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Low-Dose Aspirin and Preterm Birth: A Randomized Controlled Trial

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PRECIS

Low-dose aspirin should be investigated as a potential agent to reduce the risk of preterm birth.

Abstract

Objective: To evaluate the association between low-dose aspirin initiated prior to conception and the risk of preterm birth.

Methods: This was a secondary analysis of the Effects of Aspirin in Gestation and Reproduction trial. Women with a history of pregnancy loss (original stratum: one loss < 20 weeks of gestation during the previous year; expanded stratum: one or two losses with no restrictions on timing or gestational age of the losses) were randomized to either daily low-dose aspirin (81 mg, n=615) and folic acid or folic acid alone (placebo; n=613). Preterm birth was compared between groups using intent-to-treat analysis.

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Results: Preterm birth rates were 4.1% (22/535 low-dose aspirin) and 5.7% (31/543 placebo) (RR = 0.72, 95% CI 0.42 to 1.23); spontaneous preterm birth rates were 1.1% (6/535 low-dose aspirin) and 2.2% (12/543 placebo) (RR = 0.51, 95% CI 0.19 to 1.34); medically indicated preterm birth rates were 2.6% (14/535 low-dose aspirin) and 2.9% (16/543 placebo) (RR = 0.89, 95% CI 0.44 to 1.80). After restriction to confirmed pregnancies using inverse probability weighting, preterm birth rates were 5.7% and 9.0% (RR = 0.63, 95% CI 0.37 to 1.09) and spontaneous preterm birth rates were 1.4% and 3.2% (RR = 0.44, 95% CI 0.17 to 1.18). In confirmed pregnancies in the original stratum, preterm birth occurred in 3.8% and 9.7% of the low-dose aspirin and placebo groups, respectively (RR = 0.39, 95% CI 0.16 to 0.94).

Conclusions: Preconception low-dose aspirin was not significantly associated with the overall rate of preterm birth. Although the study was underpowered for this secondary analysis, numeric trends in favor of benefit, particularly in the women with a recent, single early pregnancy loss warrant further investigation.

INTRODUCTION

Preterm birth is a major cause of neonatal morbidity and mortality (1,2) and contributes to numerous chronic medical problems (3,4,5). The estimated cost for neonatal and infant care associated with preterm birth and low birth weight in the United States was estimated to be 26.2 billion dollars in 2005 (6). Despite considerable research and clinical efforts, the rate of preterm birth continued to rise in the United States through 2006, when the overall rate of preterm birth increased to 12.8%, representing a 19% increase since 1990 (7). Since that time, rates have stabilized, slightly decreasing to 11.5% in 2012 (8).

Low-dose aspirin is attractive as a potential prophylactic agent against preterm birth, since it is inexpensive, widely available and has a reasonable safety profile during pregnancy (9,10). It has the potential to reduce medically indicated preterm birth by reducing the risk of preeclampsia, small for gestational age, and placental insufficiency (9) and spontaneous preterm birth by decreasing uterine contractility and inflammation via cyclooxygenase inhibition (11). Low-dose aspirin has not been extensively evaluated with prevention of preterm birth as the primary outcome of interest. Nonetheless, many trials of low-dose aspirin assessed preterm birth as a secondary outcome. In a large systematic review of low dose aspirin initiated during pregnancy, data were available regarding preterm birth from 29 studies including over 30,000 women. These authors noted an 8% reduction in delivery < 37 weeks of gestation in women treated with antiplatelet agents (RR 0.92, 95% CI 0.88–0.97) (9). The reduction may be even greater if treatment is initiated early in pregnancy or preconception as it has been shown that low-dose aspirin started before 16 weeks of gestation was associated with a greater reduction in preterm birth compared with low-dose aspirin started after 16 weeks (RR 0.35, 95% CI 0.22–0.57 compared with 0.90, 95% CI 0.83–0.97) (12). However, these studies did not distinguish between spontaneous and medically indicated preterm birth and it is unclear whether pre-conception treatment with low-dose aspirin further reduces the risk of preterm birth.

We recently completed the Effects of Aspirin in Gestation and Reproduction trial, which compared the association with live birth rates in women with prior pregnancy loss treated

pre-conception with low-dose aspirin and placebo (13). Our objective for this analysis was to evaluate the association between low-dose aspirin initiated prior to conception and the risk of preterm birth.

MATERIALS AND METHODS

The Effects of Aspirin in Gestation and Reproduction trial was a multi-center, block-randomized, double-blinded, placebo-controlled trial of 1,228 women in the U.S. (2007–2011). The trial was funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (US National Institutes of Health). 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. The trial was registered with www.clinicaltrials.gov, number NCT00467363. Details of study design, methods, participant characteristics, and primary findings have been described (14). Briefly, women 18 to 40 years old with a history of 1 – 2 pregnancy losses who were trying to conceive were eligible for the study. The primary outcome was live birth (13) and a planned secondary outcome was preterm birth. Based on reproductive history noted at baseline, participants were stratified into two groups: 1) original: women with exactly 1 documented pregnancy loss at <20 weeks of gestation during the past 12 months; 2) expanded: women with 1 or 2 prior pregnancy losses, regardless of gestational length of or time since the loss occurred. Participants were block-randomized by study center and stratum to receive either the intervention (81 mg low-dose aspirin daily plus 400 mcg of folic acid) (n=615) or an identical looking placebo containing only 400 mcg of folic acid (n=613). Participants were followed for up to 6 menstrual cycles or through gestation if they became pregnant.

Reproductive, medical and obstetric history was obtained at baseline via questionnaire and from medical record abstraction. A positive pregnancy test was defined as a positive clinic urine pregnancy test (> 20 IU/L of human chorionic gonadotropin), and a clinically confirmed pregnancy was defined as evidence of an intrauterine pregnancy on ultrasound. Gestational age was determined by an ultrasonogram conducted in early pregnancy (mean 6.9 weeks of gestation; SD 1.1) for 97% (697/720) of clinically confirmed pregnancies among women who completed the trial; for the remaining 3% (23/720) pregnancies, gestational age was determined using menstrual cycle dating from home-based fertility monitors provided by the study. Pregnancy outcomes, including delivery date, were assessed by post-partum phone interview and through medical record review by trained Effects of Aspirin in Gestation and Reproduction trial research staff.

Preterm birth was defined as delivery between 20 weeks and zero days and 36 weeks and six days' gestation. Cases of preterm birth were prospectively identified during the study and had further review of abstracted records by a Maternal Fetal Medicine (MFM) physician to vet and categorize the outcome as spontaneous, medically indicated, or an unknown or elective preterm birth. Spontaneous preterm birth was any preterm birth preceded by spontaneous labor (cervical change or ≥ 4 cm cervical dilation in the presence of contractions), preterm premature rupture of membranes, or both. Medically indicated preterm birth was any preterm birth not classified as spontaneous preterm birth for which at

least one medical indication for delivery was noted in the medical record. The remaining preterm births were categorized as an unknown or elective preterm birth.

Information on preeclampsia/gestational hypertension (18), birthweight, mode of delivery (vaginal vs. cesarean), multifetal gestation, Apgar score (1 and 5 minutes), neonatal sex, and any events of neonatal death were abstracted from delivery records by Effects of Aspirin in Gestation and Reproduction trial research staff. Fetal growth restriction was defined as birth weight less than 10% for gestational age (15). Stillbirth was defined as death of the fetus at 20 weeks of gestation.

Statistical analysis

Demographic and baseline characteristics were compared by treatment arm using *t*-tests and Fisher's exact tests, where appropriate. Risk ratios, risk differences and 95% confidence intervals (CI) for preterm birth, spontaneous preterm birth, and medically indicated preterm birth for low-dose aspirin compared with placebo were estimated using binomial regression and these analyses were restricted to women with complete follow-up. In order to evaluate low-dose aspirin effects within stratum (original or expanded, based on eligibility criteria described above), a stratified analysis for all trial outcomes was also performed. All analyses used the intent-to-treat approach. Additional exploratory analyses were performed to evaluate the effect of low-dose aspirin compared with placebo among women with and without a history of preterm birth.

Because pregnancy outcomes are conditional upon becoming pregnant and factors that affect conception may also affect adverse pregnancy outcomes, we also repeated the analysis using data restricted to clinically confirmed pregnancies, as well as restricted to only pregnancies reaching at least 20 weeks of gestation. In order to correctly estimate the effect of low-dose aspirin compared with placebo on preterm birth in these pregnancies, inverse probability weights were used to control for potential selection bias introduced by restricting the analytical cohort post-randomization. Inverse probability weighting is a technique to remove bias through reweighting the observations. Weights were constructed based on factors associated with becoming pregnant such as maternal age (< 35 vs. ≥ 35 years old), race (white, non-white), parity (nulliparous, multiparous), marital status (married, not-married), and history of preterm birth (yes, no).

As a sensitivity analysis we also evaluated the potential impact of early withdrawal from the trial on preterm birth. We compared results from scenarios where we assumed the same proportion of preterm births occurred among the withdrawals as we observed among the women who completed the study, as well as scenarios where we assumed different proportions of preterm births by treatment arm for women who withdrew.

RESULTS

Participant characteristics were similar between those randomized to low-dose aspirin compared with placebo (Table 1). Most participants were white and had experienced a pregnancy loss within the past 8 months. As previously reported (13), 88% (n=1078) of randomized participants completed the study (Figure 1(13)), of which 757 had a positive

pregnancy test, 720 had clinically confirmed pregnancies, and 595 had live births. Characteristics also were similar between groups in the subset of women with clinically confirmed pregnancies (data not shown). There were 53 preterm births, resulting in an overall occurrence of preterm birth of 4.9% (7.4% among women who had clinically confirmed pregnancies). Of the preterm births, 18 (34.0%) were classified as spontaneous, 30 (56.6%) as medically indicated, and 5 (9.4%) as elective/unknown (Table 2).

In the intent-to-treat analysis of the 1078 women who completed the trial (Table 3), 4.1% (22/535) of women treated with low-dose aspirin and 5.7% (31/543) treated with placebo had preterm birth (RR=0.72, 95% confidence interval [CI] 0.42, 1.23). The occurrence of spontaneous preterm birth was 1.1% (6/535) in women treated with low-dose aspirin compared to 2.2% (12/543) in the placebo group (RR=0.51, 95% CI 0.19, 1.34). Though the occurrence of preterm birth tended to be lower in the low-dose aspirin group, both overall and within eligibility strata, none of the comparisons were statistically significant. A similar proportion of women in both groups had medically indicated preterm births as well as preeclampsia/gestational hypertension (GHTN).

Among clinically confirmed pregnancies, the RRs for any preterm birth, spontaneous preterm birth, and medically indicated preterm births were 0.63, 0.44, and 0.76, respectively, though no comparisons were statistically significant (Table 3). However, we noted a significant reduction in preterm birth among women treated with low-dose aspirin in the original stratum (RR 0.39, 95% CI 0.16, 0.94), primarily due to a reduction in spontaneous preterm births in this group. Similar results were noted in analyses limited to pregnancies reaching 20 weeks of gestation (Table 3).

Risk differences between low-dose aspirin and placebo arms among clinically confirmed pregnancies, overall and by eligibility stratum, are presented in Figure 2. Similar to the RR analysis, findings were statistically significant for preterm birth among the original eligibility stratum only (risk difference of -0.059 [95% CI -0.113, -0.005]).

Among women with a history of preterm birth (n=73), the occurrence of preterm birth in the index pregnancy was 14.3% (5/35) and 18.4% (7/38) in the low-dose aspirin and placebo groups, respectively (RR=0.78, 0.27–2.22). Among women without a history of preterm birth (n=1005) the occurrence of preterm birth was 3.4% (17/500) and 4.8% (24/505) in the low-dose aspirin and placebo arms, respectively (RR=0.72, 0.38–1.32). Sensitivity analysis was performed comparing possible study results based on assuming various pregnancy outcomes for the 150 women who withdrew from the study (80 in the low-dose aspirin arm, 70 in the placebo arm). Under reasonable assumptions (< 30%) for the risk of preterm birth for the women that withdrew, we observed similar effects of low-dose aspirin on preterm birth as in our primary analyses.

DISCUSSION

This secondary analysis of the EAGeR study of preconception aspirin to reduce the risk of pregnancy loss, suggests that a randomized clinical trial powered to address the rates of preterm birth in women treated with preconception low dose aspirin or not would be of

value. While this secondary analysis is underpowered to answer this question, the results suggest that there may be a benefit of preconception low dose aspirin to decrease the rate of preterm birth

Preconception treatment with low-dose aspirin did not significantly reduce the risk of preterm birth overall in our study. However, there was a non-significant reduction in the risk of preterm birth among women taking low-dose aspirin preconception. Moreover, there was a significant reduction in preterm birth among clinically confirmed pregnancies in women with only one early pregnancy loss within a year of enrollment. No definitive conclusions can be made from these data given the lack of statistical significance in the overall cohort and given that preterm birth was a secondary outcome resulting in small numbers of preterm births in the trial overall. Accordingly, low-dose aspirin cannot be recommended in general for the prevention of preterm birth at this time. Nonetheless, these data are exciting and suggest that preconception low-dose aspirin treatment may have a favorable association with preterm birth in certain women and justify further research regarding preconception low-dose aspirin and preterm birth.

These data are consistent with observations from previous studies using low-dose aspirin in pregnancy. The vast majority of studies initiated treatment with aspirin after conception, however, often in the second trimester. Also, no study, including the current study, assessed preterm birth as a primary outcome, and most others targeted preeclampsia and / or fetal growth restriction. Even so, available data regarding preterm birth from over 30,000 women noted a RR for preterm of 0.92 (95% CI 0.88 – 0.97).⁹ Unfortunately, studies did not distinguish between spontaneous and medically indicated preterm births, which may be important given that our data indicate a protective association between low-dose aspirin may be more likely for spontaneous, but not medically indicated, preterm births.

Indeed, the association noted in our study was almost entirely due to a decrease in spontaneous preterm birth among low-dose aspirin– treated pregnancies in the original stratum. As expected, the majority of preterm births occurred after 34 weeks of gestation. However, the association with decreased preterm birth also was present prior to 34 weeks of gestation (data not shown). Furthermore, the magnitude of the association with preterm birth was clinically important. It is uncertain whether the association is due to an increased benefit from treatment initiated prior to conception and / or very early in pregnancy.

In contrast, there was no trend towards a decrease in medically indicated preterm births. Moreover, aspirin was not associated with preeclampsia / GHTN, the most common reason identified for medically indicated preterm delivery. This is divergent to most but not all other studies (9). It is unclear whether the lack of benefit with regard to preeclampsia prophylaxis was due to insufficient power or due to the use of preconception treatment. It is also unclear why the association was more pronounced in women with only one early recent pregnancy loss (the only group in which the reduction in preterm birth was statistically significant). Interestingly, in our previous report of this trial, low-dose aspirin had a more favorable association in this subset of women also with regard to live births, likely due to an effect on fecundity rather than prevention of pregnancy loss (13). Women in the expanded strata often had recurrent pregnancy loss, perhaps comprising a different population.

There is strong biological plausibility that aspirin may decrease the risk for preterm birth. Cyclooxygenase inhibition can decrease prostaglandin formation, which is known to play a role in normal and abnormal labor (16). Also, numerous other inflammatory mediators that contribute to preterm labor may be inhibited by aspirin (16). Indeed, cyclooxygenase inhibitors are used as tocolytics (11) and regular dose aspirin is associated with a delay in the onset of labor (17). Low-dose aspirin also has the potential to decrease the risk for medically indicated preterm births by lowering the chances of developing preeclampsia or fetal growth restriction, though the present data do not lend support to this mechanism (9).

The Effects of Aspirin in Gestation and Reproduction trial was not powered to assess the association of aspirin with subtypes of preterm birth (medically indicated or spontaneous), as this was not the main outcome of the study. Accordingly, our findings may have been due to chance. Also, the rates of preterm birth were relatively low compared to the United States overall. The rigors of our study likely biased participants towards high education and socioeconomic status, reducing the risk of preterm birth. We estimate that approximately 3,000 women with singleton pregnancies would need to be enrolled per treatment arm to have adequate power (80%) to detect a 1.6% absolute risk difference in preterm birth, assuming the rates of preterm birth we observed in low-dose aspirin vs. placebo. Furthermore, this study included only women with 1 or 2 prior pregnancy losses, and their age was relatively high, further limiting the generalizability of the current data.

This study also had numerous strengths. In particular, we utilized a block-randomized, placebo controlled, double blind trial with excellent compliance representing over 1078 women and 720 clinically confirmed pregnancies. All participants had rigorous gestational dating criteria and all preterm births and other adverse obstetric outcomes were vetted by medical chart review by Maternal Fetal Medicine physicians. Also, data were analyzed not only by intent-to-treat analysis, but also using appropriate weighting techniques for post-randomization evaluation of only the women becoming pregnant, and all analyses were stratified by spontaneous and medically indicated preterm birth. Finally, this is one of the only trials to assess preterm birth in women treated with low-dose aspirin prior to conception.

In summary, preconception treatment with low-dose aspirin did not significantly reduce the rate of preterm birth in the overall cohort. However, there was a suggestion of a reduction in spontaneous preterm birth and a reduction in preterm birth in women with a single early pregnancy loss within a year prior to enrollment. Although cyclooxygenase inhibitors have the potential to cause fetal harm, adverse maternal and fetal events are quite rare when low doses are taken (9,18). Even a small reduction in preterm birth would have tremendous medical, social and financial benefits given the wide availability, low cost, relative safety, stability, and ease of administration of low-dose aspirin. Needless to say, low-dose aspirin treatment is an extremely attractive potential prophylactic agent for preterm birth, especially in low resource settings, that deserves further attention. We cannot recommend wide use of low-dose aspirin for the prevention of preterm birth based on our study. However, these data justify appropriately designed clinical trials to assess the potential benefits of low-dose aspirin on preterm birth.

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REFERENCES

1. Mathews TJ, Menacker F, MacDorman MF. Infant mortality statistics from the 2002 period: linked birth/infant death data set. *Natl Vital Stat Rep* 2004;53:10:1–29.
2. Anderson RN, Smith BL. Deaths: leading causes for 2001. Deaths and percentage of total deaths for the 10 leading causes of neonatal and postnatal deaths: United States 2001. *Natl Vital Stat Rep* 2003;52:L1–85.
3. Goldenberg RL, Rouse DJ. Prevention of premature birth. *N Engl J Med* 1998;339:313–320. [PubMed: 9682045]
4. McCormick MC, Richardson DK. Premature infants grow up. *N Engl J Med* 2002;346:197–8. [PubMed: 11796855]
5. Saigal S, Doyle LW. Preterm birth 3. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 2008;371:261–9. [PubMed: 18207020]
6. Behrman RE, Butler AS, Eds. Committee on Understanding Premature Birth and Assuring Healthy Outcomes. *Preterm Birth: causes, Consequences, and Prevention* National Academies Press, Washington, DC, 2007.
7. Martin JA, Hamilton BE, Martin JA, Sutton PD, Ventura SJ, Menacker F, Kimeyer S, Mathews TJ. Births: Final data for 2006. *National Vital Statistics Report NVSS* 2009;57:1–104.
8. Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2012. *Natl Vital Stat Rep* 2013;62(3):1–20.
9. Duley L, Henderson-Smith DJ, Meher S, King JF. Antiplatelet agents for preventing preeclampsia and its complications (review). *The Cochrane Collaboration The Cochrane Library* 2010, Issue 10.
10. Marret S, Marchand L, Kaminski M, et al. Prenatal low-dose aspirin and neurobehavioral outcomes of children born very preterm. *Pediatrics* 2010;125:e29–34. [PubMed: 20026499]
11. Abramovici A, Cantu J, Jenkins SM. Tocolytic therapy for acute preterm labor. *Obstet Gynecology Clin North Am* 2012;39:77–87.
12. Roberage S, Nicolaides KH, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. *Ultrasound Obstet Gynecol* 2013;41(5):491–9. [PubMed: 23362106]
13. Schisterman EF, Silver RM, Leshner L et al. Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomized trial. *Lancet* 2014; 10.1016/S0140-6736(14)60167.
14. Schisterman EF, Silver RM, Perkins NJ, et al. A randomized trial to evaluate the Effects of low dose Aspirin in Gestation and Reproduction (EAGeR): Design and baseline characteristics. *Paediatric and Perinat Epidemiol*, 2013 27:598–609.
15. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol* 1996;87:163–8. [PubMed: 8559516]
16. MacIntyre DA, Sykes L, Teoh TG, Bennett PR. Prevention of preterm labor via the modulation of inflammatory pathways. *J Mat Fetal Neonatal Med* 2012;25 Suppl 1:17–20.
17. Lewis RB, Schulman JD. Influence of acetylsalicylic acid, an inhibitor of prostaglandin synthesis on the duration of human gestation and labour. *Lancet* 1973;2(7839):1159–61. [PubMed: 4127544]
18. Task force on hypertension in pregnancy. Hypertension in pregnancy. *Obstet Gynecol* 2013;122:1122–31. [PubMed: 24150027]

Figure 1:
Participant flow for the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial.
*Confirmed pregnancy totals from raw data.

Figure 2:

Absolute difference in risk (with 95% confident intervals) of preterm birth by treatment arm and original versus expanded eligibility criteria among clinically confirmed pregnancies: the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial. Inverse probability weights were used to account for different rates of conception by intervention arm and analyses were then restricted to confirmed pregnancies.

Table 1.

Demographics and baseline characteristics by treatment arm

Characteristics ^a	Low-Dose Aspirin	Placebo	
N (%)	N=615	N=613	P
Age, y: Mean $\pm$ SD	28.8 $\pm$ 4.9	28.7 $\pm$ 4.7	0.68
Race			
White	576 (93.7)	586 (95.6)	0.16
Non-White	39 (6.3)	27 (4.4)	
BMI, kg/m ² , Mean $\pm$ SD	26.3 $\pm$ 6.8	26.5 $\pm$ 6.4	0.68
> High School Education	526 (85.7)	531 (86.6)	0.68
Employed	451 (76.1)	444 (75.1)	0.74
Time from last loss to randomization (months)			
0 to 4 Months	331 (54.9)	320 (52.2)	0.71
4 to 8 Months	103 (17.1)	119 (19.7)	
8 to 12 Months	50 (8.3)	49 (8.1)	
>12 Months	119 (19.7)	118 (19.5)	
Number of previous pregnancies resulting in live birth			
0	283 (46.0)	288 (47.0)	0.84
1	221 (35.9)	222 (36.2)	
2	111 (18.0)	103 (16.8)	
Number of previous pregnancy losses			
1	422 (68.6)	403 (65.7)	0.30
2	193 (31.4)	210 (34.3)	
Smoking in past year			
Never	529 (87.0)	538 (88.3)	0.22
6 times/week	41 (6.7)	46 (7.6)	
Daily	38 (6.3)	25 (4.1)	
Pregnancy history			
Preterm birth ^b	40 (6.5)	41 (6.7)	0.91
Preeclampsia ^b	33 (5.4)	22 (3.6)	0.17
Ectopic ^b	11(1.8)	10 (1.6)	1.00
Stillbirth ^b	36 (5.9)	27 (4.4)	0.30
Multiples ^b	18 (2.9)	23 (3.8)	0.43
Elective abortions ^b	15 (2.4)	22 (3.6)	0.25
Therapeutic abortion ^b	26 (4.2)	16 (2.6)	0.16
Gestational diabetes ^c	4 (0.7)	5 (0.8)	0.75
Small for gestational age fetus ^c	8 (1.3)	5 (0.8)	0.58

Characteristics ^a N (%)	Low-Dose Aspirin N=615	Placebo N=613	P
Birth defect ^{cd}	13 (2.1)	9 (1.5)	0.52
Neonatal/infant death ^c	8 (1.3)	6 (1.0)	0.79

P-values were calculated using *t*-tests for continuous variables and Fisher's exact tests for categorical variables.

^aInformation on characteristics was missing for body mass index (n=20), education (n=1), time from last loss to randomization (n=19), smoking (n=11) and employment (n=44). Percent was calculated from non-missing data.

^bInformation derived from history reported on health and reproduction baseline questionnaire or from medical chart review of pregnancy history.

^cInformation derived from history reported on health and reproduction baseline questionnaire only.

^dBirth defects include structural defects and chromosomal abnormalities.

Table 2.

Pregnancies resulting in preterm birth by treatment arm

Characteristics N (%)	Total N=53 ^a	Low-Dose Aspirin N=22	Placebo N=31
Gestational age, weeks: Median (min, max)	35.6 (21.6, 36.9)	35.9 (21.6, 36.7)	35.3 (31.1, 36.9)
Gestational age category			
20–31 weeks	5 (9.4)	3 (13.6)	2 (6.5)
32–34 weeks	12 (22.6)	3 (13.6)	9 (29.0)
35–36 weeks	36 (67.9)	16 (72.7)	20 (64.5)
Preterm birth category			
Spontaneous	18 (34.0)	6 (27.3)	12 (38.7)
Medically indicated	30 (56.6)	14 (63.6)	16 (51.2)
Elective/unknown	5 (9.4)	2 (9.1)	3 (9.7)
Preeclampsia/hypertension	12 (23.1)	5 (22.7)	7 (23.3)
Preeclampsia/hypertension severity			
Chronic hypertension	1 (1.9)	0 (0)	1 (3.3)
Gestational hypertension	1 (1.9)	0 (0)	1 (3.3)
Mild preeclampsia	5 (9.6)	3 (13.6)	2 (6.7)
Severe preeclampsia	5 (9.6)	2 (9.1)	3 (10.0)
Birthweight, g: Mean $\pm$ SD	2514 $\pm$ 669	2437 $\pm$ 808	2570 $\pm$ 554
Intrauterine growth restriction	2 (4.0)	1 (5.0)	1 (3.3)
Gestational diabetes	6 (11.8)	2 (10.0)	4 (12.9)
Mode of delivery			
Vaginal	34 (64.2)	13 (59.1)	21 (67.7)
Cesarean	19 (35.9)	9 (40.9)	10 (32.3)
Apgar score, 1 min: Median (min, max)	8 (0, 9)	8 (1, 9)	8 (0, 9)
Apgar score, 5 min: Median (min, max)	9 (0, 10)	9 (1, 9)	9 (0, 10)
Multifetal gestation ^b	2 (3.8)	0 (0)	2 (6.5)
Sex of fetus			
Male	23 (43.4)	11 (50.0)	12 (38.7)
Female	28 (52.8)	11 (50.0)	17 (54.8)
Female-Female (twin)	1 (1.9)	0 (0)	1 (3.2)
Male-Female (twin)	1 (1.9)	0 (0)	1 (3.2)
Neonatal death	3 (5.7)	2 (9.1)	1 (3.2)

Percent was calculated from non-missing data.

^aInformation was missing for preeclampsia/gestational hypertension (n=1), birthweight (n=1), intrauterine growth restriction (n=3), gestational diabetes (n=2), and Apgar scores (n=1).

^bTwo twin pregnancies were among the preterm births. For both, average birthweight and Apgar scores were calculated.

Table 3.
Maternal Complications by Treatment Arm and Original and Expanded Eligibility Criteria

Type of Analysis	Outcomes: N (%)	Overall				Original				Expanded				
		Total	LDA	Placebo	RR	95% CI	LDA	Placebo	RR	95% CI	LDA	Placebo	RR	95% CI
All women		N=1078	N=535	N=543			N=242	N=250			N=293	N=293		
	Preterm birth	53 (4.9)	22 (4.1)	31 (5.7)	0.72	0.42, 1.23	7 (2.9)	16 (6.4)	0.45	0.19, 1.08	15 (5.1)	15 (5.1)	1.00	0.50, 2.00
	Spontaneous preterm birth	18 (1.7)	6 (1.1)	12 (2.2)	0.51	0.19, 1.34	2 (0.8)	6 (2.4)	0.34	0.07, 1.69	4 (1.4)	6 (2.0)	0.67	0.19, 2.34
	Medically indicated preterm birth	30 (2.8)	14 (2.6)	16 (2.9)	0.89	0.44, 1.80	5 (2.1)	8 (3.2)	0.65	0.21, 1.95	9 (3.1)	8 (2.7)	1.13	0.44, 2.88
	Preeclampsia/GHTN	48 (4.4)	23 (4.3)	25 (4.6)	0.93	0.54, 1.62	12 (5.0)	17 (6.8)	0.73	0.36, 1.49	11 (3.8)	8 (2.7)	1.38	0.56, 3.37
	Late fetal death, stillbirth, or preterm birth	60 (5.6)	25 (4.7)	35 (6.4)	0.73	0.44, 1.19	8 (3.3)	19 (7.6)	0.44	0.19, 0.97	17 (5.8)	16 (5.5)	1.06	0.55, 2.06
Confirmed Pregnancies ^a		N=721	N=372	N=349			N=180	N=161			N=194	N=187		
	Preterm birth	52 (7.3)	21 (5.7)	31 (9.0)	0.63	0.37, 1.09	7 (3.8)	16 (9.7)	0.39	0.16, 0.94	15 (7.7)	15 (8.0)	0.97	0.48, 1.95
	Spontaneous preterm birth	16 (2.3)	5 (1.4)	11 (3.2)	0.44	0.17, 1.18	2 (0.9)	6 (3.5)	0.27	0.05, 1.34	4 (1.8)	6 (2.9)	0.62	0.18, 2.18
	Medically indicated preterm birth	31 (4.4)	14 (3.8)	17 (5.0)	0.76	0.37, 1.55	5 (2.9)	8 (5.0)	0.58	0.19, 1.74	9 (4.9)	9 (4.7)	1.05	0.40, 2.73
	Preeclampsia/GHTN	48 (6.6)	22 (6.0)	25 (7.2)	0.83	0.48, 1.44	11 (6.3)	17(10.4)	0.60	0.29, 1.23	11 (5.7)	8 (4.3)	1.34	0.55, 3.26
	Late fetal death, stillbirth, or preterm birth	59.4(8.2)	24.2(6.5)	35.2(10.1)	0.64	0.39, 1.06	7.8 (4.4)	18.6(11.6)	0.38	0.17, 0.85	17.0 (8.8)	15.9 (8.5)	1.03	0.53, 2.02
Pregnancies >20 weeks ^b		N=600	N=308	N=292			N=152	N=137			N=159	N=153		
	Preterm birth	53 (8.8)	21 (6.9)	31(10.8)	0.64	0.37, 1.10	7 (4.7)	16(11.4)	0.41	0.17, 1.00	16 (9.8)	15 (9.8)	1.00	0.49, 2.06
	Spontaneous preterm birth	16 (2.6)	5 (1.6)	11 (3.7)	0.43	0.16, 1.14	2 (1.1)	6 (4.1)	0.26	0.05, 1.31	3 (2.0)	5 (3.5)	0.58	0.16, 2.05
	Medically indicated preterm birth	32 (5.4)	14 (4.7)	18 (6.1)	0.76	0.37, 1.57	6 (3.7)	8 (5.9)	0.62	0.20, 1.90	10 (6.5)	9 (5.9)	1.10	0.41, 2.95
	Preeclampsia/GHTN	49 (8.1)	23 (7.5)	26 (8.8)	0.85	0.49, 1.47	12 (7.6)	17 (12.3)	0.62	0.30, 1.27	12 (7.4)	8 (5.4)	1.38	0.57, 3.37

Abbreviations: RR, risk ratio; CI, confidence interval

Bolded risk ratios indicated statistically significant results at alpha= 0.05.

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Inverse probability weights were used to account for different rates of confirmed pregnancies by intervention arm; weighting resulted in a slight difference in the number of events compared with the observed data. Totals do not always equal the sum of intervention and eligibility groups due to rounding. Clinically confirmed pregnancies were defined as evidence of an intrauterine pregnancy on sonogram.

q_i Inverse probability weights were used to account for different rates of pregnancies lasting longer than 20 weeks by intervention arm; weighting resulted in slight difference in the number of events compared with the observed data. Totals do not always equal the sum of intervention and eligibility groups due to rounding.