Preconception low-dose aspirin increases the male-to-female sex ratio in a randomized trial among women with prior pregnancy loss

Supplementary Materials:

CONSORT Check list

Adverse events

Supplementary Table 1: Baseline characteristics by treatment assignment

CONSORT 2010 checklist of information to include when reporting a randomized trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomized trial in the title	**1**
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts[21 31])	**2**
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	**3**
	2b	Specific objectives or hypotheses	**3**
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	**11**
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	**11**
Participants	4a	Eligibility criteria for participants	**11**
	4b	Settings and locations where the data were collected	**11**
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	**11-12**
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	**12-13**
	6b	Any changes to trial outcomes after the trial commenced, with reasons	**N/A**
Sample size	7a	How sample size was determined	**15**
	7b	When applicable, explanation of any interim analyses and stopping guidelines	**N/A**
Randomization:			
Sequence generation	8a	Method used to generate the random allocation sequence	**11**
	8b	Type of randomization; details of any restriction (such as blocking and block size)	**11**
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until	**11**

Section/Topic	Item No	Checklist item	Reported on page No
		interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	**11**
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	**11**
	11b	If relevant, description of the similarity of interventions	**11**
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	**12-13**
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	**14-15**
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	**24**
	13b	For each group, losses and exclusions after randomization, together with reasons	**24**
Recruitment	14a	Dates defining the periods of recruitment and follow-up	**11**
	14b	Why the trial ended or was stopped	**12**
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	**Supplemental materials p.6**
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	**4, 11**
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	**4**
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	**25-27**
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	**5-6**

Section/Topic	Item No	Checklist item	Reported on page No
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[28])	**Supplementary Materials p.5**
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	**10**
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	**10**
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	**7-10**
Other information			
Registration	23	Registration number and name of trial registry	**11**
Protocol	24	Where the full trial protocol can be accessed, if available	**N/A**
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	**17**

Adverse events

A safety questionnaire elicited symptoms, which were similar between treatment groups (20). Serious adverse events were recorded on case report forms by study staff and reviewed by a committee physician investigators and by the Data Safety and Monitoring Board. Two neonatal deaths occurred in the low-dose aspirin group: one was due to cervical insufficiency, and the other was due to chronic vaginal bleeding, chorioamnionitis, and preterm birth. One neonatal death occurred in the placebo group. There were four cases of minor birth defects in each group, and no major birth defects. The minor birth defects in the low-dose aspirin group were either cleft lip (n=1) or ventricular septal defect (n=3), which is one of the most prevalent birth defects in the general population. Transient pulmonary hypertension occurred in one infant in the low-dose aspirin group. Case report forms of minor adverse events were also reviewed by the committee. Vaginal bleeding was more common in the low-dose aspirin group (n=24 *versus* n=8 among the placebo group, P=0.004). Women in the low-dose aspirin group who experienced bleeding did not have an increased risk of pregnancy loss.

REFERENCES

20. Schisterman, E.F., Silver, R.M., Lesher, L.L., Faraggi, D., Wactawski-Wende, J., Townsend, J.M., Lynch, A.M., Perkins, N.J., Mumford, S.L., and Galai, N. 2014. Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. *Lancet* 384:29-36.

Supplementary Table 1. Characteristics of 1,228 women by treatment assignment: EAGeR Trial, United States, 2006-2012.

	Low-dose aspirin (n=615)	Placebo (n=613)
Age (years)	28.8 (4.9)	28.7(4.7)
Race		
White	576 (94%)	584 (96%)
Non-white	39 (6%)	27 (4%)
Education		
>12 years	526 (86%)	531 (87%)
12 years	75 (12%)	70 (11%)
<12 years	13 (2%)	12 (2%)
Missing	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 (15%)
$20,000-39,999	147 (24%)	165 (27%)
≤$19,999	51 (8%)	43 (7%)
Missing	1 (<1%)	0
Employment		
Employed	451 (73%)	444 (72%)
Unemployed	142 (23%)	147 (24%)
Missing	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 (19%)
9-12 months	50 (8%)	49 (8%)
>12 months	119 (19%)	118 (19%)
Missing	12 (2%)	7 (1%)
Previous live births		
0	283 (46%)	288 (47%)
1	221 (36%)	222 (36%)
2	111 (18%)	103 (17%)
Previous pregnancy losses		
1	422 (69%)	403 (66%)
2	193 (31%)	210 (34%)
BMI (kg/m^2)	26.3 (6.8)	26.5 (6.4)

Supplementary Table 1 continued on next page…

Supplementary Table 1, continued…

	Low-dose aspirin (n=615)	Placebo (n=613)
Smoking in past year		
Daily	38 (6%)	25 (4%)
Occasional	41 (7%)	46 (8%)
Never	529 (86%)	538 (88%)
Missing	7 (1%)	4 (<1%)
Alcoholic drinks consumed in a typical occasion over past year:		
≥4	27 (4%)	34 (6%)
1-3	178 (29%)	167 (27%)
Non-drinker	398 (65%)	408 (67%)
Missing	12 (2%)	4 (<1%)
Outcome:		
Live-born boy	164 (27%)	128 (21%)
Live-born girl	145 (24%)	158 (26%)
Pregnancy[A] loss	85 (14%)	77 (13%)
Completed study without pregnancy[A]	141 (23%)	180 (29%)
Withdrew	80 (13%)	70 (11%)

[A] A pregnancy that was detected by urine hCG test.