Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial

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Summary

Background **Preconception-initiated low-dose aspirin might positively affect pregnancy outcomes, but this possibility has not been adequately assessed. Our aim was to investigate whether low-dose aspirin improved livebirth rates in women with one to two previous pregnancy losses.**

Methods **In this multicentre, block-randomised, double-blind, placebo-controlled trial, women aged 18–40 years who were attempting to become pregnant were recruited from four medical centres in the USA. Participants were stratified by eligibility criteria—the original stratum was restricted to women with one loss at less than 20 weeks' gestation during the previous year, whereas the expanded stratum included women with one to two previous losses, with no restrictions on gestational age or time of loss. Women were block-randomised by centre and eligibility stratum in a 1:1 ratio. Preconception-initiated daily low-dose aspirin (81 mg per day) plus folic acid was compared with placebo plus folic acid for up to six menstrual cycles; for women who conceived, study treatment continued until 36 weeks' gestation. Participants, trial staff, and investigators were masked to the assigned treatment. The primary outcome was livebirth rate, which was analysed by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00467363.**

Findings **Overall, 1228 women were recruited and randomly assigned between June 15, 2007, and July 15, 2011, 1078 of whom completed the trial and were included in the analysis (535 in the low-dose aspirin group and 543 in the placebo group). 309 (58%) women in the low-dose aspirin group had livebirths, compared with 286 (53%) in the placebo group (p=0·0984; absolute difference in livebirth rate 5·09% [95% CI −0·84 to 11·02]). Pregnancy loss occurred in 68 (13%) women in the low-dose aspirin group, compared with 65 (12%) women in the placebo group (p=0·7812). In the original stratum, 151 (62%) of 242 women in the low-dose aspirin group had livebirths, compared with 133 (53%) of 250 in the placebo group (p=0·0446; absolute difference in livebirth rate 9·20% [0·51 to 17·89]). In the expanded stratum, 158 (54%) of 293 women in the low-dose aspirin group and 153 (52%) of 293 in the placebo group had livebirths (p=0·7406; absolute difference in livebirth rate 1·71% [−6·37 to 9·79]). Major adverse events were similar between treatment groups. Low-dose aspirin was associated with increased vaginal bleeding, but this adverse event was not associated with pregnancy loss.**

Interpretation **Preconception-initiated low-dose aspirin was not significantly associated with livebirth or pregnancy loss in women with one to two previous losses. However, higher livebirth rates were seen in women with a single documented loss at less than 20 weeks' gestation during the previous year. Low-dose aspirin is not recommended for the prevention of pregnancy loss.**

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Introduction

Pregnancy loss is a common adverse event, estimated to occur in up to 30% of conceptions.[1] Women who have had a pregnancy loss are at increased risk of having a subsequent loss and other adverse pregnancy events.[2] The pathophysiological mechanisms that lead to adverse pregnancy outcomes are not fully understood, although decreased blood flow and increased inflammation can have important roles.[3] Since aspirin can improve blood flow and reduce inflammation in reproductive organs,[4] it might be useful for the improvement of pregnancy outcomes.

Post-conception use of low-dose aspirin has been studied extensively with respect to recurrent pregnancy loss (usually defined as at least two losses) and is often prescribed to prevent pregnancy loss, despite its unproven efficacy.[5–14] Preconception use of low-dose aspirin improves endometrial growth and vascularisation in women undergoing in-vitro fertilisation (IVF).[15] Thus, preconception-initiated low-dose aspirin might positively affect downstream pregnancy outcomes during a crucial treatment window. However, this possibility has not been extensively assessed.

The aim of the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial was to assess whether daily preconception-initiated treatment with low-dose aspirin improves the livebirth rate compared with placebo in women with one to two previous pregnancy losses.

Methods

Study design and participants

EAGeR was a multicentre, block-randomised, double-blind, placebo-controlled clinical trial in four university medical centres in the USA. Inclusion and exclusion criteria have been detailed elsewhere.[16] Briefly, initial inclusion criteria (applied for recruitment of the original stratum) included women aged 18–40 years who were actively trying to conceive and who had a history of only one previous pregnancy loss at less than 20 weeks' gestation during the previous year; up to one previous livebirth; up to one elective termination or ectopic pregnancy; regular menstrual cycles of 21–42 days in length during the preceding 12 months; and no history of infertility. These criteria were chosen because women with a recent pregnancy loss might have a healing endometrium and thereby benefit from the positive effect of low-dose aspirin on blood flow, and because this population would be especially motivated to participate in the trial. Participants were recruited from the community as well as from the four clinical study centres.

Because of slow recruitment, the study was expanded to include four sites (rather than two as originally planned) and the inclusion criteria were extended to women who had one or two pregnancy losses, including at more than 20 weeks' gestation; pregnancy losses that occurred more than 1 year before enrolment; and up to two previous livebirths. These criteria were applied for recruitment of the expanded stratum. All other criteria were identical between the two eligibility strata.[16] To allow the assessment of outcomes specifically for the stratum recruited under the original eligibility criteria, participants were independently randomised within each eligibility stratum (original and expanded). Participants were questioned about the details of previous losses, and these losses were verified with serum human chorionic gonadotropin (hCG) results, ultrasound findings, physician investigation, medical records, and histology findings. Participants were excluded if they had a major medical problem, a known contraindication to aspirin, or an indication for anticoagulant treatment.

The institutional review board at each participating centre approved the study, and participants provided written informed consent. A data safety and monitoring board provided oversight.

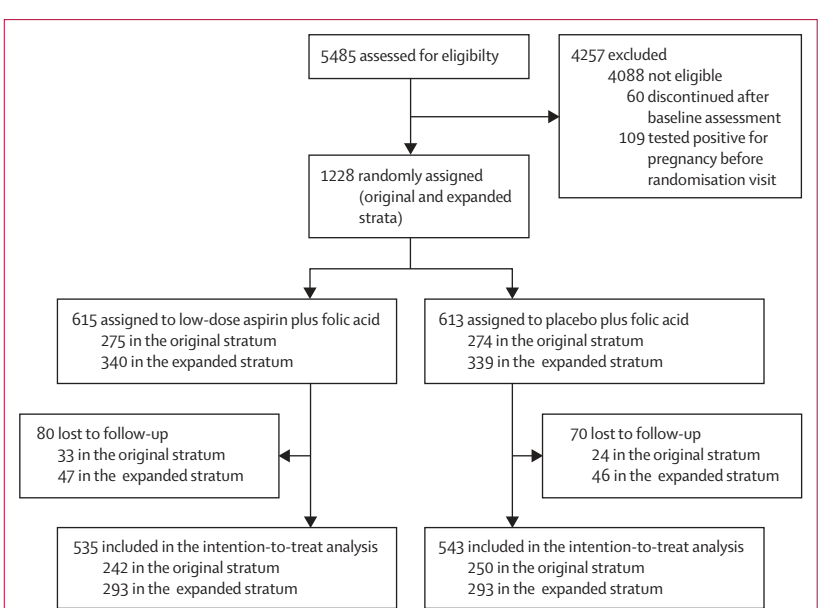

Figure 1: **Trial profile**

Randomisation and masking

Participants were randomly assigned in a 1:1 ratio to low-dose aspirin or placebo by study coordinators at each centre according to a computerised randomisation algorithm. The algorithm was developed by the study data coordinating centre and based on a permuted-block design, with block lengths of six or eight within each eligibility stratum (original and expanded) and centre. Participants, trial staff, and investigators were masked to the assigned treatment throughout the trial.

Procedures

Women received daily low-dose aspirin (81 mg [standard low dose in the USA]) plus 400 µg folic acid or placebo plus 400 µg folic acid. Study tablets (aspirin and placebo) were manufactured to be identical in appearance and weight, with folic acid given separately as a supplement. Study tablets were taken daily until completion of six menstrual cycles while attempting pregnancy, or until 36 weeks' gestation for those who became pregnant (up to roughly 60 weeks).

Study visits took place every 2 weeks for the first 2 months, and were monthly thereafter. Adherence was self-reported daily and assessed by weighing of drug bottles at each study visit. Participants provided urine and blood samples and completed questionnaires at each study visit. Baseline questionnaires elicited demographic data and information about reproductive history and health behaviours, and follow-up questionnaires assessed safety and pregnancy events during the trial. All adverse events were reported directly to study staff by participants or through the questionnaires, which were reviewed by the adverse events committee. When indicated, participant medical records for the reported event were reviewed by the adverse events committee, which was masked to the assigned treatment. Participants in both treatment groups used fertility monitors (Clearblue Easy Fertility Monitor, Inverness Medical Innovations, Waltham, MA, USA) after receiving standard training to assist with the timing of intercourse. The study protocol has been reported previously.[16]

Pregnancy was initially verified by a clinic urine pregnancy test and then confirmed by ultrasound at 6–7 weeks' gestation. If evidence of pregnancy was not apparent on ultrasound after a positive pregnancy test,

the case was classified as a periconception 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 periconception losses. Participants who became pregnant were followed monthly until the pregnancy ended.

Outcome measures

The primary outcome was livebirth. Secondary outcomes were implantation (positive urine pregnancy test), confirmed pregnancy (gestational sac on ultrasound, clinical recording of fetal heart tones, or a later-stage confirmation of pregnancy), pregnancy loss (<20 weeks' gestation, after confirmation of pregnancy), birthweight, and serious obstetric complications (pre-eclampsia, gestational diabetes, gestational hypertension, or preterm birth [<37 weeks' gestation]). These outcomes were obtained prospectively by maternal report and abstraction from medical records by trained staff. Gestational age was estimated from the early study ultrasound at 6–7 weeks' gestation. For participants with a pregnancy loss before the early ultrasound, gestational age was defined as the number of days between detection of ovulation by the fertility monitor and the date of the loss, plus 14 days.

Statistical analysis

The study was initially designed to detect a 10% absolute difference in livebirth rate with 80% power and a type I error rate of 5%, on the assumption that participants taking placebo who achieved pregnancy would have a livebirth rate of 75%.[16] Therefore, a sample size of 1254 was needed, on the basis of an assumed 40% pregnancy rate over 6 months of attempting. To account for a potential 20% loss to follow-up, the recruitment target was 1600 participants. Additional power calculations, done before the start of the study, incorporated the probability of conception over six cycles to obtain unconditional livebirth probabilities. These calculations confirmed that 1600 recruited participants would provide power of more than 80% to detect a 10% increase in livebirths from low-dose aspirin.

Analyses were based on the intention-to-treat principle (excluding participants lost to follow-up), with outcomes in the two groups compared by use of Fisher's exact and Student's *t* tests. SAS version 9.3 (SAS Institute, Cary, NC,

	Low-dose aspirin (n=615)	Placebo (n=613)
Age (years)	28·8 (4·9)	28·7 (4·7)
Race		
White	576 (94%)	586 (96%)
Non-white	39 (6%)	27 (4%)
Marital status		
Married	575 (94%)	549 (90%)
Living with partner	31 (5%)	43 (7%)
Other	9 (1%)	21 (3%)
Education		
Beyond high school	526 (86%)	531 (87%)
Up to high school	88 (14%)	82 (13%)
Missing data	1 (<1%)	0
Annual household income (US$)		
≥$100 000	241 (39%)	250 (41%)
$75 000–99 999	84 (14%)	65 (11%)
$40 000–74 999	91 (15%)	90 (14%)
$20 000–39 999	147 (24%)	165 (27%)
≤$19 999	51 (8%)	43 (7%)
Missing data	1 (<1%)	0
Employment		
Employed	451 (73%)	444 (72%)
Unemployed	142 (23%)	147 (24%)
Missing data	22 (4%)	22 (4%)
Time from last pregnancy loss to random assignment (months)		
≤4 months	331 (54%)	320 (52%)
5–8 months	103 (17%)	119 (20%)
9–12 months	50 (8%)	49 (8%)
>12 months	119 (19%)	118 (19%)
Missing data	12 (2%)	7 (1%)
(Continues in next column)		
(Continued from previous column)		
Number of previous pregnancies, not including losses		
0	263 (43%)	263 (43%)
1	212 (34%)	221 (36%)
2	127 (21%)	120 (20%)
3	13 (2%)	9 (1%)
Number of previous livebirths		
0	283 (46%)	288 (47%)
1	222 (36%)	222 (36%)
2	111 (18%)	103 (17%)
Number of previous pregnancy losses		
1	422 (69%)	403 (66%)
2	193 (31%)	210 (34%)
BMI (kg/m²)	26·3 (6·8)	26·5 (6·4)
Smoking in past year		
Never	529 (86%)	538 (88%)
Fewer than six times per week	41 (7%)	46 (7%)
Daily	38 (6%)	25 (4%)
Missing data	7 (1%)	4 (1%)
Alcohol consumption in past year		
Often	18 (3%)	8 (1%)
Sometimes	187 (30%)	193 (31%)
Never	398 (65%)	408 (67%)
Missing data	12 (2%)	4 (1%)

Data are n (%) or mean (SD). BMI=body-mass index.

***Table 1*: Demographic and baseline characteristics**

USA) was used for all statistical analyses. Analyses were done for the entire population as well as stratified by the two eligibility strata (original and expanded). An exploratory analysis was done to assess potential differences between treatment groups at different stages of the reproductive process. A sensitivity analysis was used to assess the effect of early participant withdrawal from the trial on the outcome of livebirth.

This trial is registered with ClinicalTrials.gov, number NCT00467363.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The data coordinating centre, led by NG and DF, had full access to the data throughout the trial, and did analyses as requested by the data safety monitoring board. On trial completion, the investigators employed by the funder (EFS, NJP, and SLM) and the data coordinating centre investigators (NG and DF) had full access to all study data. The corresponding author had the final responsibility for the decision to submit for publication.

Results

1228 women were recruited and randomly assigned in blocks (by centre and eligibility stratum) between June 15, 2007, and July 15, 2011. 1078 participants completed the study and were included in the analysis (figure 1). Treatment groups were similar with respect to the assessed demographic and baseline characteristics (table 1).

Among all trial participants, the treatment groups did not differ significantly with respect to the primary outcome of livebirth rate, although a significant difference was seen in the original stratum (table 2). Table 3 shows the results for the secondary outcomes. More women receiving low-dose aspirin had positive urine hCG pregnancy tests than those taking placebo, both in the original stratum and in both strata combined. The number of ultrasound-confirmed pregnancies was also higher in the low-dose aspirin group than in the placebo group, for both the original stratum and both strata combined, although no significant difference was seen in the expanded stratum alone. No significant differences were seen between treatment groups in either stratum for pregnancy complications that occurred after implantation, including pregnancy loss (table 3). The differences in livebirths by

	Low-dose aspirin	Placebo	Relative risk (95% CI)	Absolute difference in livebirth rate (95% CI)	p value
Overall					
Participants	535	543	..	..	..
Livebirths	309 (58%)	286 (53%)	1·10 (0·98 to 1·22)	5·09 (−0·84 to 11·02)	0·0984
Original stratum					
Participants	242	250	..	..	..
Livebirths	151 (62%)	133 (53%)	1·17 (1·01 to 1·37)	9·20 (0·51 to 17·89)	0·0446
Expansion stratum					
Participants	293	293	..	..	..
Livebirths	158 (54%)	153 (52%)	1·03 (0·89 to 1·20)	1·71 (−6·37 to 9·79)	0·7406

Data are n or n (%), unless otherwise indicated.

Table 2: **Primary outcome**

	Total (n=1078)	Overall				Original stratum				Expanded stratum			
		Low-dose aspirin (n=535)	Placebo (n=543)	Relative risk (95% CI)	p value*	Low-dose aspirin (n=242)	Placebo (n=250)	Relative risk (95% CI)	p value*	Low-dose aspirin (n=293)	Placebo (n=293)	Relative risk (95% CI)	p value*
hCG-positive pregnancy test	757 (70%)	394 (74%)	363 (67%)	1·10 (1·02 to 1·19)	0·0165	189 (78%)	166 (66%)	1·18 (1·05 to 1·31)	0·0048	205 (70%)	197 (67%)	1·04 (0·93 to 1·16)	0·5333
Ultrasound-confirmed pregnancy	720 (67%)	374 (70%)	346 (64%)	1·10 (1·01 to 1·19)	0·0329	180 (74%)	159 (64%)	1·17 (1·04 to 1·32)	0·0113	194 (66%)	187 (64%)	1·04 (0·92 to 1·17)	0·6033
Pregnancy loss	133 (12%)	68 (13%)	65 (12%)	1·06 (0·77 to 1·46)	0·7812	30 (12%)	28 (11%)	1·11 (0·68 to 1·80)	0·7800	38 (13%)	37 (13%)	1·03 (0·67 to 1·57)	1·0000
Preterm birth	53 (5%)	22 (4%)	31 (6%)	0·72 (0·42 to 1·23)	0·2603	7 (3%)	16 (6%)	0·45 (0·19 to 1·08)	0·0865	15 (5%)	15 (5%)	1·00 (0·50 to 2·01)	1·0000
Gestational hypertension	1 (<1%)	0	1 (<1%)	NA	1·0000	0	0	NA	1·0000	0	1 (<1%)	NA	1·0000
Gestational diabetes	22 (2%)	11 (2%)	11 (2%)	1·01 (0·44 to 2·32)	1·0000	2 (1%)	3 (1%)	0·69 (0·12 to 4·09)	1·0000	9 (3%)	8 (3%)	1·13 (0·44 to 2·88)	1·0000
Pre-eclampsia	62 (6%)	32 (6%)	30 (6%)	1·08 (0·67 to 1·76)	0·7943	16 (7%)	20 (8%)	0·83 (0·44 to 1·56)	0·6059	16 (5%)	10 (3%)	1·60 (0·74 to 3·47)	0·3159
Birthweight (g)	3321 (535)	3327 (521)	3315 (550)	12 (−74 to 99)†	0·7802	3318 (531)	3341 (553)	23 (−104 to 150)†	0·7189	3336 (512)	3292 (549)	44 (−75 to 163)†	0·4657
Gestational age at birth (weeks)	38·8 (1·9)	38·8 (2·0)	38·8 (1·8)	0·0 (−0·3 to 0·3)†	0·9647	39·0 (2·0)	38·9 (1·8)	0·1 (−0·3 to 0·6)†	0·6106	38·6 (2·0)	38·7 (1·8)	0·1 (−0·9 to 0·5)†	0·6298

Data are n (%) or mean (SD), unless otherwise indicated. *Fisher's exact test. †Mean difference (95% CI).

Table 3: **Secondary outcomes**

treatment group in the original stratum were due to differences in pregnancy rates (whether based on a positive pregnancy test or confirmed pregnancy) rather than any outcome conditional on pregnancy (ie, early pregnancy losses, stillbirths, etc; figure 2).

Safety symptoms were assessed via questionnaire and results were similar for the two treatment groups (table 4). Staff-documented case report forms of serious adverse events were continuously monitored by a physicians' committee of investigators and by the data safety and monitoring board. No major birth defects were reported, and no difference was seen in the proportion of minor birth defects between the groups (four in each group). Of the four birth defects in the low-dose aspirin group, one was a cleft lip and three were ventricular septal defects, which is one of the most common fetal malformations in the general population. One case of transient pulmonary hypertension occurred in an infant in the low-dose asprin group. Three cases of neonatal death occurred; of the two deaths in the low-dose aspirin group, one was due to cervical insufficiency and the other was attributed to chronic vaginal bleeding, chorioamnionitis, and preterm birth. The committee also vetted the case report forms of minor adverse events, reporting that vaginal bleeding was more common in women who received low-dose aspirin (n=24 women) than in those given placebo (n=8 women; p=0·0038). However, the rate of pregnancy loss was not raised in women taking low-dose aspirin who experienced bleeding.

1212 women completed the adherence questionnaire after the first menstrual cycle during follow-up, with 606 in each treatment group. Self-reported adherence to treatment assignment was similar between groups. 93 (15%) of women in the low-dose aspirin group permanently stopped taking the study drug, compared with 79 (13%) in the placebo group. Similarly, 34 (6%) women assigned to low-dose aspirin temporarily stopped taking the study drug, compared with 48 (8%) who stopped taking placebo. Weighing of drug bottles suggested similar rates of adherence (data not shown).

A sensitivity analysis done in the original stratum suggested that low-dose aspirin would have been associated with a significant increase in livebirth rate for all reasonable assumptions about potential livebirth rates in the participants who withdrew early from each treatment group (data not shown).

Discussion

Overall, preconception-initiated treatment with low-dose aspirin was not significantly associated with livebirth rates, pregnancy loss, or other pregnancy complications. To our knowledge, this is the first study to show that preconception-initiated low-dose aspirin does not decrease the risk of pregnancy loss in women without a history of recurrent pregnancy loss (ie, only one to two previous losses). Thus, our data do not support the

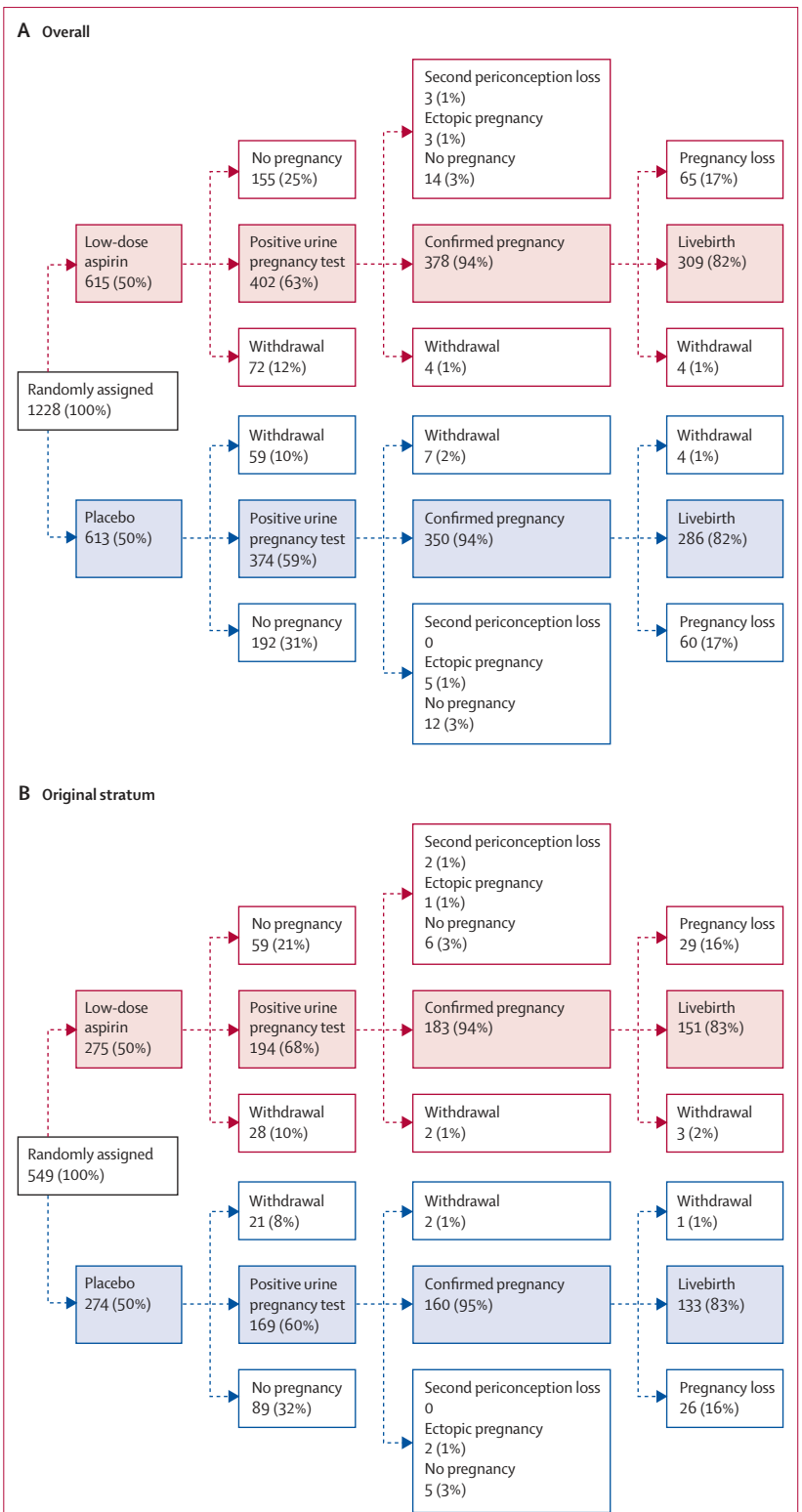

Figure 2: **Probabilities of transition between various intermediate and final outcomes in the trial for (A) the overall study population and (B) the original eligibility stratum only**
Data are n (%) for various outcomes, with percentages corresponding to conditional probabilities of transition from one outcome or stage to the next.

	Total (n=1228)	Overall			Original stratum			Expanded stratum		
		Low-dose aspirin (n=615)	Placebo (n=613)	Relative risk (95% CI)	Low-dose aspirin (n=275)	Placebo (n=274)	Relative risk (95% CI)	Low-dose aspirin (n=340)	Placebo (n=339)	Relative risk (95% CI)
Gastrointestinal discomfort	798 (65%)	407 (66%)	391 (64%)	1·04 (0·96 to 1·13)	193 (70%)	173 (63%)	1·11 (0·99 to 1·25)	214 (63%)	218 (64%)	0·98 (0·87 to 1·10)
Unusual bleeding	441 (36%)	236 (38%)	205 (33%)	1·15 (0·99 to 1·33)	100 (36%)	94 (34%)	1·06 (0·85 to 1·33)	136 (40%)	111 (33%)	1·22 (1·00 to 1·49)
Allergic reaction	48 (4%)	26 (4%)	22 (4%)	1·18 (0·68 to 2·06)	12 (4%)	11 (4%)	1·09 (0·49 to 2·42)	14 (4%)	11 (3%)	1·27 (0·58 to 2·76)
Unusual rashes	111 (9%)	60 (10%)	51 (8%)	1·17 (0·82 to 1·67)	25 (9%)	23 (8%)	1·08 (0·63to 1·86)	35 (10%)	28 (8%)	1·25 (0·78 to 2·00)
Swelling	135 (11%)	75 (12%)	60 (10%)	1·25 (0·90 to 1·72)	30 (11%)	30 (11%)	1·00 (0·62 to 1·61)	45 (13%)	30 (9%)	1·50 (0·97 to 2·31)

Data are n (%), unless otherwise indicated. Women were counted if they have reported the symptom at least once during follow-up.

Table 4: **Self-reported symptoms**

Panel: Research in context

Systematic review

Aspirin has been used to treat various reproductive outcomes. Relevant to our work in this trial, we assessed the scientific literature with respect to the use of aspirin to prevent pregnancy loss in women with recurrent pregnancy loss (ie, more than two losses) both with and without antiphospholipid syndrome, and preconception treatment for women undergoing in-vitro fertilisation (IVF). Although a systematic review[9] reported in 2012 (including 13 studies and 849 participants) showed that combined unfractionated heparin and aspirin treatment reduced pregnancy loss by 54% in women with recurrent pregnancy loss associated with antiphospholipid antibodies, similar results were not seen in women without antiphospholipid syndrome.[7] Studies in women with a history of at least two miscarriages and without antiphospholipid syndrome were summarised in a systematic review[7] reported in 2009 (including two studies and 189 participants), which did not show a benefit from aspirin treatment. Because only one of the two included studies was placebo-controlled, the reviewers called for large, randomised, placebo-controlled trials to be done. In IVF populations, a systematic review and meta-analysis[17] reported in 2011 (including 13 trials and 2653 participants) showed no significant differences between livebirth rates, clinical pregnancy rates, or miscarriage rates in women treated with aspirin compared with placebo. Results from a meta-analysis of individual patient data (1119 participants) also showed no effects of aspirin on clinical or ongoing pregnancy rates.[18] However, a systematic review[19] with less stringent quality criteria (including 17 studies and 6403 participants) showed that aspirin increased pregnancy rates in IVF patients, although it had no effect on livebirth rates. We searched PubMed and the Cochrane Library for any additional original articles or systematic reviews reported since these previous reviews up to Sept 18, 2013, using the terms "aspirin", "miscarriage", "pregnancy loss", and "pregnancy". We did not identify any relevant studies done in populations without a history of recurrent pregnancy loss (only one to two losses) and without antiphospholipid syndrome.

Interpretation

Preconception-initiated treatment with low-dose aspirin does not increase the rate of livebirth or reduce the rate of pregnancy loss in women with a history of one to two previous pregnancy losses. However, it might increase pregnancy rates in women with a single recent loss. Our results do not support the use of low-dose aspirin to decrease the risk of pregnancy loss. Further research should be done to investigate the potential effects of low-dose aspirin on fecundity and implantation.

general use of low-dose aspirin to decrease the risk of pregnancy loss (panel).

Our results are consistent with findings from several trials in women with recurrent losses (ie, two or more losses) who started aspirin treatment after conception, which showed no benefit of low-dose aspirin for the prevention of pregnancy loss.[7] Low-dose aspirin combined with heparin confers some benefit to a subset of women with recurrent pregnancy loss due to antiphospholipid syndrome.[20–23] One small trial[6] (n=364 participants) assessed the reproductive effects of low-dose aspirin, low-dose aspirin plus heparin, or placebo on recurrent pregnancy loss, with 94 (26%) of the couples recruited before conception.[6] The results showed no benefit from either treatment regimen compared with placebo. A possible explanation for these negative findings could be the late initiation of low-dose aspirin treatment in pregnancy. Since placentation and organogenesis occur very early in pregnancy, post-conception initiation of low-dose aspirin might miss the crucial window for positive intervention, emphasising the need for preconception trials.

A study population that has been consistently assessed before conception is patients undergoing IVF. Two meta-analyses[17,18] showed that low-dose aspirin had no significant effect on the clinical pregnancy rate (risk ratio 1·03, 95% CI 0·91–1·17) or livebirth rate (0·91, 0·72–1·15) in women undergoing IVF. Results of a systematic review[19] with less stringent quality criteria than these meta-analyses showed that although pregnancy rates were increased with low-dose aspirin (odds ratio 1·19, 1·01–1·39), livebirth rates were not affected (1·08, 0·82–1·68). Our study is the first to show that low-dose aspirin does not decrease pregnancy loss when started before conception in women with a history of only one to two previous pregnancy losses. Low-dose aspirin alone has therefore not been shown to reduce pregnancy loss in any population.

In our trial, low-dose aspirin was associated with an increase in livebirth rate in women with a single, well documented pregnancy loss before 20 weeks' gestation during the previous year (ie, the original stratum). The effect could not be attributed to a lower pregnancy loss rate and was probably due to increased conception or implantation rates in women treated with low-dose aspirin. Furthermore, in the overall study population (ie, both strata combined), low-dose aspirin was associated

with an increased rate of positive urine pregnancy tests. This effect was more pronounced in the original stratum, and not detectable in the expanded stratum alone. These data suggest that low-dose aspirin might have a favourable effect on fecundity or implantation for a subgroup of women, which is consistent with findings from some IVF studies, which have shown effects on implantation,[15] but not livebirth rates.[19]

The EAGeR trial differs from previous studies in several important ways. First, our study population did not have a history of recurrent pregnancy loss, but consisted of women with only one or two previous losses, most of which had occurred in the recent past. Women who have had several pregnancy losses probably have different underlying pathological features from those with only one or two previous losses. Second, low-dose aspirin was started before conception, which could affect important early pregnancy events such as placentation, vascularisation, and organogenesis. Previously, preconception-initiated low-dose aspirin has only been assessed in a much smaller study[6] of non-IVF patients with recurrent pregnancy loss. Third, women in our study were block-randomised by eligibility stratum. This approach enabled assessment of the effect of low-dose aspirin on pregnancy outcomes in a more homogeneous group with very strict eligibility criteria (original stratum), as well as a more heterogeneous group, which more closely resembles the general population of women attempting pregnancy (expanded stratum).

Notably, the original stratum included the most reproductively healthy women, who were the least likely to be infertile or have a condition predisposing them to recurrent pregnancy loss. The fact that low-dose aspirin had a significant effect on positive urine pregnancy tests for both strata combined lends support to the notion that low-dose aspirin could have favourable effects on fecundity in women with one to two previous losses. However, the finding of a significant effect on our primary outcome in only one stratum, and the fact that a positive urine pregnancy test was a secondary outcome, should prompt caution. Our results should be regarded as hypothesis-generating and do not allow for definitive conclusions. They do not justify the use of low-dose aspirin to increase fecundity in similar women in the absence of further studies.

Importantly, our study showed that low-dose aspirin was not associated with an increase in major adverse events, either in pregnant women or in their fetuses and newborn babies. Indeed, randomised clinical trials[24–26] with thousands of participants have shown no increase in adverse fetal sequelae in maternal doses of up to 150 mg per day.

Our study had several limitations. First, too few cases were seen 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 than average, so these results might not be applicable to women with lower socioeconomic status. Finally, 150 (12%) of 1228 women were lost to follow-up, which could be a potential source of bias. However, in view of the fact that loss to follow-up was similar between treatment groups, and based on the results of the sensitivity analysis, bias from loss to follow-up seems unlikely.

The 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 up with frequent scheduled study visits, the use of fertility monitors, and early ultrasound to precisely document pregnancy and pregnancy loss. Moreover, low-dose aspirin use was started before conception, setting this trial apart from most previous studies. Finally, the number of participants (even within the separate eligibility strata) was quite large compared with other studies.

In summary, daily low-dose aspirin started before conception was not associated with an increase in livebirths or a decrease in pregnancy loss in women with one to two previous losses. However, it was associated with an increased rate of positive urine pregnancy tests and a nearly 10% increase in livebirth rate in women with a single pregnancy loss at less than 20 weeks' gestation during the previous year. Because of the low cost, availability, and apparent safety of low-dose aspirin, these findings should prompt further investigation into its effects on fecundity and implantation. However, our data do not support the general use of low-dose aspirin to decrease pregnancy loss or increase livebirth rates.

Contributors

EFS conceived and designed the study. RMS, LLL, DF, JW-W, JMT, AML, NG, and NJP contributed to the study design, enrolment of patients, and interpretation of the data. NG, DF, EFS, NJP, and SLM analysed and contributed to the interpretation of the data. EFS, RMS, NG, NJP, and SLM drafted the report, and all authors edited and revised the report. All authors are responsible for the integrity of the data and accuracy of the analysis, and all approved the final report.

Declaration of interests

We declare that we have no competing interests.

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