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Metabolic syndrome and the effectiveness of low-dose aspirin on reproductive outcomes

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Abstract

Background: Metabolic syndrome is associated with increases in both inflammation and aspirin resistance, but effectiveness of aspirin in improving reproductive health among women with metabolic syndrome is unknown. We evaluated the effectiveness of low-dose aspirin in improving reproductive outcomes across metabolic syndrome score.

Methods: The EAGeR trial randomly assigned 1228 women with a history of pregnancy loss to receive 81 mg aspirin or placebo for up to six menstrual cycles of attempting pregnancy and, if they became pregnant, throughout pregnancy. We assessed components of metabolic syndrome at enrollment, including: waist circumference ≥88 cm, triglycerides ≥150 mg/dL, high-density lipoprotein ≤50 mg/dL, blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic, and glucose ≥100 mg/dL. We summed components to calculate metabolic syndrome score.

Results: A total of 229 participants (20%) met full criteria for metabolic syndrome, 207 (18%) had two components, 366 (31%) one component, and 372 (32%) no components. Among those without any component of metabolic syndrome, aspirin was associated with 10.7 (95% CI 1.2, 20.2) more pregnancies and 13.7 (95% CI 3.3, 24.0) more live births per 100 couples. Effects were attenuated as metabolic syndrome score increased and we observed no clear effect of aspirin on pregnancy or live birth among women with metabolic syndrome.

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Conclusions: Low-dose aspirin is most effective in increasing pregnancy and live birth among women with no or few components of metabolic syndrome. Reduced effectiveness among women with metabolic syndrome may be due to differences in effective dose or aspirin resistance.

Keywords

Aspirin; reproduction; pregnancy; pregnancy loss; metabolic syndrome

Introduction

There is increasing evidence that early cardiometabolic dysregulation, including insulin resistance, dyslipidemia, obesity and high blood pressure, may predispose women to adverse reproductive events.[1–3] Together, these markers of cardiometabolic dysregulation constitute the metabolic syndrome, which is robustly associated with long-term risk of cardiovascular disease[4] and more common among women with a history of adverse reproductive events.[5,6] Several factors associated with metabolic syndrome are hypothesized to impair reproduction, including increased burden of inflammation and oxidative stress. These mechanisms may lead to imbalances in the pro-oxidative state associated with successful follicular development and ovulation,[7] damage to endothelial tissue leading to impairment in placentation,[8] and an abnormal thrombotic response that has been observed among women with recurrent pregnancy loss.[9]

Because mechanisms related to inflammation and platelet aggregation may underlie some of the interindividual difference in adverse reproductive events,[10] aspirin has been evaluated as a potential therapeutic agent to restore impaired fecundity and reduce risk of pregnancy loss. Prior findings from the Effect of Aspirin on Gestation and Reproduction (EAGeR) trial, enrolling 1228 women attempting pregnancy with 1–2 prior pregnancy losses and no history of infertility, suggest that daily low-dose aspirin may improve chance of pregnancy and live birth among women with a single recent pregnancy loss.[11] Other randomized clinical trials evaluating aspirin and reproduction have reported inconsistent associations between aspirin and fecundability and pregnancy loss, although they have focused on women with recurrent pregnancy loss (3 or more prior losses)[12] or undergoing assisted reproduction.[13] Although findings are suggestive of a protective effect of aspirin on reproduction, conflicting findings across study populations and heterogeneity of potential pathologies underlying impaired reproductive health suggests effectiveness of aspirin may vary by underlying risk factors.

Since individuals with metabolic syndrome have greater total inflammation and enhanced platelet aggregation,[14] the anti-inflammatory and anti-platelet actions of aspirin[15] may be more efficacious in improving reproductive outcomes among affected women. Indeed, in the EAGeR trial, a stronger relationship of aspirin with fecundability was observed among women with higher c-reactive protein levels.[16] Conversely, individuals with metabolic conditions such as metabolic syndrome, type 2 diabetes, and obesity have a greater frequency of aspirin resistance,[14,17,18] including poorer inhibition of platelet cyclooxygenase 1 with aspirin therapy.[19] This potential modifying effect was also observed in the EAGeR trial, where aspirin appeared to be less effective in restoring fecundability among participants with a higher body mass index.[16] Given the relationship between obesity

and inflammation, these disparate findings for low-grade inflammation and the chronic inflammatory milieu that accompanies obesity begs further interrogation as to their relationship with effectiveness of aspirin therapy for reproductive health. As these factors are more broadly representative of cardiometabolic dysregulation, exploration of the spectrum of common markers of cardiometabolic dysregulation that fall under the umbrella of metabolic syndrome, including lipid dysregulation and elevated blood pressure, is important to help enlighten prior findings. We hypothesized that the effect of aspirin on reproductive outcomes would vary by metabolic syndrome and within levels of its components.

Methods

The EAGeR trial (2007–2011) was a randomized, placebo-controlled, double-blind trial of the efficacy of daily low-dose aspirin in improving fecundability and preventing pregnancy loss.[20] Women were eligible if they were actively attempting pregnancy and had a history of one or two prior pregnancy losses and no more than two live births. Women were excluded if they were less than 18 or greater than 40 years of age; had irregular menstrual cycles or regular cycles less than 21 or greater than 42 days; had a history of infertility or were receiving/planning infertility treatment; or had a major medical problem (including hypertension, hyperlipidemia and/or polycystic ovary syndrome), a known contraindication to aspirin or an indication for anticoagulant treatment. The institutional review boards at all participating institutions approved the study protocol and all participants provided informed consent prior to data collection. The trial was registered at clinicaltrials.gov, number NCT00467363.

Trial Design

Two to four days after the beginning of menses, participants were block-randomized in a 1:1 ratio to receive either daily 81 mg aspirin plus 400 μg folic acid or daily placebo plus folic acid. Randomization was completed using a computerized algorithm based on a permuted block design. Aspirin and placebo study tablets were manufactured to be identical in appearance and weight. Participants continued taking aspirin or placebo for up to six menstrual cycles of attempting pregnancy, and, for those who became pregnant, through 36 weeks' gestation. Adherence was both self-reported and assessed through study medication bottle weights. Participants, trial staff, and investigators remained blinded to the treatment assignment throughout the trial. At enrollment, participants completed demographic and medical history questionnaires, had anthropomorphic measures taken, and provided blood samples. Participants were instructed in the use of a fertility monitor (Clearblue Easy Fertility Monitor, Inverness Medical Innovations, Waltham, MA) to plan timing of study visits to specific days of the menstrual cycle.

Metabolic Syndrome Score

We calculated metabolic syndrome score based on the presence of five cardiometabolic components following the National Cholesterol Education Program Adult Treatment Panel III criteria for women: high waist circumference (≥88 cm), high circulating triglyceride level (≥150 mg/dL), low circulating high-density lipoprotein level (<50 mg/dL), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) and

high circulating glucose level (≥100 mg/dL).[21,22] Measures were collected between days 2–4 of the first menstrual cycle of follow-up. Metabolic syndrome score ranged from 0 (no components) to 5 (all components). Meeting full criteria for metabolic syndrome was defined as having three or more components.

Waist circumference and blood pressure were measured by trained study staff at enrollment. Two waist circumference measures were averaged to produce summary waist circumference and three systolic and diastolic blood pressure measures averaged to produce summary systolic and diastolic blood pressure. Triglycerides, high-density lipoprotein level, glucose, and high sensitivity c-reactive protein were measured in serum provided at enrollment and stored at −80°C. Participants were not required to fast at biospecimen collection (84% reported a meal within 8 hours). The Roche COBAS 6000 chemistry analyzer (Roche Diagnostic, Indianapolis, IN) was used to measure triglycerides, high-density lipoprotein, serum glucose, and high-sensitivity c-reactive protein. Triglycerides were analyzed using the GPO-Trinder methodology and high-density lipoprotein a modified direct enzymatic method. Inter-assay coefficients ranged from 1.6% to 3.2% at mean lipid concentrations for manufacturer controls. Serum glucose had a limit of detection of 2 mg/dL and inter-assay coefficient of 1.3% at 97.2 mg/dL and 1.8% at 223.3 mg/dL, and high-sensitivity c-reactive protein a limit of detection of 0.15 mg/L, with inter-assay coefficients of variation of 5.1% at 1.05 mg/L and 6.7% at 3.12 mg/L.

Reproductive outcomes

We assessed pregnancy at the end of each menstrual cycle with at-home and/or in-clinic human chorionic gonadotropin testing (Quidel Quickvue, Quidel Corporation, San Diego, CA, sensitive to 25 mIU/ml human chorionic gonadotropin). Additionally, β-human chorionic gonadotropin was assessed in stored first-morning urines collected during the last 10 days of the first two cycles and at all end of cycle visits to augment early pregnancy detection (catalogue no. 4221–16, Diagnostic Automation Inc, Calabasa, CA and catalogue no. R1S0011R, BioVendor, Asheville, NC). We assessed menstrual cycle-specific probability of pregnancy as time-to-pregnancy, the number of menstrual cycles from randomization to either positive pregnancy test or censoring. Pregnancy loss included both early losses and clinically recognized losses. Early losses were identified where a positive pregnancy test was followed by absence of clinical signs of pregnancy and clinical losses where a clinically confirmed pregnancy on ultrasound at approximately 6.5 weeks was followed by a participant- or clinician-observed loss.

Covariates

At enrollment, participants self-reported age, race, marital status, cigarette smoking, parity, time from last pregnancy to enrollment, number of prior pregnancy losses, and number of cycles attempting pregnancy prior to enrollment.

Statistical Analysis

Descriptive statistics were calculated as counts and percentages or means and standard deviations (SDs) and included only those with complete data on metabolic syndrome under a missing completely at random assumption for those analyses. Data was missing on

metabolic syndrome components for 54 participants (32 missing high-density lipoprotein and glucose, 22 triglycerides, 10 waist circumference and 8 blood pressure), and all participants had data on at least one component. We used multiple imputation using chained equations[23] to generate 20 imputed datasets to account for missing data using the following predictors in addition to the metabolic syndrome components: randomization to aspirin, study site, age, race/ethnicity, marital/partner status, smoking, c-reactive protein, number of prior losses, time since last loss and time attempting pregnancy prior to enrollment. Generalized linear models with an identity link and normal distribution with robust standard errors were used to estimate risk differences (RDs) and 95% confidence intervals (CIs) for the effect of aspirin versus placebo on risk of pregnancy, pregnancy loss, and live birth by metabolic syndrome status using the intention-to-treat approach. We assessed additive interactions with metabolic syndrome score, meeting full criteria for metabolic syndrome, and presence of each metabolic syndrome component by inclusion of an interaction term with low-dose aspirin. Analyses for pregnancy loss were restricted to women who became pregnant. To account for the potential to introduce selection bias by restricting the cohort to women who become pregnant post-randomization, models were weighted by the inverse probability of pregnancy within metabolic syndrome subgroups based on shared risk factors for pregnancy and pregnancy loss. Models for live birth included all participants who had complete data for follow-up (n=1088). We additionally evaluated ratio measures and multiplicative interactions of aspirin with metabolic syndrome score, meeting full criteria for metabolic syndrome and presence of each metabolic syndrome component. A log link and binomial distribution was used to calculate risk ratios (RR) and multiplicative interaction for pregnancy, pregnancy loss, and live birth.

We performed several secondary analyses to evaluate the robustness of our main findings. First, we compared models using a complete-case analysis to our main multiple imputation models. Second, because women were mostly non-fasting at sample collection, we conducted a secondary analysis excluding glucose in the calculation of metabolic syndrome score. Third, because effectiveness of aspirin was shown previously to vary by inflammation status,[16] we further evaluated heterogeneity across categories of high versus low high baseline c-reactive protein (≥2 vs. <2 mg/L) within each subgroup of metabolic syndrome and its components. Finally, in an alternate analysis evaluating pregnancy loss and live birth that included all participants enrolled in the study, we calculated menstrual cycle-specific odds of pregnancy and risk difference in pregnancy conditional on no pregnancy occurring in the prior cycle, and utilized a competing risks framework to calculate odds ratios and risk differences in the cycle-specific probability of a pregnancy ending in a loss (with a pregnancy ending in a live birth as a competing risk) and a pregnancy ending in a live birth (with a pregnancy ending in a loss as a competing risk) by metabolic syndrome score, meeting full criteria for metabolic syndrome and presence of each metabolic syndrome component. All analyses were conducted in SAS version 9.4 (Cary, NC).

Results

The majority of participants were white (95%) with some college education (86%) and a moderate to high household income (67% ≥$40,000/year). Mean age was 28.7 (SD 4.8) years (Table 1). Most (67%) had one prior pregnancy loss. Approximately half (53%) were

parous. A total of 229 (20%) met full criteria for metabolic syndrome (≥3 components), with 207 (18%) having two components, 366 (31%) one component, and 372 (32%) no components (Table 2). The most common component was low high-density lipoprotein (n=606, 52%), followed by high waist circumference (n=465, 40%), high triglycerides (n=280, 24%), high blood pressure (n=163, 14%) and high glucose (n=91, 8%). Among those with at least one component, the most common combinations were low high-density lipoprotein alone (n=209, 26%), low high-density lipoprotein and high waist circumference (n=117, 15%), low high-density lipoprotein with high waist circumference and high triglycerides (n=106, 13%), and high waist circumference alone (n=99, 12%). Participant demographics and health behaviors did not differ substantially by meeting criteria for metabolic syndrome except for smoking, which was more common among those with than without metabolic syndrome (8% versus 4%). A total of 797 (65%) achieved pregnancy, and, of those who became pregnant, 188 (24%) experienced a loss. Of the 1,088 participants with complete follow-up data, 597 (56%) had a live birth. Within strata of metabolic syndrome score and its components, proportion achieving a pregnancy ranged from 58% to 70%, proportion experiencing a loss from 17% to 29% and proportion with a live birth from 47% to 58% (eTable 1).

Among women with no components of metabolic syndrome, those randomized to aspirin had 10.7 more pregnancies per 100 couples attempting pregnancy than those randomized to placebo (95% CI 1.2, 20.2) (Table 3). Additionally, those randomized to aspirin had 13.7 more live births than those randomized to placebo (95% CI 3.3, 24.0), with no clear difference in number of pregnancies ending in a loss (RD −6.6, 95% CI −17.3, 4.1) (Table 3). As the number of metabolic syndrome components increased, the effect of aspirin on pregnancy and live birth moved towards the null. For example, among those who met full criteria for metabolic syndrome (three or more components), those randomized to aspirin had no clear differences in pregnancy (RD −0.036, 95% CI −0.155, 0.084, additive interaction p=0.07) or live birth (RD 0.003, 95% CI −0.133, 0.139, additive interaction p=0.13). Differences by metabolic syndrome score and meeting full criteria for metabolic syndrome were similar on the ratio scale, with aspirin associated with a 1.17-fold (95% CI 1.02, 1.34) higher chance of pregnancy and 1.27-fold (95% CI 1.06, 1.53) higher chance of live birth among those without any component of metabolic syndrome (eTable 2). Conversely, aspirin was not associated with pregnancy (RR 0.94, 95% CI 0.76, 1.17; additive interaction p=0.10) or live birth (RR 1.01, 95% CI 0.76, 1.34; additive interaction p=0.18) among those who met full criteria for metabolic syndrome. Similar trends were observed in the complete case analyses (eTables 3 and 4) and when excluding glucose (eTable 5).

When evaluating the effect of aspirin on reproductive outcomes by individual components of metabolic syndrome, we observed a similar trend of greater effectiveness of aspirin among those without each component. For example, among those with high-density lipoprotein >50 ng/mL, aspirin was associated with 4.6 (95% CI 1.1, 8.2) more pregnancies and 4.4 (95% CI 1.2, 7.6) more live births per 100 couples, whereas aspirin was not associated with pregnancy (additive interaction p=0.07) or live birth among those (0.018) with high-density lipoprotein <50 mg/dL. A similar trend of greater effectiveness of aspirin for pregnancy and live birth was observed for those with low triglycerides, low waist circumference, and low

blood pressure. The trend was reversed for glucose, although the strata with high glucose levels was small (n=91, 8%) and the majority (84%) of measures were non-fasting. Findings were similar on the ratio scale, with high-density lipoprotein >50 mg/dL associated with the highest chances of pregnancy (RR 1.14, 95% CI 1.02, 1.27; multiplicative interaction p=0.12) and live birth (RR 1.22, 95% CI 1.05, 1.41, multiplicative interaction p=0.07) (eTable 2). Triglycerides <150 mg/dL were similarly associated with the highest chances of pregnancy (RR 1.12, 95% CI 1.02, 1.23; multiplicative interaction p=0.037) and live birth (RR 1.14, 95% CI 1.01, 1.28; multiplicative interaction p=0.22. Similar findings were observed in the complete case analyses (eTables 3 and 4).

We further subdivided metabolic syndrome and its components by high versus low baseline c-reactive protein (≥2 vs. <2 mg/L), with all stratum having at least five events for each outcome (eTable 6). Within most categories of metabolic syndrome and its components, those with higher inflammation at enrollment (c-reactive protein ≥2 mg/L) benefited more from aspirin with respect to pregnancy and live birth than those with c-reactive protein <2 mg/L. Among those with c-reactive protein ≥2 mg/L and without any component of metabolic syndrome, aspirin was associated with 9.6 additional pregnancies (95% CI 0.6, 18.6), while for those with c-reactive protein <2 mg/L and without any component of metabolic syndrome, aspirin was associated with 4.3 additional pregnancies (95% CI −0.2, 8.9). However, the trend of greater magnitude of effect of aspirin on pregnancy and live birth among those with fewer metabolic syndrome components remained consistent for both high and low c-reactive protein. For example, among those with c-reactive protein ≥2 mg/L, aspirin was associated with 8.4 (95% CI −0.6, 17.3) more pregnancies among those with one component, 0.3 (−6.6, 7.3) more pregnancies among those with two components and −0.3 (95% CI −5.8, 5.1) more pregnancies among those with three or more components of metabolic syndrome.

Finally, in models calculating menstrual-cycle specific risk differences in pregnancy and pregnancies ending in a loss and live birth, similar patterns were observed for greater effectiveness of aspirin for pregnancy and a live birth among those without any component of metabolic syndrome. For those with no components (Table 4), aspirin was associated with 5.0 additional pregnancies (95% CI 0.7, 9.3) and 4.9 additional pregnancies ending in a live birth (95% CI 0.9, 8.8) per average contributed menstrual cycle, with no clear difference in pregnancies ending in a loss (RD 0.001, 95% CI −0.021, 0.024). Effectiveness of aspirin decreased with increasing number of metabolic syndrome components, with those meeting full criteria for metabolic syndrome having no clear effect of aspirin on pregnancy (RD −0.014, 95% CI −0.062, 0.033; additive interaction p=0.050) or pregnancy ending in a live birth (RD −0.012, 95% CI −0.053, 0.029; additive interaction p=0.036). Among individual metabolic syndrome components, aspirin appeared more efficacious among those with low waist circumference, high high-density lipoprotein and low triglycerides. Similar trends were observed for ratio measures (eTable 7).

Discussion

We observed that metabolic syndrome score and individual components of metabolic syndrome altered the effectiveness of preconception-initiated daily low-dose aspirin therapy

on pregnancy and live birth. Among those with no components of metabolic syndrome, aspirin was associated with a higher chance of both pregnancy and live birth. As number of metabolic syndrome components increased, the relationship between aspirin and pregnancy and live birth decreased, with no discernable effect of aspirin on pregnancy or live birth for those meeting full criteria for metabolic syndrome (three or more components). The results were consistent for individual components and when accounting for inflammatory status at enrollment. Findings suggest that aspirin may have greater effectiveness in increasing the chance of pregnancy and live birth among those with fewer risk factors for cardiometabolic disease, providing important context for understanding which patients may benefit most from aspirin therapy.

It is notable that we observed no clear effect of aspirin on pregnancy loss across metabolic syndrome and its components, consistent with overall findings in the EAGeR trial.[11] The increase in live birth appeared to be tied to increased pregnancy among those with fewer components of metabolic syndrome. This may be explained by the mechanisms through which aspirin inhibits inflammation and platelet reactivity. Aspirin non-reversibly binds to the enzyme cyclooxygenase 1 and to a lesser extent cyclooxygenase 2, which play a key role in production of prostaglandins, signaling a localized inflammatory response, and thromboxane A2, which signals formation of new platelets and platelet aggregation.[15] As inflammation may affect ovulation and endometrial receptivity[7,8] and an abnormal thrombotic response contributes to recurrent pregnancy loss,[9] inhibition of these processes by aspirin may improve fecundability. However, in the presence of the cardiometabolic dysregulation that underlies metabolic syndrome, aspirin may be less efficacious in inhibiting cyclooxygenase 1 pathways. For example, obesity has been observed to be associated with enhanced platelet activation, which may lead to greater platelet turnover and less bioavailability of aspirin.[14] Aspirin resistance is associated with markers of metabolic syndrome and occurs in almost half of metabolic syndrome patients.[24]

A similar trend has been observed for effectiveness of aspirin in reducing risk of cardiovascular disease in patients with metabolic syndrome. In a study of 135 men and postmenopausal women aged 40 or older with coronary artery disease prescribed 81 mg aspirin for a two week period, 12 of the 83 participants with metabolic syndrome (14%) had serum thromboxane B2 levels indicating inadequate inhibition of cyclooxygenase 1, while none of the 52 participants without metabolic syndrome demonstrated inadequate inhibition.[19] However, effectiveness of aspirin in reducing platelet reactivity among those with metabolic dysregulation may be improved by changing aspirin dose. For example, in a crossover study of 24 participants with type 2 diabetes, participants who received 100 mg of aspirin twice daily had lower platelet reactivity than those taking either 100 mg or 200 mg of aspirin once daily.[25] Whether aspirin resistance, differences in effective dose, or differing pathologies of impaired fecundity may explain the differences we observed in the effectiveness of aspirin by metabolic syndrome is an important point for further research.

To further explore the role of baseline inflammation in our analysis, we divided metabolic syndrome score by high versus low inflammation (≥2 vs. <2 mg/L c-reactive protein) and observed that while aspirin was more strongly associated with pregnancy and live birth among those with higher inflammation, the trend of greater aspirin effectiveness with fewer

metabolic syndrome components was consistent whether inflammation was high or low. These disparate findings for low-grade inflammation and the chronic inflammatory milieu associated with metabolic syndrome may suggest that differing etiologies underlying inflammation could have differing impacts on reproductive outcomes and the effectiveness of aspirin therapy.

We used several approaches to evaluate potential sources of bias in our analyses. We evaluated effect modification on both the additive and multiplicative scales and observed similar trends. To account for missing data on metabolic syndrome components, we utilized multiple imputation to retain all participants in analysis and compared imputed findings to those from a complete case approach. The consistency in effect estimates across approaches suggests that missing data was unlikely to have substantively influenced our findings. We additionally addressed loss-to-follow up and subsequent potential selection bias in several ways. We utilized inverse-probability weighting in our analyses of overall risk of pregnancy loss to account for exclusion of participants who did not become pregnant. In a secondary analysis, we utilized a discrete-time survival approach to calculate menstrual-cycle specific probabilities of pregnancy and pregnancies ending in a loss or live birth, which allowed for censoring of participants who were lost to follow-up prior to conception and the appropriate handling of pregnancy loss and live birth as competing risks. The consistency of findings across multiple approaches adds to confidence in their robustness.

Our study has several strengths and limitations. Because the EAGeR trial enrolled participants prior to conception, we were able to evaluate the relationship between metabolic syndrome and pregnancy prospectively. However, enrollment blood samples were non-fasting, leading to imprecision in the estimation of glucose and triglycerides, which may have limited our ability to detect differences across these components. Despite this, the smaller number of participants meeting criteria for elevated glucose and similar prevalence of metabolic syndrome to national data suggests that the use of non-fasting measures likely did not have a marked effect on our findings.[26] A strength of our study is the exclusion of women with pre-existing chronic health conditions, allowing for an investigation of metabolic syndrome in a population not under clinical care for cardiometabolic disease. However, due to this exclusion our findings may not apply to women with pre-existing chronic health conditions, and the effectiveness of aspirin in this population remains an important area for future research. Additionally, although women with polycystic ovary syndrome were excluded at enrollment, it is possible that women were enrolled with undiagnosed polycystic ovary syndrome or a subclinical polycystic ovary-like phenotype, although this is unlikely to affect the strong observed trend across metabolic syndrome components. Finally, because all participants had a history of one to two prior pregnancy losses and the study cohort was largely non-Hispanic white and of moderate-to-high socioeconomic position, findings should be generalized with caution to other groups.

While differences in the inhibition of cyclooxygenase-1 by aspirin across metabolic syndrome has been demonstrated in studies targeting cardiovascular risk prevention, our study underscores the need for further study of effective dosage and dose frequency for aspirin to optimize effectiveness for improving reproductive outcomes. These findings support prior research suggesting that aspirin may be efficacious in ameliorating pathways

associated with impaired fecundability, with robust associations observed among women with no risk factors for metabolic disease who make up a large proportion of those attempting pregnancy. Our observation that aspirin may be less efficacious among women at higher risk for cardiometabolic disease warrants more research to determine the mechanisms underlying these differences and whether additional intervention strategies (e.g. higher dosage or alternate/combination therapy) may be more efficacious among those with metabolic syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Participant characteristics by metabolic syndrome, the EAGeR Trial (2007–2011) (n=1174)[a]

	Metabolic syndrome (score ≥3)[b] n=229		No metabolic syndrome (score <3)[b] n=945	
Race (n, %)				
White	220	96	893	94
Non-white	9	4	52	6
Education (n, %)				
<high school	5	2	18	2
High school	29	13	108	11
>high school	195	85	818	87
Income (n, %)				
<$40,000	89	39	303	32
$40,000-<$100,000	51	22	262	28
≥$100,000	89	39	379	40
Partner status (n, %)				
Married	203	89	873	92
Living with partner	20	9	50	5
Other	6	3	22	2
Smoking (n, %)				
Yes	18	8	38	4
No	211	92	907	96
Parous (n, %)				
Yes	127	55	498	53
No	102	45	447	47
Number of prior losses (n, %)				
1	144	63	645	68
2	85	37	300	32
Time since last loss (n, %)				
<4 months	116	51	500	53
4-<8 months	36	16	169	18

	Metabolic syndrome (score ≥3)[b] n=229		No metabolic syndrome (score <3)[b] n=945	
8-<12 months	26	11	77	8
≥12 months	46	20	185	20
Treatment assignment (n, %)				
Low-dose aspirin	106	46	489	52
Placebo	123	54	456	48
Age (years; mean [SD])	28.8	5.0	28.7	4.8
Body mass index (kg/m^2; mean [SD])	33.2	6.6	24.5	5.0
Waist circumference (cm; mean, SD)	104.4	13.0	82.6	12.3
Triglycerides (mg/dL; mean, SD)	200.0	87.9	99.4	44.8
High-density lipoprotein (mg/dL; mean, SD)	39.5	7.3	53.6	11.8
Systolic blood pressure (mmHg; mean, SD)	122.0	12.4	109.0	10.6
Diastolic blood pressure (mmHg; mean, SD)	80.1	9.3	70.6	8.4
Glucose (mg/dL; mean, SD)	87.8	15.1	80.0	12.4

[a]Table excludes 54 women who were missing one or more component of metabolic syndrome

[b]Metabolic syndrome score = waist circumference ≥88 cm + triglycerides ≥150 mg/dL + high-density lipoprotein ≥50 mg/dL + (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) + glucose ≥100 mg/dL

Table 2.

Distribution of metabolic syndrome components: cross-tabulation with metabolic syndrome score (n=1174)[a]

	Number of metabolic syndrome components			
	None (n=372)	One (n=366)	Two (n=207)	Three or more (n=229)
	n (row %)	n (row %)	n (row %)	n (row %)
Waist circumference				
≥88 cm	0	93 (21)	135 (30)	218 (49)
<88 cm	372 (51)	273 (38)	72 (10)	11 (2)
Triglycerides				
≥150 mg/dL	0	23 (9)	67 (25)	178 (66)
<150 mg/dL	372 (41)	343 (38)	140 (15)	51 (6)
High-density lipoprotein				
<50 mg/dL	0	202 (34)	171 (29)	222 (37)
≥50 mg/dL	372 (64)	164 (28)	36 (6)	7 (1)
Blood pressure				
≥130 mmHg systolic or ≥85 mmHg diastolic	0	21 (13)	26 (17)	110 (70)
<130 mmHg systolic and <85 mmHg diastolic	372 (37)	345 (34)	181 (18)	119 (12)
Glucose				
≥100 mg/dL	0	27 (30)	15 (17)	48 (53)
<100 mg/dL	372 (34)	339 (31)	192 (18)	181 (17)

[a]Table excludes 54 women who were missing one or more component of metabolic syndrome

Table 3.

Low-dose aspirin and risk differences (RD) relative to placebo per 100 couples attempting pregnancy for pregnancy, pregnancy loss and live birth by metabolic syndrome, metabolic syndrome score and metabolic syndrome components

	Pregnancy			Pregnancy loss[a]			Live birth		
	RD	95% CI	p-int[b]	RD	95% CI	p-int[b]	RD	95% CI	p-int[b]
Metabolic syndrome score									
0	10.7	(1.2, 20.2)		−6.6	(−17.3, 4.1)		13.7	(3.3, 24.0)	
1	3.9	(−5.7, 13.5)	0.33	0.1	(−10.8, 11.0)	0.39	2.0	(−8.6, 12.6)	0.12
2	−0.2	(−13.0, 12.6)	0.18	−1.4	(−16.1, 13.2)	0.58	−1.1	(−15.7, 13.4)	0.10
3+	−3.6	(−15.5, 8.4)	0.07	2.2	(−11.4, 15.9)	0.32	0.3	(−13.3, 13.9)	0.13
Metabolic syndrome									
No	5.7	(−0.2, 11.7)		−2.7	(−9.4, 4.0)		6.0	(−0.6, 12.6)	
Yes	−3.6	(−15.6, 8.5)	0.18	2.2	(−11.5, 15.9)	0.53	0.3	(−13.3, 13.9)	0.46
Waist circumference									
<88 cm	5.7	(−1.0, 12.5)		−1.0	(−8.6, 6.6)		6.8	(−0.6, 14.3)	
≥88 cm	−0.05	(−8.7, 8.6)	0.30	−3.1	(−13.1, 7.0)	0.75	1.7	(−8.1, 11.4)	0.41
High-density lipoprotein									
>50 mg/dL	8.9	(1.3, 16.6)		−5.3	(−13.9, 3.2)		11.1	(2.7, 19.5)	
≤50 mg/dL	−0.2	(−7.7, 7.3)	0.10	1.7	(−6.8, 10.3)	0.25	−0.5	(−8.9, 7.9)	0.06
Triglycerides									
<150 mg/dL	7.3	(1.2, 13.4)		−3.6	(−10.5, 3.3)		7.1	(0.4, 13.8)	
≥150 mg/dL	−6.9	(−18.0, 4.2)	0.028	4.7	(−7.8, 17.2)	0.25	−2.5	(−15.0, 10.0)	0.19
Blood pressure									
<130 mmHg systolic and <85 mmHg diastolic	4.8	(−0.9, 10.5)		−2.7	(−9.2, 3.8)		5.9	(−0.5, 12.2)	
≥130 mmHg systolic or ≥85 mmHg diastolic	−0.03	(−14.6, 14.6)	0.55	4.4	(−12.1, 20.9)	0.43	0.8	(−15.5, 17.0)	0.57
Glucose									
<100 mg/dL	4.0	(−1.6, 9.5)		−1.9	(−8.2, 4.4)		5.0	(−1.1, 11.2)	
≥100 mg/dL	8.5	(−11.3, 28.3)	0.67	0.4	(−22.7, 23.5)	0.85	8.7	(−14.2, 31.7)	0.76

[a]Models for pregnancy loss weighted by the strata-specific inverse probability of pregnancy based on the effect modifier (metabolic syndrome, metabolic syndrome score or metabolic syndrome component), low-dose aspirin treatment assignment, BMI, c-reactive protein, race/ethnicity, partner status, cigarette smoking, time since last pregnancy loss and site.

[b]P-value for the additive interaction of metabolic syndrome, metabolic syndrome score or metabolic syndrome component and low-dose aspirin.

BMI indicates body mass index, CI confidence interval.

Table 4.

Low-dose aspirin and menstrual-cycle specific risk differences per 100 couples attempting pregnancy for pregnancy, a pregnancy ending in a loss and a pregnancy ending in a live birth by metabolic syndrome, metabolic syndrome score and metabolic syndrome components: competing risks analysis

	Pregnancy			Pregnancy ending in a loss			Pregnancy ending in a live birth		
	RD	95% CI	p-int[a]	RD	95% CI	p-int[a]	RD	95% CI	p-int[a]
Metabolic syndrome score									
0	5.0	(0.7, 9.3)		0.1	(−2.1, 2.4)		4.9	(0.9, 8.8)	
1	2.3	(−2.3, 7.0)	0.41	0.7	(−1.8, 3.3)	0.73	1.0	(−3.0, 5.1)	0.18
2	−0.9	(−6.3, 4.5)	0.09	0.5	(−1.9, 2.9)	0.82	−1.3	(−6.4, 3.7)	0.06
3+	−1.4	(−6.2, 3.3)	0.050	0.03	(−2.7, 2.7)	0.96	−1.2	(−5.3, 2.9)	0.036
Metabolic syndrome									
No	2.6	(−0.1, 5.3)		0.4	(−1.0, 1.8)		2.0	(−0.4, 4.4)	
Yes	−1.0	(−6.2, 3.3)	0.15	0.03	(−2.6, 2.7)	0.80	−1.2	(−5.3, 2.9)	0.19
Waist circumference									
<88 cm	3.4	(0.3, 6.4)		0.7	(−0.9, 2.4)		2.6	(−0.2, 5.3)	
≥88 cm	−0.8	(−4.5, 2.9)	0.09	−0.3	(−2.2, 1.5)	0.40	−0.6	(−3.8, 2.6)	0.14
High-density lipoprotein									
>50 mg/dL	4.7	(1.1, 8.2)		0.3	(−1.6, 2.2)		4.1	(0.9, 7.3)	
≤50 mg/dL	−0.5	(−3.7, 2.7)	0.038	0.5	(−1.2, 2.2)	0.86	−0.9	(−3.7, 1.9)	0.023
Triglycerides									
<150 mg/dL	3.0	(0.3, 5.8)		0.4	(−1.0, 2.7)		2.5	(−0.02, 5.0)	
≥150 mg/dL	−2.1	(−6.6, 2.3)	0.056	0.1	(−2.4, 2.7)	0.085	−2.2	(−6.1, 1.6)	0.045
Blood pressure									
<130 mmHg systolic and <85 mmHg diastolic	2.1	(−0.5, 4.7)		0.3	(−1.1, 1.6)		1.7	(−0.6, 4.0)	
≥130 mmHg systolic or ≥85 mmHg diastolic	0.01	(−5.7, 5.7)	0.51	0.9	(−2.5, 4.3)	0.73	−0.5	(−5.4, 4.4)	0.42
Glucose									
<100 mg/dL	1.6	(−0.8, 4.1)		0.3	(−1.0, 1.6)		1.2	(−1.0, 3.4)	
≥100 mg/dL	4.5	(−4.0, 13.1)	0.53	1.2	(−3.4, 5.7)	0.71	4.1	(−3.4, 11.5)	0.47

[a]P-value for the additive interaction of metabolic syndrome, metabolic syndrome score or metabolic syndrome component and low-dose aspirin.