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Preconception Low Dose Aspirin and Pregnancy Outcomes: Findings from the EAGeR (Effects of Aspirin in Gestation and Reproduction) Randomized Trial

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Abstract

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Contributors

EFS conceived the idea and designed the study. RMS, LLL, DF, JW-W, JMT, AML, NG, NJP contributed to the study design, enrollment of patients, and interpretation of the data. NG, DF, EFS, NJP, SLM analyzed the study and contributed to the interpretation of the data. EFS, RMS, NG, NJP, SLM drafted the report, but all listed contributors edited and revised the report. The Data Coordinating Center (DCC), led by Drs. Galai and Faraggi, had full access to the data throughout the trial, and performed analysis as requested by the Data Safety Monitoring Board (DSMB). Upon trial completion, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) investigators (EFS, NJP, SLM) and DCC investigators (NG, DF) had full access to complete study data. All authors take responsibility for the integrity of the data and accuracy of data analysis, and approved the final manuscript. EFS is the guarantor.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Background—Our objective was to determine whether preconception-initiated low dose aspirin (LDA) improved live birth rates in women with one to two prior pregnancy losses.

Methods—This multi-center, block-randomized, double-blind, placebo-controlled trial recruited from four medical centers in the US (2006–2012). Women aged 18–40 years attempting pregnancy were stratified by eligibility criteria: “original”: women with one loss <20 weeks’ gestation during the past year; or “expanded”: women with one to two prior losses regardless of gestational length or time of loss. Women were block-randomized (615 LDA, 613 placebo) by center and eligibility stratum. Preconception-initiated daily LDA (81 mg/day) was compared with placebo for up to six menstrual cycles; for those who conceived, study treatment continued until 36 weeks’ gestation. The primary outcome was live birth rate. The trial was registered on ClinicalTrials.gov (#NCT00467363).

Findings—Overall, 1078 women completed the trial (LDA 535, placebo 543). Live birth rates were 58% (309/535) in women assigned LDA vs. 53% placebo (286/543; risk difference [RD] 5%; 95% confidence interval [CI] –0.8, 11). Pregnancy loss rates were similar between groups (13% [68/535] LDA, 12% [65/543] placebo; $p=0.7812$). In the original stratum, live birth rates were 62% (151/242) LDA vs. 53% (133/250) placebo (RD 9%; 95% CI 0.5, 18), and in the expanded, 54% (158/293) LDA vs. 52% (153/293) placebo (RD 2%; 95% CI –6, 10). Major adverse events were similar between treatment arms. LDA was associated with increased bleeding per vaginam, but this was not associated with losses.

Interpretation—Preconception-initiated LDA was not significantly associated with live birth or pregnancy loss among women with one to two prior losses. However, higher live birth rates were observed among women with a single documented loss at <20 weeks’ gestation during the previous year. LDA is not recommended for the prevention of pregnancy loss.

Keywords

low dose aspirin; conception; pregnancy loss; fertility; live birth

INTRODUCTION

Pregnancy loss is a common adverse event and is estimated to occur in up to 30% of conceptions.¹ Women who experience a pregnancy loss are at higher risk of having a subsequent loss and other adverse pregnancy events.² The pathophysiological mechanisms leading to adverse pregnancy outcomes are not fully understood, although decreased blood flow and/or increased inflammation may play significant roles.³ Since aspirin may improve blood flow and reduce inflammation in reproductive organs,⁴ it has the potential to improve pregnancy outcomes.

Post-conception use of low dose aspirin (LDA) has been extensively studied with respect to recurrent pregnancy loss (usually defined as at least two losses) and is commonly prescribed to prevent pregnancy loss despite its unproven efficacy.^{5–14} Preconception use of LDA has been shown to improve endometrial growth and vascularization in women undergoing *in vitro* fertilization (IVF).¹⁵ Thus, preconception-initiated LDA may positively affect downstream pregnancy outcomes during a critical window. However, preconception-initiated LDA has not been extensively evaluated.

The objective of the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial was to determine whether daily preconception-initiated LDA treatment (81 mg) improves the live birth rate in women with one or two prior documented pregnancy losses compared with placebo.

METHODS

Design and target population

EAGeR was a multi-center, block-randomized, double-blind, placebo-controlled clinical trial in the US. Each participating center's Institutional Review Board approved the study, and participants provided written informed consent. The trial was registered on ClinicalTrials.gov (#NCT00467363), and a Data Safety and Monitoring Board (DSMB) provided oversight.

Inclusion and exclusion criteria have been described in detail elsewhere.¹⁶ Briefly, initial inclusion criteria, henceforth referred to as the “original” eligibility criteria, included women actively trying to conceive with a history of only one prior pregnancy loss at <20 weeks' gestation during the past year, and had up to one prior live birth, up to one elective termination/ectopic pregnancy, regular menstrual cycles of 21–42 days in length during the preceding 12 months, no history of infertility and aged 18 to 40 years. This population was chosen because women with a recent pregnancy loss may have a “healing” endometrium and benefit from LDA's effect on improving blood flow. In addition, they would be motivated to participate in trial with an intensive protocol. Participants were recruited using both community and health care based strategies.

Due to the limited number of eligible women after two months of recruitment (only nine were enrolled), inclusion criteria were extended to women who had one or two pregnancy losses, including those at >20 weeks' gestation, with pregnancy losses occurring more than one year prior to enrollment, and with up to two prior live births. These criteria were termed “expanded” eligibility. All other criteria were identical between the two strata.¹⁶ In order to assess the effect of LDA in the original eligibility stratum, participants were independently randomized within each eligibility strata (original and expanded). Participants were questioned about the details of prior losses, and prior losses were verified using serum hCG lab results, sonogram findings, physician report, medical records, and histology reports. Women were excluded if they had a major medical problem or known contraindication to aspirin, indication for anticoagulant therapy, or infertility.

Study protocol

Eligible women were randomized to daily LDA (81 mg; standard low dose in the US) plus folic acid (400 mcg) or placebo plus folic acid. Study medications were manufactured to be identical by appearance and weight (over-coated tablets [UPM pharmaceutical, Baltimore, MD for the first batch only] or over-encapsulated tablets [ThermoFisher, Rockville, MD for subsequent batches]), with folic acid given separately as a supplement (generic). Study pills were taken daily until completion of six menstrual cycles while attempting pregnancy or 36 weeks' gestation for those who became pregnant (up to approximately 60 weeks).

Adherence was self-reported daily and additionally assessed by weighing medication bottles at each study visit. Participants provided urine and blood specimens and completed questionnaires during scheduled clinic visits. Fertility monitors were used by participants in both treatment arms after standardized training to assist with timing of intercourse (Clearblue Easy™ Fertility Monitor; Inverness Medical). Protocol details are described elsewhere.¹⁶

Pregnancy was initially verified by a clinic urine pregnancy test and then confirmed by ultrasound at six to seven weeks' gestation. If evidence of pregnancy was not apparent on the sonogram after a positive pregnancy test, the case was considered a peri-conception loss and the participant continued on the non-pregnancy follow-up schedule. Participation in the study ended when a woman either completed six menstrual cycles in the trial without becoming pregnant, or had two peri-conception losses. Participants who became pregnant were followed monthly until the pregnancy ended.

Randomization and masking

Participants were randomized by study coordinators at each clinic according to a computerized randomization algorithm developed by the Data Coordinating Center (DCC), and based on a permuted block design with blocks of length six or eight, within each stratum (original/expanded) and center. Participants, trial staff, and investigators remained blinded to the treatment assignment throughout the trial.

Outcome measures

The primary outcome was live birth. Secondary outcomes included implantation (positive urine pregnancy test (PPT)), confirmed pregnancy (the sonogram showed a gestational sac, clinical documentation of fetal heart tones, or a later stage confirmation of pregnancy), pregnancy loss (<20 weeks' gestation after documentation of confirmed pregnancy), birth weight, and obstetrical complications. Complications included preeclampsia, gestational diabetes, gestational hypertension, and preterm birth (<37 weeks) and were obtained prospectively by maternal report and medical record abstraction by trained staff. Gestational age was based on the six to seven week study sonogram. For participants with a pregnancy loss before the early sonogram, gestational age was defined as the number of days between ovulation detected on the fertility monitor to the date of the loss plus 14 days.

Statistical analysis

The study was initially designed to detect a 10% absolute difference in live birth rate with 80% power and a 5% type I error rate, assuming participants taking placebo who achieved pregnancy had a 75% live birth rate.¹⁶ Therefore, a sample size of 1254 was needed assuming a 40% pregnancy rate over six months of trying. Accounting for a potential 20% loss to follow-up, 1600 was the recruitment target. Additional calculations based on unconditional probabilities of live birth indicated a power of 90% to detect a 10% increase in LDA assuming a 50% live birth rate in the placebo arm, with a sample size of 1076 complete cases. The final overall number recruited was 1228 due to slower than anticipated rate of recruitment and funding constraints. However, the actual loss to follow-up of 12% (n=150) was less than the 20% expected; follow-up was complete for 1078 participants.

Outcomes in the LDA and placebo groups were compared using Fisher's exact test and t-tests and were based on the intent-to-treat principle. Results are presented overall and stratified by the original/expanded eligibility strata. There was an *a priori* plan to perform analyses on the entire cohort, as well as for each stratum, which was the rationale for randomization within strata. An exploratory analysis of transition probabilities for outcomes was also conducted to evaluate potential differences between treatment arms. Adverse events were monitored and recorded throughout the trial by a committee blinded to treatment status. A sensitivity analysis was used to assess the impact of early participant withdrawal from the trial on the outcome of live birth.

Role of the funding source

The sources of funding had no role in study design, data collection, analysis, interpretation, or writing the report. The DCC, led by Drs. Galai and Faraggi, had full access to the data throughout the trial, and performed analysis as requested by the DSMB. Upon trial completion, NICHD investigators (EFS, NJP, SLM) and DCC investigators (NG, DF) had full access to complete study data. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

RESULTS

The study was conducted between June 2007 and August 2012 in four major university medical centers in the US. Participant flow is shown in Figure 1. A total of 1228 women were block randomized (615 LDA, 613 placebo) by center and stratum, and 1078 participants completed the study (535 LDA, 543 placebo) and were included in the analysis. Early withdrawal rates were 13% for LDA and 13% for placebo.

Characteristics of participants, by treatment arm, are shown in Table 1. Mean age was 28.7 years and mean body mass index was 26.4 kg/m²; participants were mostly white (95%; 1162/1228), married or living with a partner (98%; 1198/1228), and had above a high school education (86%; 1057/1228). Most women had only one prior pregnancy loss (67%; 825/1228), and for 53% (651/1228) the interval between the most recent pregnancy loss and randomization was less than 4 months. Treatment arms were similar with regard to all characteristics assessed.

Overall, the live birth rate was 58% (309/535) in the LDA group compared with 53% (286/543) in the placebo group ($p=0.0984$, Table 2). In the original stratum, 62% (151/242) of the LDA group had live births versus 53% (133/250) taking placebo ($p=0.0446$). In the expanded stratum, live birth rates were 54% (158/293) for LDA and 52% (153/293) for placebo ($p=0.7406$).

Secondary outcomes are provided in Table 3. Overall, 74% (394/535) of women receiving LDA had positive urine hCG pregnancy tests compared to 67% (363/543) taking placebo ($p=0.0150$). In the original stratum, corresponding rates of positive hCG tests were 78% (189/242) for LDA and 66% (166/250) for placebo ($p=0.0020$). Ultrasound confirmed pregnancy rates were also higher in the LDA group both for the overall cohort (70% [374/535] LDA versus 64% [346/543] placebo, $p=0.0319$) and for the original stratum (74%

[180/242] LDA versus 64% [159/250] placebo, $p=0.0059$). In the expanded stratum, confirmed pregnancy rates were similar between treatment groups ($p=0.7278$). There were no significant differences between treatment groups in either stratum for pregnancy complications occurring subsequent to implantation including pregnancy loss (Table 3). The differences in live births by treatment arm in the original stratum are due to differences in pregnancy rates (whether based on a positive pregnancy test or confirmed pregnancy) rather than any outcome conditional on pregnancy (i.e., early pregnancy losses, stillbirths, etc.) (Figure 2).

Safety symptoms were assessed via questionnaire and reported rates were comparable between treatment arms (Table 4). Staff-documented case report forms (CRFs) of serious adverse events were continuously monitored by a physicians' committee of investigators as well as the DSMB. No birth defects were observed. Three cases of neonatal death occurred; two in the LDA arm. One was due to cervical insufficiency and the other attributed to chronic bleeding per vaginam, chorioamnionitis, and preterm birth. The committee vetted the CRFs of minor adverse events as well, finding bleeding per vaginam to be more common among women who received LDA ($n=24$ women) versus placebo ($n=8$ women; $p=0.0038$). However, the rate of pregnancy loss was not elevated in women taking LDA who experienced bleeding.

Self-reported adherence to treatment assignment was similar between groups: 15% [93/606] of women in the LDA group permanently stopped study medication compared to 13% [79/606] in the placebo group, and 6% [34/606] of women taking LDA temporarily stopped the medication versus 8% [48/606] taking placebo. Similar rates of adherence between groups also were noted based on weighing of medication bottles (data not shown).

A sensitivity analysis performed in the original stratum indicated that LDA would have been associated with a significant increase in the live birth rate for all reasonable assumptions about potential live birth rates among participants withdrawing early in each treatment arm (data not shown).

DISCUSSION

Overall, preconception-initiated treatment with LDA was not significantly associated with live birth rates, pregnancy loss, or other pregnancy complications. To our knowledge, this is the first study to demonstrate that preconception-initiated LDA does not decrease the risk of pregnancy loss among women without a history of recurrent pregnancy loss (i.e., only one to two prior losses). Thus, our data do not support the general use of LDA to decrease the risk of pregnancy loss.

Our results are consistent with multiple trials in women with recurrent losses (two or more losses) that have initiated aspirin therapy post-conception and reported no benefit of LDA in preventing pregnancy loss (2009 Cochrane review).⁷ LDA combined with heparin has been shown to confer some benefit in a subset of women with recurrent pregnancy loss due to antiphospholipid syndrome.^{22–25} One small study ($n=364$) assessed the reproductive effects of LDA, LDA plus heparin, or placebo on recurrent pregnancy loss where 26% (94/364) of

the couples were recruited prior to conception.⁶ This trial showed no benefit of either medication to prevent recurrent pregnancy losses compared to placebo.⁶ A possible explanation for these null findings could be the late initiation of LDA treatment in pregnancy. Given that placentation and organogenesis occur very early in pregnancy, post-conception initiation of LDA may miss the critical window for positive intervention, highlighting the need for preconception trials. A study population that has been consistently evaluated preconception is patients undergoing IVF. Two recent meta-analyses found that LDA had no significant effect on the clinical pregnancy rate (RR 1.03, 95% CI: 0.91, 1.17) or live birth rate (RR 0.91, 95% CI: 0.72, 1.15) in women undergoing IVF.^{19–20} A systematic review with less stringent quality criteria found that although pregnancy rates were increased with LDA (OR 1.19, 95% CI: 1.01, 1.39), live birth rates were not affected (OR 1.08, 95% CI: 0.82, 1.68).²¹ Our study is the first and largest to show that LDA does not decrease pregnancy loss when initiated preconception among women with a history of only one to two prior pregnancy losses. Taken together with previous findings, LDA alone has not been shown to reduce rates of pregnancy loss in any population.

In our trial, LDA was associated with an increase in the live birth rate in women with a single well-documented pregnancy loss at <20 weeks gestation during the last year (original stratum). The effect could not be attributed to a lower pregnancy loss rate and was likely due to increased conception or implantation rates among women treated with LDA. Also, in the overall cohort, LDA was associated with an increased rate of PPT (74% [394/535] versus 67% [363/543]; $p=0.0251$). The effect was more pronounced in the original stratum (78% [189/242] versus 66% [166/250]; $p=0.0020$) and was virtually null for the expanded stratum (70% [205/293] versus 67% [197/293], $p=0.4766$). These data indicate that LDA may have a favorable effect on fecundity or implantation for a sub-group of women, and is not inconsistent with some IVF studies showing effects on implantation¹⁵ but not live birth rates.²¹

The EAGeR trial differs from previous studies in several important ways. First, our population did not have a history of recurrent pregnancy loss, but was comprised of women with only one or two prior losses, mostly recent. Women with multiple pregnancy losses likely have a different underlying pathology. Second, LDA was initiated preconception in our study, which may influence critical early pregnancy events such as placentation, vascularization, and organogenesis. Previously, preconception-initiated LDA has only been assessed in a much smaller study of non-IVF patients with recurrent pregnancy loss.⁶ Third, women in our study were block-randomized to either original or expanded strata. This enabled evaluation of the effect of LDA on pregnancy outcomes in a more homogeneous group with very strict eligibility criteria (original), as well as a more heterogeneous group, which more closely resembles the general population of women attempting pregnancy (expanded). It is noteworthy that the original stratum included the “healthiest” women from a reproductive standpoint, and were the least likely to have a condition predisposing them towards infertility or pregnancy loss. The fact that LDA had a significant effect on PPTs for the entire cohort supports the notion that LDA may have favorable effects on fecundity among women with one to two prior losses. Conversely, the observation of a significant effect on our primary outcome in only one stratum, and the fact that a PPT was a secondary outcome, should prompt caution. Our results should be considered hypothesis generating

and do not allow for definitive conclusions. They do not justify the current use of LDA to increase fecundity in similar women in the absence of further studies.

Importantly, our study found LDA was not associated with an increase in major adverse events in either pregnant women or their fetuses/newborns. Indeed, randomized clinical trials including thousands of women have shown no increase in adverse fetal sequelae in maternal doses of up to 150 mg per day.^{26–28}

Our study had several limitations. First, there were too few cases to definitively exclude the possibility of rare but serious adverse events. Second, the rigors of the study protocol were such that participants tended to have higher income and more education, and thus these results may not apply to women with lower socioeconomic status. Finally, 12% [150/1228] of women were lost to follow-up, which could be a potential source of bias if differential by treatment assignment. However, loss to follow-up was similar between treatment arms, suggesting this bias was not a likely, based on the sensitivity analysis.

The many strengths of the study included its rigorous design and high participant adherence to an extensive protocol. Trial outcomes were well-defined and well-documented. Participants were followed with frequent scheduled study visits, the use of fertility monitors, and early ultrasounds in order to precisely document pregnancy and pregnancy loss. Moreover, LDA use was initiated preconception, setting this trial apart from most prior studies. Finally, the number of participants was quite large relative to other studies, even within each stratum.

In summary, LDA initiated prior to conception was not associated with an increase in live births or a decrease in pregnancy loss in women with one to two prior losses. Daily preconception-initiated LDA was associated with an increased rate of PPTs and a nearly 10% increase in live birth rate in women with a single pregnancy loss at <20 weeks' gestation during the past year. Considering the low cost, availability, and apparent safety of LDA, these findings should prompt further investigation into the effects of LDA on fecundity and implantation. However, our data do not support the general use of LDA to decrease pregnancy loss or increase live birth rates.

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Reference List

1. Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. *N Engl J Med*. 1999; 340:1796–1799. [PubMed: 10362823]
2. Risch HA, Weiss NS, Clarke EA, Miller AB. Risk factors for spontaneous abortion and its recurrence. *Am J Epidemiol*. 1988; 128:420–430. [PubMed: 3273482]

3. Silver, RM.; Branch, DW. Sporadic and recurrent pregnancy loss. In: Reece, EA.; Hobbins, JC., editors. *Medicine of the fetus and mother*. 2nd Edition ed.. Philadelphia: J.B. Lippincott Company; 1999. p. 195-216.
4. Vane JR, Botting RM. The mechanism of action of aspirin. *Thromb Res*. 2003; 110:255–258. [PubMed: 14592543]
5. Di NM, Peters L, Middeldorp S. Anticoagulants for the treatment of recurrent pregnancy loss in women without antiphospholipid syndrome. *Cochrane Database Syst Rev*. 2005; (2):CD004734. [PubMed: 15846729]
6. Kaandorp SP, Goddijn M, van der Post JA, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *N Engl J Med*. 2010; 362:1586–1596. [PubMed: 20335572]
7. Kaandorp S, Di NM, Goddijn M, Middeldorp S. Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. *Cochrane Database Syst Rev*. 2009; (1):CD004734. [PubMed: 19160241]
8. Empson M, Lassere M, Craig JC, Scott JR. Recurrent pregnancy loss with antiphospholipid antibody: a systematic review of therapeutic trials. *ObstetGynecol*. 2002; 99:135–144.
9. Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database Syst Rev*. 2005; (2):CD002859. [PubMed: 15846641]
10. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *ObstetGynecol*. 2002; 100:408–413.
11. Gris JC, Mercier E, Quere I, et al. Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. *Blood*. 2004; 103:3695–3699. [PubMed: 14739212]
12. Li DK, Liu L, Odouli R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ*. 2003; 327:368. [PubMed: 12919986]
13. Rai R, Backos M, Baxter N, Chilcott I, Regan L. Recurrent miscarriage--an aspirin a day? *Hum Reprod*. 2000; 15:2220–2223. [PubMed: 11006203]
14. Tulppala M, Marttunen M, Soderstrom-Anttila V, et al. Low-dose aspirin in prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production. *Hum Reprod*. 1997; 12:1567–1572. [PubMed: 9262298]
15. Rubinstein M, Marazzi A, Polak de FE. Low-dose aspirin treatment improves ovarian responsiveness, uterine and ovarian blood flow velocity, implantation, and pregnancy rates in patients undergoing in vitro fertilization: a prospective, randomized, double-blind placebocontrolled assay. *FertilSteril*. 1999; 71:825–829.
16. 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 Perinatal Epidemiology*. 2013 In press.
17. Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. *Hum Reprod*. 1999; 14:2868–2871. [PubMed: 10548638]
18. Clark P, Walker ID, Langhorne P, et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. *Blood*. 2010; 115:4162–4167. [PubMed: 20237316]
19. Siristatidis CS, Dodd SR, Drakeley AJ. Aspirin for in vitro fertilisation. *Cochrane Database Syst Rev*. 2011; (8):CD004832. [PubMed: 21833951]
20. Groeneveld E, Broeze KA, Lambers MJ, et al. Is aspirin effective in women undergoing in vitro fertilization (IVF)? Results from an individual patient data meta-analysis (IPD MA). *Hum Reprod Update*. 2011; 17:501–509. [PubMed: 21422062]
21. Dentali F, Ageno W, Rezoagli E, et al. Low-dose aspirin for in vitro fertilization or intracytoplasmic sperm injection: a systematic review and a meta-analysis of the literature. *J ThrombHaemost*. 2012; 10:2075–2085.
22. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. *JAMA*. 2006; 295:1050–1057. [PubMed: 16507806]

23. Tuthill JJ, Khamashta MA. Management of antiphospholipid syndrome. *J Autoimmun.* 2009; 33:92–98. [PubMed: 19559568]
24. Mak A, Cheung MW, Cheak AA, Ho RC. Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive antiphospholipid antibodies: a meta-analysis of randomized controlled trials and meta-regression. *Rheumatology (Oxford).* 2010; 49:281–288. [PubMed: 19965971]
25. Laskin CA, Spitzer KA, Clark CA, et al. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. *J Rheumatol.* 2009; 36:279–287. [PubMed: 19208560]
26. Knight M, Duley L, Henderson-Smart DJ, King JF. Antiplatelet agents for preventing and treating pre-eclampsia. *Cochrane Database Syst Rev.* 2000; (2):CD000492. [PubMed: 10796208]
27. Duley L, Henderson-Smart D, Knight M, King J. Antiplatelet drugs for prevention of preeclampsia and its consequences: systematic review. *BMJ.* 2001; 322:329–333. [PubMed: 11159655]
28. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. *Lancet.* 1994; 343:619–629. [PubMed: 7906809]

Research in context

Systematic review

Aspirin has been used to treat a variety of reproductive outcomes. Relevant to our work in this trial, we evaluated the literature with respect to the use of aspirin as a therapy to prevent pregnancy loss among women with recurrent pregnancy loss (more than two losses) both with and without antiphospholipid syndrome, and preconception treatment among women undergoing *in vitro* fertilization (IVF).

Although a systematic review published in 2012 (13 studies, 849 participants) showed that combined unfractionated heparin and aspirin therapy reduced pregnancy loss by 54% among women with recurrent pregnancy loss associated with antiphospholipid antibodies,⁹ similar results were not observed among women without antiphospholipid syndrome.⁷ Studies among women with a history of at least two miscarriages and without antiphospholipid syndrome were summarized in a systematic review published in 2009 (two studies, 189 participants), which did not show a benefit of aspirin treatment.⁷ As only one of those studies was placebo-controlled, the review called for the need for future large randomized placebo-controlled trials. In IVF populations, a systematic review published in 2011 (13 trials, 2653 participants) showed that there were no significant differences between live birth rates, clinical pregnancy rates, or miscarriage rates among women treated with aspirin versus placebo.¹⁹ However, a systematic review with less stringent quality criteria (17 studies, 6403 patients) observed that aspirin increased pregnancy rates in IVF patients, though had no effect on the live birth rate.²¹

We performed an additional search using PubMed and Cochrane Library to identify additional original articles or systematic reviews published since the date of these reviews up to September 18, 2013, with the terms “aspirin”, “miscarriage”, “pregnancy loss”, and “pregnancy”. No relevant studies were found that were conducted in populations without a history of recurrent pregnancy loss (only one to two losses) and without antiphospholipid syndrome. Therefore this study reports the only direct comparison of the efficacy and safety of preconception-initiated aspirin treatment among women with only one to two prior pregnancy losses.

Interpretation

Preconception-initiated treatment with LDA does not increase the rate of live birth or decrease the rate of pregnancy loss among women with a history of one or two prior pregnancy losses. However, it may increase pregnancy rates among women with a single recent loss. Interpreted in the context of previous randomized controlled trials, our study is consistent with previous findings that do not support the use of LDA to decrease the risk of pregnancy loss. Further research should be done to investigate the potential effects of LDA on fecundity and implantation.

EAGeR CONSORT Flow Diagram

Figure 1.
Participant Flow for the EAGeR Trial

a.

b.

Figure 2.

a. Transition Probabilities for the Overall EAGeR Trial. Numbers represent n (%) for various outcomes, with percentages calculated conditionally from the total number of women in the previous stage. PPT: urine positive pregnancy test.

b. Transition Probabilities for the Original Stratum of the EAGeR Trial. Numbers represent n (%) for various outcomes, with percentages calculated conditionally from the total number of women in the previous stage. PPT: urine positive pregnancy test.

Table 1Demographics and baseline characteristics by Treatment Arm: The EAGeRTrial.^a

Characteristics N (%)	Total N=1228	LDA N=615	Placebo N=613
Age, y: Mean $\pm$ SD	28.7 $\pm$ 4.8	28.8 $\pm$ 4.9	28.7 $\pm$ 4.7
Race			
White	1162 (95)	576 (94)	586 (96)
Non-White	66 (5)	39 (6)	27 (4)
Marital status			
Married	1124 (92)	575 (94)	549 (90)
Living with partner	74 (6)	31 (5)	43 (7)
Other	30 (2)	9 (1)	21 (3)
Education			
> High School	1057 (86)	526 (86)	531 (87)
High School	170 (14)	88 (14)	82 (13)
Missing	1 (0)	1 (0)	0 (0)
Household income (annual)			
\$100,000	491 (40)	241 (39)	250 (41)
\$75,000–\$99,999	149 (12)	84 (14)	65 (11)
\$40,000–\$74,999	181 (15)	91 (15)	90 (14)
\$20,000–\$39,999	312 (25)	147 (24)	165 (27)
\$19,999	94 (8)	51 (8)	43 (7)
Missing	1 (0)	1 (0)	0 (0)
Employment			
Employed	895 (73)	451 (73)	444 (72)
Unemployed	289 (23)	142 (23)	147 (24)
Missing	44 (4)	22 (4)	22 (4)
Time from last loss to randomization (months)			
4 Months	651 (53)	331 (54)	320 (52)
5–8 Months	222 (18)	103 (17)	119 (20)
9–12 Months	99 (8)	50 (8)	49 (8)
>12 Months	237 (19)	119 (19)	119 (19)
Missing	19 (2)	12 (2)	7 (1)
Number of previous pregnancies, not including losses			
0	526 (43)	263 (43)	263 (43)
1	433 (35)	212 (34)	221 (36)
2	247 (20)	127 (21)	120 (20)
3	22 (2)	13 (2)	9 (1)
Number of previous live births			
0	577 (47)	287 (47)	290 (47)

Characteristics N (%)	Total N=1228	LDA N=615	Placebo N=613
1	438 (36)	218 (35)	220 (36)
2	213 (17)	110 (18)	103 (17)
Number of previous pregnancy losses			
1	825 (67)	422 (69)	403 (66)
2	403 (33)	193 (31)	210 (34)
BMI, kg/m ² , Mean $\pm$ SD	26.4 $\pm$ 6.6	26.3 $\pm$ 6.8	26.5 $\pm$ 6.4
Smoking in past year			
Never	1067 (87)	529 (86)	538 (88)
<6 times/week	87 (7)	41 (7)	46 (7)
Daily	63 (5)	38 (6)	25 (4)
Missing	11 (1)	7 (1)	4 (1)
Alcohol consumption in past year			
Often	26 (2)	18 (3)	8 (1)
Sometimes	380 (31)	187 (30)	193 (31)
Never	806 (66)	398 (65)	408 (67)
Missing	16 (1)	12 (2)	4 (1)

^aInformation on covariates was missing for income (n=1), time from last loss to randomization (n=19), smoking (n=11), alcohol (n=16), education (n=2), and employment (n=44).

Table 2

Primary Outcome by Treatment Arm and Original/Expanded Eligibility Criteria: The EAGeR Trial.

	LDA	Placebo
No. Participants Randomized	615	613
No. Participants Withdrew	80	70
Intention-to-treat population		
OVERALL		
No. of participants	535	543
Live birth - no. (%)	309 (58)	286 (53)
Relative risk (95% CI)	1.10 (0.98, 1.22)	
Absolute difference in live-birth rate (95% CI) - %	5.09 (−0.84, 11.02)	
ORIGINAL		
No. of participants	242	250
Live birth - no. (%)	151 (62)	133 (53)
Relative risk (95% CI)	1.17 (1.01, 1.37)	
Absolute difference in live-birth rate (95% CI) - %	9.20 (0.51, 17.89)	
EXPANDED		
No. of participants	293	293
Live birth - no. (%)	158 (54)	153 (52)
Relative risk (95% CI)	1.03 (0.89, 1.20)	
Absolute difference in live-birth rate (95% CI) - %	1.71 (−6.37, 9.79)	

Table 3

Secondary Outcomes by Treatment Arm and Original/Expanded Eligibility Criteria: The EAGeR Trial.

Outcomes: N (%)	Overall			Original			Expanded		
	Total N=1078	LDA N=535	Placebo N=543	RR (95% CI)	LDA N=242	Placebo N=250	RR (95% CI)	LDA N=293	Placebo N=293
HCG Positive Pregnancy Test	757 (70)	394 (74)	363 (67)	1.10(1.02,1.19)	189(78)	166(66)	1.18(1.05,1.31)	205(70)	197(67)
Ultrasound Confirmed pregnancy	720(67)	374(70)	346(64)	1.10(1.01,1.19)	180(74)	159(64)	1.17(1.04,1.32)	194(66)	187(64)
Pregnancy loss	133 (12)	68 (13)	65 (12)	1.06(0.77,1.46)	30 (12)	28 (11)	1.11(0.68,1.80)	38 (13)	37 (13)
Preterm Birth	53(5)	22(4)	31(6)	0.72(0.42,1.23)	7(3)	16(6)	0.45(0.19,1.08)	15(5)	15(5)
Gestational hypertension	1 (0-1)	0 (0)	1 (0-2)	N/A	0 (0)	0 (0)	N/A	0 (0)	1 (0-3)
Gestational diabetes	22 (2)	11 (2)	11 (2)	1.01(0.44,2.32)	2 (1)	3 (1)	0.69(0.12,4.09)	9 (3)	8 (3)
Preeclampsia	62 (6)	32 (6)	30 (6)	1.08(0.67,1.76)	16 (7)	20 (8)	0.83(0.44,1.56)	16 (5)	10 (3)
Mean $\pm$ SD Birth weight, grams	3321 $\pm$ 535	3327 $\pm$ 521	3315 $\pm$ 550	12 (-74,99)*	3318 $\pm$ 531	3341 $\pm$ 553	23(-104,150)	3336 $\pm$ 512	3292 $\pm$ 549
Gestational age at birth, weeks	38.8 $\pm$ 1.9	38.8 $\pm$ 2.0	38.8 $\pm$ 1.8	0.0(-0.3, 0.3)*	39.0 $\pm$ 2.0	38.9 $\pm$ 1.8	0.1(-0.3,0.6)	38.6 $\pm$ 2.0	38.7 $\pm$ 1.8

* Mean Difference (95% CI)

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