Original Research

Complications and Safety of Preconception Low-Dose Aspirin Among Women With Prior Pregnancy Losses

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OBJECTIVE: To evaluate complications and safety of preconception low-dose aspirin in 1,228 U.S. women (2007–2011).

METHODS: Evaluation of the safety of low-dose aspirin in the participants and their fetuses was a planned secondary analysis of the Effects of Aspirin in Gestation and Reproduction trial, a multicenter, block-randomized, double-blind, placebo-controlled trial investigating the effect of low-dose aspirin on the incidence of live birth. Women aged 18–40 years with a history of one to two pregnancy losses trying to conceive were randomized to daily low-dose aspirin (81 mg, n=615) or placebo (n=613) and were followed for up to six menstrual cycles or through gestation if they became pregnant. Emergency care visits and possible aspirin-related symptoms were assessed at each study follow-up using standardized safety interviews. In addition, complications for both the participant and her fetus or neonate were captured prospectively using case report forms, interviews conducted during pregnancy and postpartum, and medical records.

RESULTS: The proportion of women with at least one possible aspirin-related symptom during the trial was similar between treatment arms (456 [74%] low-dose aspirin compared with 447 [73%] placebo, *P*=.65) as was the proportion with at least one emergency care visit (104 [17%] low-dose aspirin compared with 99 [16%] placebo, *P*=.76). Maternal complications were evenly distributed by treatment arm with the exception of vaginal bleeding, which was more commonly reported in the low-dose aspirin arm (22% compared with 17%, *P*=.02). The distribution of fetal and neonatal complications—which included three stillbirths, three neonatal deaths, and 10 neonates with birth defect(s)—was similar between treatment arms.

CONCLUSION: Although rare but serious complications resulting from low-dose aspirin cannot be ruled out, preconception low-dose aspirin appears to be well tolerated by women trying to conceive, women who become pregnant, and by their fetuses and neonates.

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Systematic reviews of numerous randomized trials have found that low-dose aspirin during pregnancy can reduce the risk of preeclampsia.[1,2] In fact,

recent recommendations support the use of daily low-dose aspirin from the 12th week of gestation onward for the prevention of preeclampsia in women at high risk for this condition, citing the low incidence of harm associated with low-dose aspirin.[3–5] Evidence of low harm is based on studies that have primarily evaluated low-dose aspirin initiated after the first trimester.[2] Newer findings, however, suggest that low-dose aspirin may be more effective in improving pregnancy outcomes associated with preeclampsia if therapy is started earlier in pregnancy.[6] Previous findings from the Effects of Aspirin in Gestation and Reproduction trial have shown that preconception low-dose aspirin may also be associated with other improved pregnancy outcomes–higher live birth rate and lower risk of preterm birth–in normotensive women with a history of one pregnancy loss (less than 20 weeks of gestation) within the past year.[7,8] Given the benefits of low-dose aspirin on preeclampsia and potentially other reproductive outcomes, there may be increasing interest in initiating this widely available and low-cost therapy before conception, even among women with a low risk of developing preeclampsia. Therefore, evaluation of maternal and fetal and neonatal complications and safety associated with preconception low-dose aspirin use in low-risk women is critical and timely.

The objective of our study was to evaluate the risk of side effects and maternal and fetal and neonatal complications associated with preconception low-dose aspirin use among women in the Effects of Aspirin in Gestation and Reproduction trial.

MATERIALS AND METHODS

The study design of the Effects of Aspirin in Gestation and Reproduction trial has been described in detail.[9,10] Briefly, the trial was a multicenter, block-randomized, double-blind, placebo-controlled trial of 1,228 U.S. women conducted in 2007–2011. Study sites were located in: Salt Lake City, Utah; Denver, Colorado; Scranton, Pennsylvania; and Buffalo, New York. Women 18–40 years old with a history of one or two pregnancy losses who were trying to conceive by natural conception were eligible for the study (Clinical Trials Registration: number NCT00467363). Women with contraindications to aspirin, a clinical indication for aspirin therapy, or any major medical disorder (eg, hypertension) were ineligible.[7,10] The primary objective of the trial was incidence of live birth.[7] We present a planned secondary analysis of the trial: to evaluate the safety of low-dose aspirin in participants and their fetuses.

Participants were block-randomized by study center and eligibility stratum to either the intervention (81 mg low-dose aspirin daily; n=615) or an identical-looking placebo (n=613) with both study arms provided with 400 micrograms folic acid daily as a separate supplement. Participants were followed for up to six menstrual cycles or through gestation if they became pregnant. Institutional review board approval was obtained at each of the clinical sites and the data coordinating center. All participants provided written informed consent. A data safety and monitoring board ensured continued patient safety and ongoing monitoring of viability of the trial. Compliance to treatment assignment was measured by regularly administered questionnaires and bottle weighing at study visits.

Information on demographics and baseline characteristics was obtained from questionnaires administered at the first study visit. Pregnancy history was derived from information reported on the health and reproduction baseline questionnaire and from medical record abstraction for women who became pregnant during the study. Modified National Institute for Health and Care Excellence guidelines were used to categorize participants at risk for preeclampsia.[11] Baseline body mass index was calculated using height and weight measured at baseline by trained study staff.

Medical complications and possible aspirin-related symptoms, including but not limited to trial adverse events, were captured using multiple sources: case or incident report forms completed by study staff; systematic safety interviews administered by staff; other questionnaires completed by participants during pregnancy and postpartum; and medical record abstraction. Adverse events, defined in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines,[3] were monitored prospectively and were reported within 24 hours of becoming aware of each event. A multidisciplinary adverse events committee periodically reviewed all reported events and determined by consensus for each event the final diagnosis, severity, expectedness, and relatedness to low-dose aspirin. Trial adverse events have been previously reported.[7]

The current report describes maternal health outcomes and complications highlighted in a recent systematic review of randomized trials of low-dose aspirin in pregnant women[2]: maternal death, bleeding (subcategorized into: vaginal bleeding; subchorionic hemorrhage; combined vaginal bleeding [restricted to during pregnancy only] or subchorionic hemorrhage; and epistaxis), premature separation of the placenta (including both partial and complete abruption); and postpartum hemorrhage. We also report preterm contractions, emesis, and kidney stones as a result of

their frequent incidence in pregnancy. Other pregnancy outcomes–including but not limited to preeclampsia, preterm birth, pregnancy loss, and cesarean delivery–have been reported previously.[7,8] The following fetal and neonatal health outcomes were also selected for evaluation: fetal death (more than 20 weeks of gestation); neonatal death (within 4–6 weeks after birth); newborn received specialized care (neonatal intensive care unit, special care unit, intermediate care, or stepdown unit); intracranial or intraventricular hemorrhage; pulmonary hypertension; and structural birth defects.[2]

Safety interviews were administered during the trial at regularly scheduled follow-ups conducted either in person or by telephone. While participants were attempting to conceive, follow-ups occurred at the middle and end of each menstrual cycle (timed using fertility monitors and took place approximately every 2 weeks). If the participant became pregnant, the safety interview was administered every 4 weeks up until 36 weeks of gestation. The safety interview follow-ups began with: "Since your last visit to our clinic or your last phone interview, have you experienced any of the following health problems?" and listed 10 symptoms that have been associated with aspirin use in adults[12]: gastrointestinal discomfort, unusual or excessive bleeding, allergic reaction, unusual rashes, swelling, breathing difficulties, asthma attack, kidney problems, elevation in blood pressure, and development of nasal polyps. Participants could report experiencing a symptom even if it was not diagnosed or recognized by a medical care provider; possible symptoms could also be reported by participants assigned to the placebo. Two additional questions were added to the interview approximately 15 months into recruitment (approximately 30% of study timeline) to better assess the symptoms of nausea, vomiting, or both and vaginal bleeding, which were subcategories of gastrointestinal discomfort and unusual or excessive bleeding, respectively. Lastly, each safety interview included a question regarding emergency care visits: "Have you been to an ER or been admitted to a hospital since the last visit or the last phone interview?"

Complications during pregnancy were assessed using a pregnancy questionnaire completed by the participant, which was administered during the prenatal study clinic visits (every 4 weeks up until 36 weeks of gestation). The pregnancy questionnaire captured information on: vaginal bleeding; nausea and vomiting; abdominal cramping; and reasons for any visit to the doctor during the previous 4 weeks. Complications discovered after a live birth were identified using a postpartum questionnaire conducted by telephone approximately 4–6 weeks postdelivery. The postpartum questionnaire included open-ended questions about medical problems encountered after delivery for the participant and her infant separately.

Standardized medical record chart abstraction forms captured complications and conditions documented during the following clinical encounters for each participant (if applicable): prenatal visits, ultrasonograms, pregnancy loss visits, hospitalizations and emergency care visits before delivery, and delivery visits. In addition, certain complications and conditions were also assessed during an early pregnancy viability ultrasonogram conducted for study purposes. Chart abstraction captured information using checkboxes and open-ended fields. At least one chart abstraction form included a checkbox assessing: subchorionic hemorrhage, vaginal bleeding, preterm contractions, preterm labor, labor, placental abruption, emesis, and postpartum hemorrhage. In addition, blood transfusion during or after delivery was specifically assessed in the delivery record chart abstraction form and this (as well as what the mother reported during the postpartum interview) was considered an indicator of postpartum hemorrhage for our analysis. Lastly, each of the fetal and neonatal outcomes was included as a checkbox on at least one chart abstraction form.

After completion of the study, case report forms and free-text data from open-ended questions on questionnaires and medical records were reviewed independently by two board-certified reproductive endocrinologists (S.Z. and K.K.) and a perinatal epidemiologist (K.A.) blinded to treatment assignment. Adverse events and health conditions were classified using standardized medical terminology software (MedDRA) at the preferred term level; up to six preferred terms were allowed per report (eg, preterm contractions, vaginal bleeding, and vomiting could be identified as separate medical complications involved in a single adverse event described in a case report form).

Demographic and baseline characteristics were summarized by treatment arm. Possible aspirin-related symptoms reported during the follow-up safety interviews were collapsed by individual participant (any report compared with no report) and compared by assigned treatment arm among all women randomized (ie, intention-to-treat analysis) and also after stratifying by pregnancy status at the time of interview (ie, modified intention-to-treat analysis). Maternal and fetal and neonatal complications were similarly collapsed by individual participants using all other information

available across the trial (case report forms, questionnaires, chart abstractions–as described previously) and compared by treatment arm. Structural congenital anomalies were considered separately and listed by treatment arm.

Because pregnancy outcomes are conditional on becoming pregnant and factors that affect conception may also affect adverse pregnancy outcomes, we constructed inverse probability weights to control for bias potentially introduced by stratifying by pregnancy status, a potential consequence of treatment assignment.[8] These weights effectively reweighted the participants so that baseline characteristics were more evenly distributed between those who became pregnant during the trial and those who did not, allowing for unbiased stratification by pregnancy status (ie, removing bias potentially caused by "breaking" the randomization and evaluating some outcomes only among women who became pregnant). Using inverse probability weights, we estimated the proportion of women reporting any possible aspirin-related symptom among those who completed safety interviews while pregnant and the proportion of fetuses and neonates with any complications, both of which were conditional on becoming pregnant during the trial. In addition, we used the inverse probability weights for the analysis of the combined outcome of vaginal bleeding during pregnancy, subchorionic hemorrhage, or both.

A series of Fisher exact tests were used to determine differences by treatment arm with α equal to 0.05; correction for multiple comparisons was not applied to maximize the detection of differences between study arms. For analyses using inverse probability-weighted data, weighted χ^2 tests were used in place of a Fisher exact test. Unadjusted log-binomial models (unweighted or using inverse probability weights) were used to estimate risk differences and 95% confidence intervals. Reports of unusual or excessive bleeding symptoms were categorized by follow-up visit during which the report was obtained; comparisons between treatment arms for each visit used the Fisher exact test.

SAS 9.3 was used for all statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT00467363.[10]

RESULTS

Table 1 shows demographics and baseline characteristics of participants randomized by treatment arm. Most participants were white, married, and had experienced a pregnancy loss within the past 4 months. Characteristics were similar by treatment arm with the exception of marital status (P=.03), which indicated a higher proportion of women was married in the low-dose aspirin arm. Compliance with treatment assignment was similar between treatment arms (15% [93] of women in low-dose aspirin and 13% [79] in placebo self-reported permanently stopping the study drug).[7]

Follow-up safety interviews were filled out by 1,211 of 1,228 study participants and included 13,064 separate interviews. On average, 6.7 follow-up interviews were filled out per participant (range 1–20). Most women reported at least one symptom during the course of the trial and this did not differ by treatment arm (74% [456/615] low-dose aspirin compared with 73% [447/613] placebo, P=.65) (Table 2). Gastrointestinal discomfort and unusual or excessive bleeding were the most commonly reported symptoms (and did not vary by treatment arm). The percentages of safety interviews with reported unusual or excessive bleeding by follow-up visit are presented in Figure 1. No differences between treatment arms by visit were statistically significant.

As expected, symptoms were more commonly reported among women interviewed while pregnant (83% low-dose aspirin compared with 82% placebo, P=.73) compared with women interviewed while they were not pregnant (53% [319/605] low-dose aspirin compared with 51% [307/606] placebo, P=.49) (Table 3). For interviews conducted while the participant was not pregnant, only "swelling" significantly varied by treatment arm (3% [20/605] low-dose aspirin compared with 2% [9/606] placebo, P=.04); among women who were pregnant at the time of the interview, there were no differences in symptoms reported by treatment arm.

In terms of maternal complications, the proportions of participants with preterm contractions, subchorionic hemorrhage, epistaxis, emesis, kidney stones, premature separation of placenta, and postpartum hemorrhage were similar between treatment arms. Vaginal bleeding occurred in a higher proportion of participants in the low-dose aspirin arm (22% [138/615] low-dose aspirin compared with 17% [104/613] placebo, P=.02) as did the combined outcome of vaginal bleeding during pregnancy, subchorionic hemorrhage, or both (26% in low-dose aspirin compared with 20% in placebo, P=.01) (Table 4). Emesis was the most common maternal complication and occurred in a similar proportion of participants between treatment arms (49% [299/615] low-dose aspirin compared with 46% [279/613] placebo, P=.28). No maternal deaths were reported. As previously reported,[7] pregnancy loss was similar between treatment arms (13% low-dose aspirin compared with 13% placebo, P=.78).

Table 1. Demographic and Baseline Characteristics by Treatment Arm: The Effects of Aspirin in Gestation and Reproduction Trial

Demographic and Baseline Characteristics*	Low-Dose Aspirin (n=615)	Placebo (n=613)
Age (y)	28.8±4.9	28.7±4.7
Race		
White	576 (93.7)	586 (95.6)
Nonwhite	39 (6.3)	27 (4.4)
BMI (kg/m^2)	26.3±6.8	26.5±6.4
Marital status		
Married	575 (93.5)	549 (89.6)
Living with partner	31 (5.0)	43 (7.0)
Other	9 (1.5)	21 (3.4)
More than high school education	526 (85.7)	531 (86.6)
Employed	451 (76.1)	444 (75.1)
Time from last loss to randomization (mo)		
0 to 4 or less	331 (54.9)	320 (52.8)
4 to 8 or less	103 (17.1)	119 (19.6)
8 to 12 or less	50 (8.3)	49 (8.1)
More than 12	119 (19.7)	118 (19.5)
No. of previous pregnancies resulting in a live birth		
0	283 (46.0)	288 (47.0)
1	221 (35.9)	222 (36.2)
2	111 (18.0)	103 (16.8)
No. previous pregnancy losses		
1	422 (68.6)	403 (65.7)
2	193 (31.4)	210 (34.3)
Smoking in past year		
Never	529 (87.0)	538 (88.3)
6 or fewer times/wk	41 (6.7)	46 (7.6)
Daily	38 (6.3)	25 (4.1)
Modified NICE guidelines risk classification for preeclampsia†		
Moderate	108 (17.1)	91 (14.8)
High	33 (5.4)	22 (3.6)
Pregnancy history		
Preterm birth‡	40 (6.5)	41 (6.7)
Preeclampsia‡	33 (5.4)	22 (3.6)
Stillbirth‡	36 (5.9)	27 (4.4)
Birth defect§‖	13 (2.1)	9 (1.5)
Neonatal or infant death§	8 (1.3)	6 (1.0)

BMI, body mass index; NICE, the National Institute for Health and Care Excellence.
Data are mean±standard deviation or n (%).
* Information on characteristics was missing for BMI (n=20), education (n=1), time from last loss to randomization (n=19), smoking (n=11), and employment (n=44).
† Moderate risk for preeclampsia included one or more of the following risk factors: aged 40 years or older at either time of randomization or beginning of study pregnancy if became pregnant, at least 10 years between time of last loss and either randomization or beginning of study pregnancy if became pregnant, BMI of 35 kg/m^2 or more at randomization, preeclampsia during a previous pregnancy (family history of preeclampsia was unknown), and multifetal gestation in study pregnancy. High risk for preeclampsia included women with preeclampsia during a previous pregnancy. Women with other medical conditions who would have been categorized as a high risk for preeclampsia (such as chronic kidney disease, autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome, type 1 or type 2 diabetes, or chronic hypertension) were ineligible for the study.
‡ Information derived from history reported on health and reproduction baseline questionnaire or from medical chart review of pregnancy history.
§ Information derived from history reported on health and reproduction baseline questionnaire only.
‖ Birth defects included structural defects, chromosomal abnormalities, or both only.

Few fetal and neonatal complications occurred. There were three fetal deaths at more than 20 weeks of gestation (one in low-dose aspirin compared with two in placebo, *P*=.57) and three neonatal deaths (two in low-dose aspirin compared with one in placebo, *P*=.71) (Table 5). The fetal death in the low-dose aspirin group was the result of a cord accident. In the placebo group, one fetal death was diagnosed with trisomy 18 and the other cause of fetal death was unknown. Two neonatal deaths were in severely

Table 2. Systematically Assessed, Self-Reported Aspirin-Related Symptoms and Emergency Care Visits by Treatment Arm: the Effects of Aspirin in Gestation and Reproduction Trial

Symptoms and Emergency Care Visits	Low-Dose Aspirin (n=615)	Placebo (n=613)	RD	95% CI	*P*
Symptom					
Any symptom	456 (74)	447 (73)	1.2	−3.7 to 6.2	.65
Any gastrointestinal discomfort	388 (63)	367 (60)	3.2	−2.2 to 8.7	.27
Any nausea or vomiting*	274 (45)	270 (44)	0.5	−5.0 to 6.1	.86
Any unusual or excessive bleeding	214 (35)	196 (32)	2.8	−2.4 to 8.1	.30
Any vaginal bleeding*	125 (20)	119 (19)	0.9	−3.6 to 5.4	.72
Any allergic reaction	22 (4)	14 (2)	1.3	−0.6 to 3.2	.24
Any unusual rashes	55 (9)	43 (7)	1.9	−1.1 to 5.0	.25
Any swelling	72 (12)	55 (9)	2.7	−0.7 to 6.1	.13
Any breathing difficulty	65 (11)	68 (11)	−0.5	−4.0 to 3.0	.79
Any kidney problems	25 (4)	29 (5)	−0.7	−3.0 to 1.6	.58
Any asthma attack	13 (2)	19 (3)	−1.0	−2.8 to 0.8	.29
Any blood pressure elevation	23 (4)	14 (2)	1.5	−0.5 to 3.4	.18
Any nasal polyps	0 (0)	0 (0)	NA	NA	NA
Any emergency care visit	104 (17)	99 (16)	0.8	−3.4 to 4.9	.76
Any incomplete questionnaire	34 (6)	24 (4)	1.6	−0.8 to 4.0	.23

RD, risk difference; CI, confidence interval; NA, not applicable.
Data are n (%) unless otherwise specified.
P value calculated using Fisher exact test.
* Questions specifically assessing nausea or vomiting and vaginal bleeding were added to the interview approximately 15 months into recruitment.

premature neonates (less than 22 weeks of gestation) and one was the result of injury after uterine rupture resulting from a motor vehicle accident; none was the result of congenital anomalies. There was one instance in the placebo group of left cerebral artery infarction (without information on hemorrhage) and one

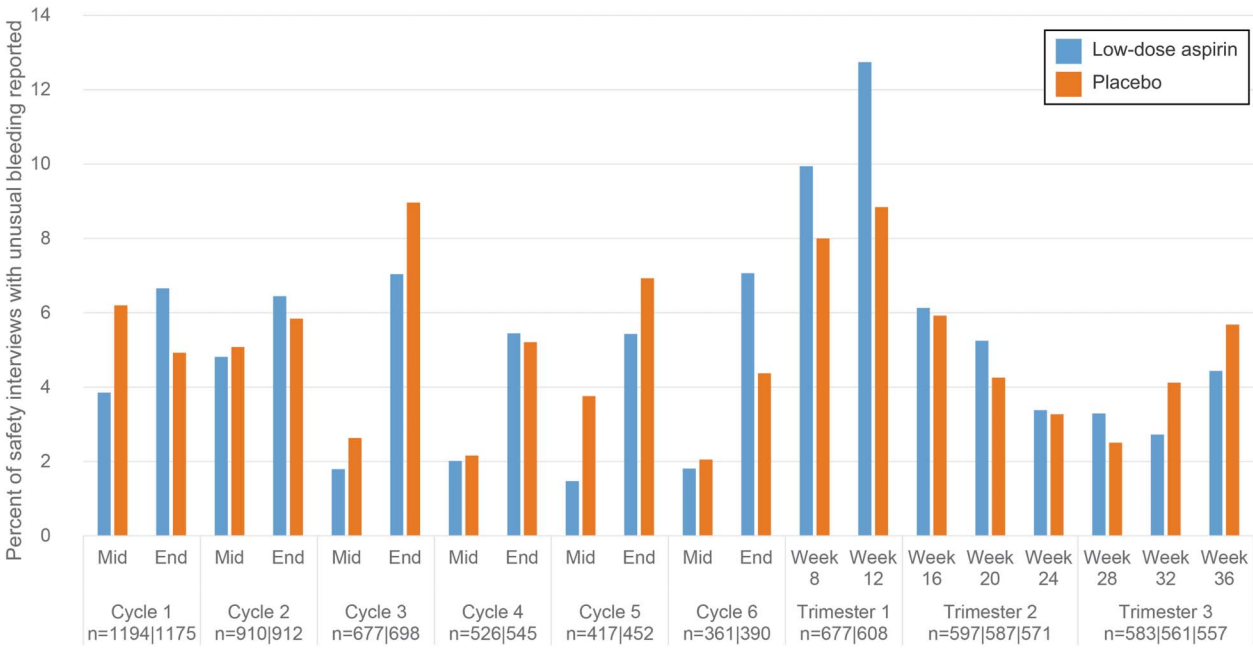

Fig. 1. Timing of systematically assessed self-reported unusual or excessive bleeding by treatment arm for the Effects of Aspirin in Gestation and Reproduction trial. Cycles 1–6 refer to safety interviews administered during the menstrual cycles while the participant attempted pregnancy. Trimesters 1–3 refer to safety interviews administered during pregnancy for women who became pregnant during the trial. N values refer to the number of safety interviews administered at each time point.
Ahrens. Safety of Preconception Low-Dose Aspirin. Obstet Gynecol 2016.

Table 3. Systematically Assessed, Self-Reported, Aspirin-Related Selected Symptoms and Emergency Care Visits by Pregnancy Status and Treatment Arm: The Effects of Aspirin in Gestation and Reproduction Trial

Symptoms and Emergency Care Visits	Low-Dose Aspirin (n=615)	Placebo (n=613)	RD	95% CI	*P*
Not pregnant at time of interview (n=1,211)	605	606			
Symptom					
Any symptom	319 (53)	307 (51)	2.1	−3.6 to 7.7	.49
Any gastrointestinal discomfort	219 (36)	217 (36)	0.4	−5.0 to 5.8	.91
Any nausea or vomiting*	116 (19)	122 (20)	−1.0	−5.4 to 3.5	.72
Any unusual or excessive bleeding	141 (23)	134 (22)	1.2	−3.5 to 5.9	.63
Any vaginal bleeding*	78 (13)	74 (12)	0.7	−3.1 to 4.4	.73
Any swelling	**20 (3)**	**9 (2)**	1.8	0.1–3.5	**.04**
Any breathing difficulty	24 (4)	28 (5)	−0.7	−2.9 to 1.6	.67
Any emergency care visit	30 (5)	33 (5)	−0.5	−3.0 to 2.0	.80
Pregnant at time of interview (n=684)†	347.1	336.9			
Symptom					
Any symptom	287.4 (83)	275.6 (82)	1.0	−5.0 to 7.0	.73
Any gastrointestinal discomfort	268.2 (77)	254.8 (76)	1.6	−5.0 to 8.3	.61
Any nausea or vomiting*	210.5 (60)	200.9 (62)	−1.1	−8.6 to 6.4	.77
Any unusual or excessive bleeding	98.2 (28)	90.8 (27)	1.3	−5.6 to 8.3	.69
Any vaginal bleeding*	57.1 (16)	59.2 (18)	−1.1	−7.0 to 4.8	.70
Any swelling	59.1 (17)	49.2 (15)	2.4	−3.4 to 8.2	.39
Any breathing difficulty	42.7 (12)	43.8 (13)	−0.7	−5.8 to 4.4	.79
Any emergency care visit	77.3 (22)	77 (23)	−0.6	−7.1 to 5.9	.85

RD, risk difference; CI, confidence interval.
Data are n or n (%) unless otherwise specified.
P value calculated using Fisher exact test (unweighted data) or χ^2 test (weighted data).
Bold indicates $P<.05$.
* Questions specifically assessing nausea or vomiting and vaginal bleeding were added to the interview approximately 15 months into recruitment.
† For women pregnant at the time of the interview, inverse probability of conception weights was applied to control for selection bias introduced by stratifying on pregnancy status.

instance in the low-dose aspirin group of transient pulmonary hypertension, which resolved at 2 weeks of life. Structural congenital anomalies were observed among 10 neonates (none was considered major, eight were considered minor and reported previously, two were considered anomalies but not birth defects[7]): in the low-dose aspirin arm, there were three cases of ventricular septal defect, one case of cleft palate with cleft lip, and one case of fetal hydronephrosis in the right kidney; in the placebo arm, there was a case of ventricular septal defect in conjunction with two other heart defects (atrial septal defect and another heart defect that was unspecified), a case of clubfoot, a case of patent foramen ovale, a case of one functioning kidney, and a case of suspected hypospadias.

DISCUSSION

In a large, randomized, placebo-controlled trial of women with a history of pregnancy loss, low-dose aspirin initiated before conception was associated with a low incidence of harm. Although rare but serious adverse health outcomes resulting from low-dose aspirin cannot be completely ruled out, preconception low-dose aspirin appears to be well tolerated by women trying to conceive, women who become pregnant, and by their fetuses and neonates. Adverse effects in both women and their fetuses or neonates were similar between the low-dose aspirin and placebo treatment arms with the exception of medical record-based reporting of unusual or excessive vaginal bleeding (22% low-dose aspirin, 17% placebo). However, as previously reported, pregnancy loss was similar between treatment arms.[7] In light of our recent findings of higher live birth and lower preterm birth with low-dose aspirin treatment in women with a single recent pregnancy loss, the present findings regarding the safety of low-dose aspirin are reassuring.

Our findings are consistent with pooled analyses of low-dose aspirin use initiated after the first trimester indicating no differences in maternal death, postpartum hemorrhage, maternal blood loss, placental abruption, admission to special care baby units, intracranial or intraventricular hemorrhage, or other neonatal bleeding.[1,2] However, previous low-dose

Table 4. Maternal Health Complications by Treatment Arm: The Effects of Aspirin in Gestation and Reproduction Trial

Maternal Health Complication*	Low-Dose Aspirin (n=615)	Placebo (n=613)	RD	95% CI	*P*
Death	0 (0)	0 (0)	NA	NA	NA
Preterm contractions	29 (5)	36 (6)	−1.2	−3.7 to 1.3	.38
Bleeding					
Vaginal bleeding†	138 (22)	104 (17)	5.5	1.0–9.9	**.02**
Subchorionic hemorrhage	48 (8)	38 (6)	1.6	−1.2 to 4.5	.37
Vaginal‡ bleeding or subchorionic hemorrhage	157 (26)	122 (20)	6.2	1.4–11.0	**.01**
Epistaxis	7 (1)	1 (0)	1.0	0.1–1.9	.07
Emesis	299 (49)	279 (46)	3.1	−2.5 to 8.7	.28
Kidney stones	11 (2)	9 (1)	0.3	−1.1 to 1.7	.82
Premature separation of placenta	7 (1)	5 (1)	0.3	−0.8 to 1.4	.77
Postpartum hemorrhage	4 (1)	4 (1)	0.0	−0.9 to 0.9	1.00

RD, risk difference; CI, confidence interval; NA, not applicable.
Data are n (%) unless otherwise specified.
P value calculated using Fisher exact test.
Bold indicates $P<.05$.
* Health complications were compiled for each participant using information collected from case report forms, interviews conducted during pregnancy and postpartum, and chart abstractions of prenatal visits, ultrasonograms, pregnancy loss, emergency care, and delivery medical records. Adverse events include both self-reported and medically documented conditions.
† Vaginal bleeding included reports of unusual vaginal bleeding when not pregnant, reports of vaginal bleeding after becoming pregnant, and complaints of vaginal bleeding at the time of delivery.
‡ Vaginal bleeding only included reports of vaginal bleeding after becoming pregnant and complaints of vaginal bleeding at the time of delivery. *P* value calculated using χ^2 test. Inverse probability of conception weights was applied to control for selection bias introduced by stratifying on pregnancy status.

aspirin trials in pregnant women have not evaluated vaginal bleeding or subchorionic hemorrhage. We observed conflicting results regarding vaginal bleeding with data from systemic safety interviews showing no difference by treatment arm but medical record-based reports showing higher vaginal bleeding (with or without subchorionic hemorrhage) in the low-dose aspirin arm. One explanation may be more frequent recording in medical records of severe bleeding but less frequent recording of bleeding considered mild by the care provider. If anything, trials of low-dose aspirin in pregnant women report lower risks of health

Table 5. Fetal or Neonatal Health Complications by Treatment Arm and Eligibility Strata Among Women With Clinical Pregnancies (n=728): The Effects of Aspirin in Gestation and Reproduction Trial

Fetal or Neonatal Health Complication	Low-Dose Aspirin (n=372.7)	Placebo (n=358.9)	RD	95% CI	*P*
Fetal death (more than 20 wk of gestation)*	1 (0)	2 (1)	−0.3	−1.2 to 0.7	.57
Neonatal death†	2 (1)	1 (0)	0.3	−0.7 to 1.0	.71
Neonate received specialized care‡	25 (7)	32 (9)	−2.3	−6.3 to 1.8	.25
Intracranial hemorrhage§	0 (0)	0 (0)	NA	NA	NA
Pulmonary hypertension‖	1 (0)	0 (0)	0.3	NA	.32

RD, risk difference; CI, confidence interval; NA, not applicable.
Data are n (%) unless otherwise specified.
P value calculated using χ^2 test. Inverse probability of conception weights was applied to control for selection bias introduced by stratifying on pregnancy status.
* The fetal death in the low-dose aspirin (LDA) group was the result of a cord accident. In the placebo group one fetal death was diagnosed with trisomy 18 and the other cause of fetal death was unknown.
† Neonatal deaths were captured only if the neonate died before hospital discharge or before the mother completed her postpartum interview (approximately 6–8 weeks postpartum). The two neonatal deaths in the LDA group were in severely premature neonates, and the one death in the placebo group was the result of uterine rupture after a motor vehicle accident.
‡ Neonatal care included neonatal intensive care unit, special care unit, intermediate care, or stepdown unit.
§ One fetus in the placebo group was diagnosed with a left cerebral infarction in utero. No information was available regarding whether intracranial hemorrhage preceded the infarction.
‖ Pulmonary hypertension was reported by the mother during the postpartum interview. Delivery record was not available for abstraction for confirmation.

complications, including preeclampsia, preterm birth, intrauterine growth restriction, and perinatal mortality.[1,2] No prior low-dose aspirin trials enrolled women preconceptionally, so our findings regarding nonpregnant low-dose aspirin users are novel.

The potential for low-dose aspirin to harm fetal development was of particular concern in our trial because women received treatment during the first trimester, a time when most malformations occur. Longer term fetal harm resulting from in utero exposure to low-dose aspirin is largely unexplored, but a large randomized trial of 60 mg low-dose aspirin initiated after the first trimester demonstrated that 18-month-old children showed no increased risk of congenital malformations, major motor deficit, or severe neuromotor or developmental delay compared with unexposed children.[13] Likewise, we found a similar number of children with structural congenital malformations in each treatment arm. These findings differ from previous observational studies of aspirin use during the first trimester, which noted increased gastroschisis[14–16]; cryptorchidism[17]; and oral clefts, neural tube defects, microphthalmia, and limb body wall defects,[18] but are similar to other large studies reporting no association with birth defects overall.[19,20] Furthermore, no association between low-dose aspirin and malformations has been reported, possibly because low-dose aspirin is metabolized in maternal hepatic circulation resulting in low fetal exposure.[21] Alternatively, our study and others may be underpowered to detect effects on specific birth defects.

Of note, high doses of cyclooxygenase inhibitors, including aspirin, have been associated with premature closure of the ductus arteriosus, which may lead to persistent pulmonary hypertension.[22–24] Accordingly, our case of pulmonary hypertension in an child exposed to low-dose aspirin raises concern. However, this link, especially regarding low-dose aspirin, remains uncertain because systematic reviews have not noted this association.[1,2]

The major limitation of our study was insufficient sample size to assess rare but potentially serious complications such as specific birth defects, which are individually prevalent in fewer than 10 per 10,000 live births.[25] In addition, our population included healthy, mostly well-educated, non-Hispanic white women of high socioeconomic status with one to two prior pregnancy losses, limiting generalizability to other populations. In addition, our study excluded women with major medical disorders, which might explain the lower risk of certain pregnancy conditions compared with other populations. However, the parent study was a large randomized, double-blind, placebo-controlled trial providing balanced measured and unmeasured baseline characteristics between treatment arms. High-quality data regarding health complications were obtained through both medical records and patient questionnaires, including more than 13,000 safety interviews.

In summary, preconception low-dose aspirin was well tolerated and most self-reported symptoms were similar between treatment arms. Also, no increase in the risk of congenital malformations or other health complications was associated with low-dose aspirin. With such low and varied incidences of maternal and fetal complications to consider, large registries and meta-analyses will be needed to assess the risk of yet unknown rare but serious complications in ongoing clinical-use cohorts and additional studies, respectively. Future analyses should also consider preconception compared with postconception initiation of therapy separately.

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