Gynecol 1994;83(3):357–361
33 Campbell DM, MacGillivray I, Carr-Hill R. Pre-eclampsia in second pregnancy. Br J Obstet Gynaecol 1985;92(2): 131–140
34 Shah PS; Knowledge Synthesis Group on Determinants of LBW/PT births. Parity and low birth weight and preterm birth: a systematic review and meta-analyses. Acta Obstet Gynecol Scand 2010;89(7): 862–875
35 Fu H, Darroch JE, Henshaw SK, Kolb E; FU H. Measuring the extent of abortion underreporting in the 1995 National Survey of Family Growth. Fam Plann Perspect 1998;30(3):128–133, 138
36 Bhattacharya S, Lowit A, Bhattacharya S, et al. Reproductive outcomes following induced abortion: a national register-based cohort study in Scotland. BMJ Open 2012;2(4):
37 Edlow AG, Srinivas SK, Elovitz MA. Second-trimester loss and subsequent pregnancy outcomes: What is the real risk? Am J Obstet Gynecol 2007;197(6):e1–e6
38 Goldenberg RL, Mayberry SK, Copper RL, Dubard MB, Hauth JC. Pregnancy outcome following a second-trimester loss. Obstet Gynecol 1993;81(3):444–446