Annals of Internal Medicine ORIGINAL RESEARCH

The Effect of Preconception-Initiated Low-Dose Aspirin on Human Chorionic Gonadotropin–Detected Pregnancy, Pregnancy Loss, and Live Birth

Per Protocol Analysis of a Randomized Trial

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Background: A previous large randomized trial indicated that preconception-initiated low-dose aspirin (LDA) therapy did not have a positive effect on pregnancy outcomes. However, this trial was subject to nonadherence, which was not taken into account by the intention-to-treat approach.

Objective: To estimate per protocol effects of preconception-initiated LDA on pregnancy loss and live birth.

Design: The EAGeR (Effects of Aspirin on Gestation and Reproduction) trial was used to construct a prospective cohort for a post hoc analysis. (ClinicalTrials.gov: NCT00467363)

Setting: 4 university medical centers in the United States.

Participants: 1227 women between the ages of 18 and 40 years who had 1 or 2 previous pregnancy losses and were attempting pregnancy.

Measurements: Adherence to LDA or placebo, assessed by measuring pill bottle weights at regular intervals during follow-up. Primary outcomes were human chorionic gonadotropin (hCG)-detected pregnancies, pregnancy losses, and live births, determined by pregnancy tests and medical records.

Results: Relative to placebo, adhering to LDA for 5 of 7 days per week led to 8 more hCG-detected pregnancies (95% CI, 4.64 to 10.96 pregnancies), 15 more live births (CI, 7.65 to 21.15 births), and 6 fewer pregnancy losses (CI, −12.00 to −0.20 losses) for every 100 women in the trial. In addition, compared with placebo, postconception initiation of LDA therapy led to a reduction in the estimated effects. Furthermore, effects were obtained in a minimum of 4 of 7 days per week.

Limitation: The EAGeR trial data for this study were analyzed as observational data, thus are subject to the limitations of prospective observational studies.

Conclusion: Per protocol results suggest that preconception use of LDA at least 4 days per week may improve reproductive outcomes for women who have had 1 or 2 pregnancy losses. Increasing adherence to daily LDA seems to be key to improving effectiveness.

Primary Funding Source: National Institutes of Health.

Ann Intern Med. doi:10.7326/M20-0469 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 26 January 2021.

Aspirin is a widely available nonsteroidal anti-inflammatory drug with beneficial hemodynamic and immunomodulatory effects (1, 2). Accordingly, low-dose aspirin (LDA) is used in perinatal medicine to prevent preeclampsia in at-risk women (3) and pregnancy loss in women with antiphospholipid syndrome (4). However, in previous trials examining pregnancy outcomes, aspirin therapy was initiated after the 12th week of gestation, leaving unstudied the potential effects on the most common reproductive complications of subfertility and early pregnancy loss (5). The EAGeR (Effects of Aspirin in Gestation and Reproduction) trial was designed to fill this gap by examining the effects of preconception-initiated LDA treatment on pregnancy loss and live birth in 1227 women trying to become pregnant after 1 or 2 pregnancy losses (6).

EAGeR's primary intention-to-treat (ITT) results demonstrated a 10% increase in live births in the LDA group relative to placebo, but without the precision to warrant changes to clinical recommendations (95% CI, 0.98 to 1.22) (7). Furthermore, no impact was observed on pregnancy loss (13% in the LDA group vs. 12% in the placebo group) (7). Of interest, secondary analyses indicated that aspirin may confer some benefits, including a higher incidence of both human chorionic gonadotropin (hCG)-detected and ultrasonography-confirmed pregnancies (7), a shorter time to pregnancy among women with a single recent pregnancy loss (8), and an increase in pregnancies and live births among women with chronic inflammation (9). However, these earlier findings were subject to complications often affecting ITT analyses, most notably nonadherence to assigned treatment, which may be influenced by common pregnancy symptoms that are also potential side effects of the treatment, such as nausea and bleeding (10).

Our objective was to estimate the per protocol effects of LDA on hCG-detected pregnancy, live birth, and pregnancy loss in the EAGeR trial. We also examined the optimal timing of LDA initiation (either before conception or after recognition of pregnancy), and the variation in effects by the average number of days per week LDA was used. For the EAGeR study protocol, see **Supplement 1** (available at Annals.org).

See also:

Summary for Patients

Web-Only
Supplement

METHODS

Population

We conducted a post hoc per protocol analysis of data from the EAGeR study (2007 to 2011), a multicenter, block-randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov: NCT00467363) at 4 university medical centers in the United States (6, 7). In brief, eligible women were between 18 and 40 years of age, were actively trying to conceive, had a history of 1 or 2 documented pregnancy losses, had regular menstrual cycles of 21 to 42 days during the preceding 12 months, and had no history of infertility. Participants were followed for up to 6 cycles while attempting pregnancy, and throughout pregnancy if they conceived (total follow-up ranged from 1 to 60 weeks; median, 37 weeks). All participants provided written informed consent. The data coordinating center at each site obtained institutional review board approvals; a data safety and monitoring board ensured participant safety.

Intervention

Women were randomized 1:1 to receive aspirin, 81 mg, or placebo; all received 400 mcg of folic acid. All participants and care providers were blinded to treatment allocation. Women were instructed to take the study medication daily throughout 6 menstrual cycles, and until the 36th week of gestation if they conceived.

Covariate Data

Demographic and lifestyle information was assessed via baseline questionnaires. Bleeding and nausea or vomiting were assessed prospectively during follow-up, measured via daily diaries for the first 2 months, and by clinical questionnaires roughly once a month for the remaining follow-up. In any given week of follow-up, bleeding was defined as present if the woman had any unusual or excessive bleeding, including vaginal or other bleeding, during that week. Likewise, in any given week, nausea or vomiting was defined as present if the woman had any nausea or vomiting during that week.

Outcome

The primary outcome of interest was live birth. Secondary outcomes included hCG-detected pregnancy and pregnancy loss. Pregnancy was identified by a positive result on a "real-time" urine pregnancy test (Quickvue [Quidel]) sensitive to 25 mIU/mL hCG, conducted at home or any study visit during expected menses, and by batched urine hCG testing performed after study completion on stored samples from the last 10 days of each woman's first and second cycle (n = 21 additional pregnancies detected) (11). Pregnancy loss was defined as a positive result on urine hCG pregnancy testing at home or the clinical site, followed by absence of signs of clinical pregnancy on study ultrasonography; hCG positivity on batched augmented urine testing, followed by negative results on pregnancy testing at home or in the clinic (11); or loss after ultrasonographic confirmation. Live birth was defined as a live-born infant, as indicated on the medical record.

Adherence

Daily adherence in both the LDA and placebo groups was assessed by measuring bottle weights at regular intervals during follow-up. The median number of days between bottle weight measurements was 27 (interquartile range, 15 to 32 days). Because some biological effect may be achieved with less than daily adherence (12), daily adherence measures were averaged over a running 7-day period, yielding the proportion of each week in which either treatment or placebo was taken. A participant was deemed "adherent" if she took the assigned treatment (either LDA or placebo) for at least 5 of the 7 days.

Statistical Analyses

Descriptive Analyses

With adherence defined as use of LDA or placebo on at least 5 of 7 consecutive days, changes were evaluated visually with a locally weighted scatter plot smoother. Baseline characteristics were compared between participants defined as adherent for 70% or more of their person-time versus those adherent for less than 70% of their person-time.

Per Protocol Analysis

We used g-computation (also known as the parametric g-formula) (13) to quantify the effects of aspirin under ideal conditions in which all participants adhere to the protocols we define later. This approach is a generalization of standardization that can adjust for both baseline and time-varying confounders, and is useful when there are time-varying factors (such as bleeding or nausea) that may be linked to past and future adherence and may be associated with outcomes of interest (14, 15). We specified a causal diagram depicting the assumed causal relations among the outcomes, the time-varying confounders, and adherence to the defined protocol (Figure 1 of Supplement 2, available at Annals.org). On the basis of this causal diagram, we modeled each causal relation via generalized linear models (GLMs) in the sample of 1227 women with a total of 42 697 person-weeks. A total of 8 GLMs were fit to the data, representing models for live birth, pregnancy loss, withdrawal, no pregnancy, hCG-detected pregnancy, adherence, bleeding, and nausea or vomiting. All models were stratified by the randomized treatment indicator. Estimates of the per protocol effects were obtained from a Monte Carlo resample of M = 10 000 of all baseline data, as well as time-varying data at the first week on study. Using the 8 GLMs fit to the original data and the Monte Carlo resample, we generated outcomes over all 60 weeks of follow-up that would be observed under the desired protocols and computed the probability of hCG-detected pregnancy, pregnancy loss, and live birth from the follow-up generated with the Monte Carlo resample under the desired protocol. Full details are provided in Supplement 2.

Using g-computation, we estimated the per protocol effects on hCG-detected pregnancy, live birth, and pregnancy loss of preconception-initiated LDA taken 5 of 7 days per week. Optimal timing of aspirin initiation was explored by estimating the effects of starting treatment on the 6th, 8th, 12th, or 20th week after pregnancy is recognized. We further estimated per protocol effects if adherence was defined as taking the assigned treatment 2, 3, 4, and 6 of 7 days per week.

We computed the probability of hCG-detected pregnancy, pregnancy loss, and live birth under several scenarios:

Scenario 1: All women were assigned and adhered to placebo from the preconception period through gestation week 36 (the referent protocol).

Scenario 2: All women were assigned and adhered to aspirin therapy from the preconception period through gestation week 36.

Scenarios 3 to 6: All women were assigned and adhered to placebo before pregnancy detection, then switched and adhered to aspirin beginning at week 6, 8, 12, or 20 after pregnancy detection and continued through gestation week 36.

Comparing the outcomes from scenarios 1 (adherence to placebo) and 2 (adherence to aspirin) yields an estimate of the per protocol effect of aspirin. Comparing the outcomes from scenario 2 with those of scenarios 3 to 6 yields an estimate of the effect of aspirin if therapy was initiated only after postconception week 6, 8, 12, or 20. Data from all 1227 participants were used to compute these effects. We quantified all effects on the risk difference and risk ratio (RR) scales. The normal-interval bootstrap was used to obtain 95% CIs (16).

Baseline confounders consisted of age at study entry (in years), income (≥$40 000 vs. <$40 000), race (White vs. other), education (high school and above vs. other), marital status (married vs. other), employment status (employed vs. other), body mass index (in kilograms per square meter), exercise history (low, moderate, or high), tobacco consumption history (ever vs. never), and alcohol consumption history (ever vs. never).

Time-varying confounders included bleeding (any vs. none in a given week) and gastrointestinal symptoms (any vs. none in a given week). In addition, hCG-detected pregnancy was considered a time-varying confounder of the relation between adherence and live birth and pregnancy loss (14, 15). All continuous and categorical variables were coded by using natural cubic splines and dummy variable coding, respectively. Bleeding, nausea, and adherence were also lagged by 1 week to account for potential feedback relationships (17).

Full details on the g-computation procedure, including all models fit; the Monte Carlo resampling procedure; and the data structure used for the analysis are provided in **Supplement 2**. Information on model validation strategies and the handling and impact of missing data is also provided in **Supplement 2**. All analyses were done in R, version 4.0.2 (R Foundation). Code to reproduce all results is available on Github (https://github.com/ainaimi/EAGeR-PerProtocol).

Role of the Funding Source

The funding sources played no role in the design, conduct, and analysis of this study or in the decision to submit the manuscript for publication.

RESULTS

Overall, 1228 women were recruited into the trial (615 in the LDA group and 613 in the placebo group). One participant in the placebo group was excluded from the analysis because of missing follow-up data. During the first week of follow-up, 96% of participants were adherent to the study protocol. No summary difference was observed in adherence over all follow-up between the aspirin and placebo groups (68% vs. 66%; *P* for difference = 0.130). However, among women who conceived, adherence dropped from an average of 74% before conception to 64% after conception ($P < 0.001$) (**Figure**). Overall, 54% ($n = 664$) of the 1227 study participants adhered to the protocol for 70% or more of their person-time in the trial. These women were more likely to be married, to be White, and to have a higher income and less likely to smoke or to withdraw from the study (**Table 1**).

We also observed that adherence to either placebo or LDA was associated with higher odds of hCG-

Figure. Proportion of all 1227 women who adhered to their randomly assigned treatment for all person-weeks of the study, ranging from the first to the 60th week after randomization (*top*), and for the person-weeks before and after pregnancy was detected by human chorionic gonadotropin testing (*bottom*).

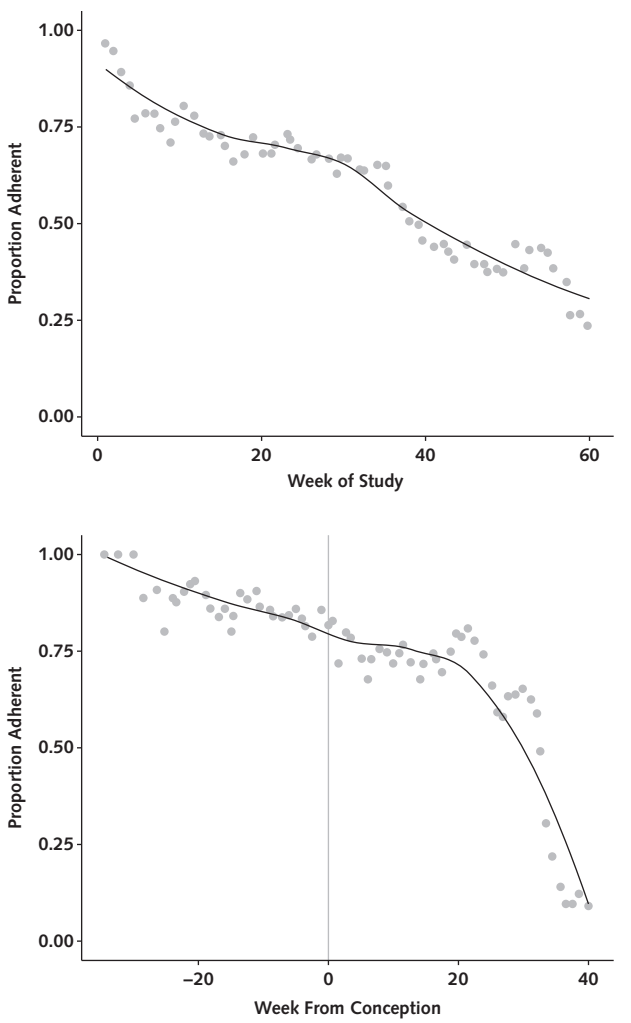

Table 1. Baseline Characteristics and Event Status, by Proportion of Adherent Person-Time, Among 1227 Women in the EAGeR Trial, 2006 to 2012*

Characteristic	Adherent Person-Time†		*P* Value‡
	<70% (*n* = 563)	≥70% (*n* = 664)	
Mean age (SD), *y*	28.4 (4.5)	29.2 (4.7)	0.002
Mean BMI (SD), kg/m^2	26.3 (6.4)	26.3 (6.7)	0.85
Assigned to LDA treatment	302 (52)	313 (48)	0.20
Original eligibility stratum§	228 (43)	320 (47)	0.171
At least high school education	473 (84)	584 (89)	0.030
Married	493 (89)	584 (96)	<0.001
Employed	419 (75)	500 (75)	0.89
Non-Hispanic White	525 (93)	636 (97)	0.011
Exercise (moderate or vigorous)	426 (73)	479 (75)	0.46
Income (≥$40 000)	348 (63)	473 (72)	0.002
Alcohol (ever consumed)	197 (35)	211 (31)	0.21
Tobacco (ever smoked)	99 (16)	53 (7)	<0.001
Trial outcome			
Live birth	252 (48)	343 (55)	0.013
Pregnancy loss	100 (18)	89 (13)	0.033
No pregnancy	84 (15)	223 (34)	<0.001
Withdrawal	127 (22)	9 (1)	<0.001

BMI = body mass index; EAGeR = Effects of Aspirin on Gestation and Reproduction; LDA = low-dose aspirin.
* Dichotomous variables were compared via proportions, continuous variables (age, BMI) via mean and SD.
† Values are numbers (percentages) of participants unless otherwise indicated.
‡ *P* values were obtained from 2-sided tests. Proportion comparisons were conducted via binomial tests. Wilcox rank-sum tests were performed to compare distributions of age and BMI.
§ Women in EAGeR were recruited into 2 eligibility strata: a homogeneous group with strict eligibility criteria (original stratum) and a more heterogeneous group that better resembled the general population of women attempting pregnancy (expanded stratum).

detected pregnancy (odds ratio, 5.70 [CI, 4.34 to 7.52]) and live birth (odds ratio, 1.33 [CI, 1.07 to 1.67]) and lower odds of pregnancy loss (odds ratio, 0.70 [CI, 0.51 to 0.95]). In line with the original ITT results (7), adherence was not associated with side effects, including bleeding (RR, 1.10 [CI, 0.92 to 1.40]) and nausea or vomiting (RR, 0.99 [CI, 0.80 to 1.21]). However, bleeding, nausea or vomiting, and hCG-detected pregnancy were strongly associated with a decrease in subsequent adherence (bleeding in the previous week: RR, 0.80 [CI, 0.76 to 0.83]; nausea or vomiting: RR, 0.84 [CI, 0.80 to 0.88]; and hCG-detected pregnancy: RR, 0.60 [CI, 0.57 to 0.62]).

Per protocol effect estimates suggested that taking aspirin over the entire follow-up resulted in more hCG-detected pregnancies (RR, 1.12 [CI, 1.02 to 1.23]), fewer pregnancy losses (RR, 0.69 [CI, 0.50 to 0.95]), and more live births (RR, 1.33 [CI, 1.08 to 1.64]) compared with taking placebo throughout follow-up. In additive terms, these estimates amount to 8 more hCG-detected pregnancies (CI, 4.64 to 10.96 pregnancies), 6 fewer pregnancy losses (CI, −12.00 to −0.20 losses), and 15 more live births (CI, 7.65 to 21.15 births) for every 100 women in the study (**Table 2**). In contrast, ITT effects suggested that 4 more hCG-detected pregnancies (CI, −1.18 to 9.56 pregnancies), 1 more pregnancy loss (CI, −3.09 to 4.68 losses), and 4 more live births (CI, −2.13 to 9.21 births) would occur for every 100 women in the LDA group versus the placebo group.

The effects of aspirin on live birth and pregnancy loss were observed when aspirin was taken early enough after conception (**Table 2**). This trend was particularly notable for pregnancy loss. Aspirin use after postconception week 6, 8, 12, or 20 attenuated RRs for pregnancy loss, with RRs ranging from 0.70 (CI, 0.47 to 1.04) if treatment was initiated 6 weeks after conception to 0.93 (CI, 0.65 to 1.33) if started 20 weeks after conception. The effect of aspirin on live birth was even greater when treatment started before and continued throughout pregnancy and notably less when treatment was delayed to gestation week 6 or beyond.

Throughout follow-up, the percentage of participants deemed adherent ranged from 74% for 2 of 7 days to 62% for 6 of 7 days. Relative to aspirin use 5 of 7 days per week, no meaningful difference in magnitude of the effect was observed when the adherence threshold was reduced to 4 of 7 days or increased to 6 of 7 days per week (**Table 3**). However, the estimated effect of aspirin use on live birth, pregnancy loss, and hCG-detected pregnancy was attenuated if adherence was less than 4 of 7 days per week.

Sensitivity analyses suggested that missing adherence, bleeding, and nausea data were unlikely to explain the differences observed between the per protocol and ITT effects (**Table 1** of **Supplement 2**). Indeed, most scenarios supported the conclusions implied by the per protocol effects in **Table 2**. Of importance, the scenarios that did not support them represented extremes corresponding to unrealistic data scenarios (such as 100% of missing adherence data set to "nonadherent" [**Table 1** of **Supplement 2**]).

DISCUSSION

We found that aspirin use at least 4 times per week before conception through gestation week 36 was associated with increased hCG-detected pregnancies and reduced pregnancy losses, thereby increasing live

Table 2. ITT and Adherence-Adjusted Effects of LDA on hCG-Detected Pregnancy, Live Birth, and Pregnancy Loss Among 1227 Women in the EAGeR Trial, 2006 to 2012*

Contrast	Risk	RD (95% CI)	RR (95% CI)
ITT			
Assigned to placebo			
Live birth (reference)	0.48	–	–
Pregnancy loss (reference)	0.15	–	–
hCG-detected pregnancy (reference)	0.62	–	–
Assigned to LDA			
Live birth	0.50	3.51 (−2.13 to 9.21)	1.08 (0.94 to 1.19)
Pregnancy loss	0.16	0.74 (−3.09 to 4.68)	1.05 (0.74 to 1.29)
hCG-detected pregnancy	0.66	4.25 (−1.18 to 9.56)	1.07 (0.97 to 1.15)
Per protocol			
Placebo throughout study			
Live birth (reference)	0.43	–	–
Pregnancy loss (reference)	0.20	–	–
hCG-detected pregnancy (reference)	0.65	–	–
LDA throughout study			
Live birth	0.58	14.50 (7.65 to 21.15)	1.33 (1.08 to 1.64)
Pregnancy loss	0.14	−6.10 (−12.00 to −0.20)	0.69 (0.50 to 0.95)
hCG-detected pregnancy	0.73	7.80 (4.64 to 10.96)	1.12 (1.02 to 1.23)
LDA starting at 6 wk			
Live birth	0.49	5.90 (0.23 to 11.75)	1.14 (1.03 to 1.26)
Pregnancy loss	0.14	−5.95 (−12.93 to 1.03)	0.70 (0.47 to 1.04)
hCG-detected pregnancy	0.63	−1.40 (−5.34 to 2.54)	0.98 (0.92 to 1.04)
LDA starting at 8 wk			
Live birth	0.50	6.45 (1.34 to 11.56)	1.15 (0.83 to 1.59)
Pregnancy loss	0.14	−5.35 (−15.70 to 5.00)	0.73 (0.52 to 1.03)
hCG-detected pregnancy	0.65	0.10 (−4.69 to 4.89)	1.00 (0.92 to 1.08)
LDA starting at 12 wk			
Live birth	0.49	5.95 (−0.72 to 12.62)	1.14 (0.83 to 1.57)
Pregnancy loss	0.17	−3.10 (−13.96 to 7.76)	0.84 (0.59 to 1.21)
hCG-detected pregnancy	0.66	1.60 (−3.12 to 6.32)	1.02 (0.92 to 1.13)
LDA starting at 20 wk			
Live birth	0.47	3.85 (−1.92 to 9.62)	1.09 (0.90 to 1.32)
Pregnancy loss	0.18	−1.35 (−11.83 to 9.13)	0.93 (0.65 to 1.33)
hCG-detected pregnancy	0.66	1.30 (−4.32 to 6.92)	1.02 (0.86 to 1.21)

EAGeR = Effects of Aspirin on Gestation and Reproduction; hCG = human chorionic gonadotropin; ITT = intention to treat; LDA = low-dose aspirin; RD = risk difference; RR = risk ratio.
* Adherence was defined as following protocol (taking LDA or placebo) 5 of 7 d per week.

births by more than 30%. These per protocol findings supplement the previous ITT results of the EAGeR trial by adjusting for nonadherence to the study protocol while accounting for time-varying, postrandomization confounding, and suggest a preventive effect of LDA on pregnancy loss. This evidence supports the need to focus on improving adherence to daily LDA to maximize the efficacy on pregnancy outcomes.

The per protocol and previous ITT effects estimated by using EAGeR data answer different questions about the impact of aspirin on pregnancy outcomes. Per protocol analyses quantify effects under ideal conditions in which all women adhere to the defined protocol. As such, they provide information on the potential effect of aspirin on individual women if they fully adhere to clinical recommendations. The validity of such analyses rests on the usual (unverifiable) assumptions required for observational studies (such as absence of confounding bias). In contrast, the ITT results quantify the effect of assigning participants to receive aspirin. They provide information on the potential impact in practice of recommending aspirin if adherence patterns were similar to those in the trial.

Table 3. Impact of the Selected Adherence Threshold on the Overall Adherence-Adjusted Effect Estimates Among 1227 Women in the EAGeR Trial, 2006 to 2012

Adherence Threshold	Observed Proportion of Women Adherent	RR (95% CI)		
		Live Birth	Pregnancy Loss	hCG-Detected Pregnancy
2 d/wk	0.74	1.12 (0.91–1.39)	0.89 (0.64–1.24)	1.06 (0.97–1.16)
3 d/wk	0.72	1.10 (0.89–1.36)	0.84 (0.62–1.14)	1.04 (0.93–1.17)
4 d/wk	0.70	1.28 (1.06–1.55)	0.71 (0.52–0.97)	1.09 (1.00–1.19)
5 d/wk	0.67	1.33 (1.08–1.64)	0.69 (0.50–0.95)	1.12 (1.02–1.23)
6 d/wk	0.63	1.30 (1.09–1.55)	0.71 (0.52–0.97)	1.10 (1.00–1.20)

EAGeR = Effects of Aspirin on Gestation and Reproduction; hCG = human chorionic gonadotropin; RR = risk ratio.

The validity of this analysis depends on the (verifiable) assumptions required for randomized trials (such as blinding).

In EAGeR, the differences observed between per protocol and ITT results may be attributed to many factors. First, the overall nonadherence rate of 25% changed during the study, particularly from before conception to after recognition of pregnancy. Indeed, 85% of participants met the adherent definition of 5 of 7 days during the preconception phase of the trial, but the percentage dropped to 67% after pregnancy detection. This differentially observed adherence helps clarify this trial's previous findings. Specifically, some secondary findings obtained by the ITT approach revealed that preconception-initiated LDA increased the pregnancy rate and shortened the time to pregnancy in certain subgroups (8, 9), which may reflect participants' relatively high adherence while trying to become pregnant.

In contrast, no analyses of the EAGeR trial that were performed with the ITT approach illustrated effects on pregnancy loss (11), which may reflect a decline in adherence among participants once they became pregnant or began having pregnancy symptoms (such as nausea). Second, nonadherence at any given time was associated with variables that were highly predictive of subsequent adherence as well as the outcomes studied (18). Indeed, such postrandomization confounding represents an important challenge in quantifying per protocol effects in randomized trials, accounted for with g-computation (10). Lastly, adherence also strongly predicted pregnancy outcomes and withdrawal. Indeed, women with better adherence were more likely to conceive and have a live birth. Furthermore, bleeding, nausea or vomiting, and hCG detection of pregnancy were all strong predictors of whether a woman would adhere to her assigned treatment in the subsequent week. Taken together, these features may also explain why similar findings were not observed in previous ITT analyses (19).

In light of the changing adherence patterns before and after pregnancy that we observed in our study, researchers and clinicians should be aware of such changes in LDA adherence behaviors. Because of these adherence patterns, universal recommendations for LDA treatment for women may not lead to meaningful changes in pregnancy outcomes. Research on improving adherence—for example, through alternative routes of LDA delivery—or provider and patient education on the need to maximize adherence may help increase the potentially beneficial effects of LDA on pregnancy outcomes.

Aspirin is well established as a safe and efficacious therapy during pregnancy to reduce preeclampsia and recurrent pregnancy loss attributed to antiphospholipid syndrome (4). Moreover, safety findings from the EAGeR trial indicate that LDA initiated before conception and continued through pregnancy is well tolerated (20). Furthermore, a recent randomized trial of approximately 12 000 women from 6 countries found lower rates of preterm birth, perinatal mortality, and fetal loss, as well as fewer hypertensive disorders of pregnancy, among women who received daily LDA than those who received placebo (21). In light of this recent trial, as well as the present study, evidence is growing of the positive effects of daily LDA use on pregnancy outcomes.

Our study is the first to our knowledge to shed light on the optimal timing of LDA therapy, suggesting maximum benefits by initiating treatment before and early in pregnancy. Indeed, the first stages of pregnancy, before a woman's usual first encounter with prenatal care, may be an early window for preventing pregnancy loss and improving the chances of live birth. Current guidelines recommending that aspirin therapy begin between gestation weeks 12 and 28 to prevent preeclampsia may be suboptimal for preventing pregnancy loss (3). Thus, initiation before conception may be the best course of action to optimize the public health impact.

The observation that aspirin's effect plateaus with use on 4 or more days per week is consistent with previous research investigating the impact of various aspirin dosing regimens on cardiovascular protection. Indeed, LDA (40 to 100 mg/d) used every third, every other, and every day produced similar cardiovascular outcomes (12, 22). A dose of 81 mg approximately every other day may be sufficient to improve pregnancy rates and reduce pregnancy loss, which may be desirable if fewer doses per week also result in fewer side effects, such as nausea and bleeding. However, because we defined adherence on a weekly basis, we could not quantify the impact of variation in daily patterns (that is, taking aspirin every day vs. every other day of the week). Trials specifically investigating different dose regimens will be required to confirm the efficacy of alternate aspirin dose regimens.

Our findings should be considered in light of important limitations. First, the EAGeR trial consisted of women who were mostly well educated and living in households with a high median income, limiting generalizability of the results. Second, too few cases of rare but adverse events, including preterm birth and preeclampsia, occurred during follow-up to be able to evaluate the per protocol effect of aspirin on these outcomes. Finally, although our analyses were subject to a large degree of missing weekly data, our sensitivity analyses showed that only extreme scenarios of the underlying missing data (that is, all missing data taking on a single value) led to estimates that would substantively change the interpretation of our findings.

In summary, following the recent call for per protocol analyses of randomized trials (10), our results suggest that preconception LDA use by women with previous pregnancy loss may improve pregnancy outcomes. Specifically, early adoption of LDA with maximal daily adherence promoted pregnancy and live birth and protected against pregnancy loss in women trying to become pregnant after a history of pregnancy loss. Efforts geared toward improving daily adherence to LDA may yield improvements in aspirin's effectiveness on reproductive outcomes for women trying to conceive.

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McGill University, Montreal, Quebec, Canada (R.W.P.); and University of Utah, Salt Lake City, Utah (R.M.S.).

Grant Support: By the National Institutes of Health (grant R01 HD093602) and the Intramural Research Program of the Eunice Kennedy Shriver National Institutes of Child Health and Human Development, National Institutes of Health (contracts HHSN 267200603423, HHSN267200603424, and HHSN267200603426).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-0469.

Data Sharing Statement: Trial data will be made accessible in an electronic repository after completion of the study's analytical phases. The data, along with a set of guidelines for researchers applying for use of the data, will be posted to a data sharing site: Eunice Kennedy Shriver National Institute of Child Health and Human Development Data and Specimen Hub (https://dash.nichd.nih.gov).

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Current author addresses and author contributions are available at Annals.org.

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