Published in final edited form as:

Lancet. 2020 January 25; 395(10220): 285–293. doi:10.1016/S0140-6736(19)32973-3.

Low-Dose Aspirin for the Prevention of Preterm Delivery in Nulliparous Women with a Singleton Pregnancy: A Randomised Multi-country Placebo Controlled Trial

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Contributions to Authorship

MKH, SSG, RJD, NG, JHF, JM, EMM, MKT, Me Mi, RS designed the study. SSG, BSK, MuMw, MS, JO, AL, AT, CLB, AM, MM, EC, WAC, JC, LF, AG, NFK, SJ, FZ, SS, RLG, KK, PD, AP, PLH, EA, PN, FE, EAL were responsible for data collection and field trial oversight. MKH, SSG, RJD, NG, JHF, JM, EMM, MKT, MM provided overall trial oversight. JM &TLN performed data management and analysed statistics. MKH, SSG, RLG, RJD, EMM, JM, TLN and RS wrote the first draft of the paper. All authors reviewed and had input to the manuscript.

Declaration of Interests: None of the authors have any interests to declare.

Data Sharing Statement: "Deidentified participant data from the study will be available at the NICHD data repository (N-DASH): https://dash.nichd.nih.gov/. Data sharing will be accessed and governed according the procedures and policies of N-Dash. A data dictionary will be provided. This data will be provided within 12 months of primary publication.

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Summary:

Background: Preterm birth remains a common cause of neonatal mortality with a disproportionate burden occurring in low and middle-income countries. Meta-analyses of low-dose aspirin to prevent preeclampsia suggest that the incidence of preterm birth may also be decreased, particularly if initiated before 16 weeks.

Methods: We completed a randomised multi-country (Democratic Republic of Congo, Guatemala, India, Kenya, Pakistan, Zambia) double masked trial of aspirin (81 mg) daily compared to placebo initiated between 6 weeks and 0 days and 13 weeks and 6 days of pregnancy in nulliparous women between14 and 40 years of age with an ultrasound confirming gestational age and singleton viable pregnancy. Randomisation (1:1) was stratified by site. The primary outcome of preterm birth, defined as delivery prior to 37 weeks gestational age, was analyzed in randomised women with pregnancy outcomes at or after 20 weeks. This study is registered with ClinicalTrials.gov, number NCT02409680, and the Clinical Trial Registry, India, number CTRI/2016/05/006970.

Findings: From March 2016 through June 2018, 11,976 women were assigned to aspirin (5,990 women) or placebo (5,986 women). Amongst randomised women, an evaluable birth outcome beyond 20 weeks occurred in 5787 women who received Aspirin and 5771 women who received placebo Preterm birth occurred in 11.6% of women randomised to aspirin and 13.1% randomised to placebo (Relative Risk [RR], 0.89; 95% CI, 0.81 to 0.98; Risk Difference, −0·02; 95% CI, −0·03, −0·01). Women randomised to aspirin were less likely to experience perinatal mortality (45.7/1000 vs 53.6/1000; RR, 0.86; 95%CI, 0.73 to 1.00). Other adverse maternal/neonatal events were similar between the two groups.

Interpretation: In nulliparous women with singleton pregnancies, low dose aspirin initiated between 6 weeks and 0 days and 13 weeks and 6 days results in lower rates of preterm delivery before 37 weeks and perinatal mortality.

Funding: Funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

Introduction:

Preterm birth, defined as delivery prior to 37 weeks, remains a predominant driver of infant mortality worldwide with the greatest burden of disease occurring in low and middle-income countries[1,2]. Though improvements in neonatal care have resulted in improved survival[3], this care is often limited or unavailable in regions with the highest burden of mortality. Beyond the newborn period, longitudinal adverse effects in health and socioeconomic outcomes have been associated with preterm birth compared to individuals delivered at term[4–6]. Despite numerous trials of secondary prevention and tocolytic therapies, effective strategies for the prevention of preterm birth have proved either elusive or resource intensive, beyond potentially a few at-risk groups [7–10].

Meta-analyses and systematic reviews of trials of low-dose aspirin in pregnant women for the purpose of prevention of preeclampsia suggest that women receiving aspirin have a lower occurrence of preterm birth in addition to lower rates of preeclampsia[11–13]. Secondary analyses of two trials of low dose aspirin in pregnancy have also suggested that the rate of preterm birth may be lower in pregnant women taking aspirin[14,15] This effect may be greater when low dose aspirin is begun before 16 weeks of gestation[12]. Though promising as a strategy, a large definitive trial of low-dose aspirin initiated early in pregnancy for primary prevention of preterm birth as the primary outcome has not been conducted. The Aspirin (Aspirin Supplementation for Pregnancy Indicated risk Reduction In Nulliparas-ClinicalTrials.gov Identifier: NCT02409680/Clinical Trials Registry-India CTRI/2016/05/006970) trial was therefore designed to test the hypothesis that low-dose aspirin (81 mg) administered daily initiated between 6 weeks 0 days and 13 weeks 6 days reduces the incidence of preterm delivery amongst nulliparous women with a singleton pregnancy. Recognising the lack of data of maternal/neonatal safety of aspirin in settings where resources may be limited, we also prospectively assessed potential harms from this therapy as part of our trial.

Methods:

Study Design:

We conducted a multinational, randomised double-masked, placebo-controlled trial assessing daily low- dose aspirin (81 mg) begun between 6 weeks and 0 days and 13 weeks and 6 days until 36 weeks and 0 days of pregnancy to prevent preterm birth before 37 weeks amongst nulliparous women with a singleton pregnancy. Nulliparous women were selected as they are unlikely to undergo treatment to prevent prematurity due to a lack of obstetrical history and have a tendency to have higher rates of preterm birth than multiparous women[16–18]. The trial was conducted by the NICHD Global Network for Women's and Children's Health Research in 7 sites in 6 countries-India (2 sites), Pakistan, Zambia, Democratic Republic of Congo, Guatemala and Kenya - between March 2016 and April 2019. The trial protocol has previously been published[19]. Prior to the initiation of the trial, the protocol was approved by the relevant ethics committees and regulatory agencies of each country as well as the ethics committees of the United States-based collaborators and that of the Research Triangle Institute (RTI) International. The trial was conducted in accordance with Good Clinical Practice Guidelines. An external independent data and safety monitoring

committee oversaw the conduct of the trial and monitored the occurrence of serious adverse events. No formal interim analyses were planned nor conducted.

Participants:

Each site established a plan to screen pregnant women residing within the study communities. Nulliparous pregnant women who were between 14 (18 when required by individual ethics boards) and 40 years of age, were identified and were individually consented for participation by trained staff. Women were required to be pregnant between 6 weeks and 0 days and 13 weeks and 6 days as by confirmed by a study ultrasound, We excluded women who had any of the following by medical history: allergy or contraindication to aspirin, previously taken aspirin therapy for more than 7 days during this pregnancy, multiple gestations, history of more than two first trimester losses, or medical conditions for which low-dose aspirin therapy is currently indicated (e.g. diabetes and hypertension). Potential participants then underwent a medical screening and must have met the following criteria: blood pressure below140/90; haemoglobin at or above 7.0 g/dl; and an ultrasound evaluation with presence of a foetal heartbeat, single gestation, and absence of a foetal anomaly. Foetuses/neonates who were subsequently found to have an anomaly were included all analyses. The crown-rump length and last menstrual period were entered into a smartphone application to determine the gestational age in accordance with American College of Obstetrics and Gynecology (ACOG) guidance[20].

Randomisation and masking:

Eligible and consented women were randomly assigned in a 1:1 ratio to a daily regime of either 81 mg of aspirin or placebo. The aspirin tablets and placebo were manufactured by Morepen Laboratories in Parwanoo, Himachal Pradesh, India and Helix Pharma Limited located in Karachi, Pakistan. Packaging and distribution were handled by Bilcare Research Global Clinical Supplies. The placebo tablets were identical to the aspirin tablets in size, weight, and appearance. The pills were packaged into blister cards containing a 2-week supply of medication. Certificates of analysis following United States Pharmacopeia reference standards were performed for each lot produced. Stability testing at 6, 12, 18, and 24 months for each lot was performed by high performance liquid chromatography for active ingredients and appearance by RTI International. The individual participant randomisation sequence was developed for each site by the data coordinating center (RTI) using a computer algorithm based on a randomly permuted block design with varied block sizes.

Procedures:

Upon determination of eligibility, women then received the next available sequentially numbered pre-packaged 2-week medication allotment for that site completing randomisation as detailed above. These were exchanged every 2 weeks by study personnel from centrally maintained storage facilities and an assessment of compliance, side-effects, interval medical contacts, and concomitant medications were documented. Throughout the study, research staff and local health providers were masked to treatment. Blood pressure assessments were made between 16 to 20 weeks, 28 to 30 weeks and then biweekly beginning at 34 weeks until delivery. Repeat haemoglobin assessments were obtained between 26-30 weeks. Maternal and neonatal outcomes were obtained through 42 days using a previously

described registry[21]. All staff were trained in the study procedures, assessment of harms and internal quality checks were designed to ensure high quality data. Review of outcomes and data consistency was performed in a masked fashion prior to data lock and analysis. Quality assessment of the ultrasound images was performed contemporaneously on 10% of studies with feedback provided to the individual sonographer using the process we have previously described[22].

Outcomes:

The primary outcome of this study was preterm birth, which was defined as any delivery at or after 20 weeks and 0 days and prior to 37 weeks and 0 days. This outcome was selected as there was data to inform a power calculation and it is a well-accepted proximal marker of both perinatal morbidity and mortality. Predefined secondary maternal outcomes were hypertensive disorders of pregnancy, early preterm (<34 weeks' gestation) hypertensive disorders of pregnancy, vaginal bleeding, antepartum haemorrhage, postpartum haemorrhage, maternal mortality through 42 days postpartum, and late abortion. Predefined secondary foetal/neonatal outcomes were perinatal mortality, early preterm birth (before 34 weeks), small for gestational age as defined by the Intergrowth standard[23], birthweight <1500 g, birthweight <2500 g, spontaneous abortion, stillbirth (both non-macerated and total stillbirth), foetal loss (defined as birth between 16-20 weeks and perinatal mortality between 20 weeks to <7 days post-delivery), and medical termination of pregnancy. Extremely preterm birth (before 28 weeks) was a post-hoc exploratory outcome. Serious adverse events were also collected through study follow-up. Definitions of secondary outcomes are provided in the Supplementary Appendix.

Statistical Analysis:

The expected incidence of the primary outcome was conservatively estimated to be 8%[1]. Assuming a 5% risk of miscarriage and a 2% rate of lost to follow up, the sample size of 11,920 participants (5,960 per arm) would provide 90% power to detect a 20% reduction in the incidence of preterm birth in women treated with low-dose aspirin assuming a two-sided type one error of 5%. Twenty percent was determined to be a minimum clinical important difference and thought to be in keeping with prior publications of early aspirin initiation[12,14]. Recognizing that missing data were likely to occur due to miscarriage and/or medical termination of pregnancy, we planned a priori to perform a modified intent to treat analysis for the primary outcome including only women who achieved a pregnancy of 20 weeks and beyond (See the Supplementary Appendix). Women who were subsequently determined to be ineligible were excluded from the analysis as part of the modified intent to treat approach. We also pre-specified a sensitivity analysis within a per-protocol population, defined primarily as a participant who consumed 90% of her prescribed regimen (See the Supplementary Appendix). Analyses of all binary outcomes included a Cochran-Mantel-Haenszel test stratified by site to formally test the primary hypothesis followed by generalized linear model-based sensitivity analyses to obtain relative risk (RR) estimates and associated confidence intervals while adjusting for site as well as to explore the treatment by site interaction.. For the primary outcome additional sensitivity analyses were completed including a generalized linear model with a binomial distribution and identity link to estimate the adjusted absolute risk difference (RD); a repeat of the primary model in the

intent to treat population using inverse probability weighting to include negative outcomes for pregnancies excluded from primary analysis due to pregnancy outcome < 20 weeks, medically terminated pregnancy ≥20 weeks, or otherwise missing outcomes ≥20 week; and a repeat of the primary model also in the intent to treat population with preterm status determined by gestational age for all pregnancies and multiple imputation for pregnancies with missing gestational age. Analyses of secondary outcomes are exploratory in nature and therefore, p-values and confidence intervals are provided for descriptive purposes only and no adjustment for multiple comparisons were made. Serious adverse events were assessed on all women who received at least one dose of drug or placebo analyzed by the actual treatment received (safety population). All data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The results of the trial were monitored by an independent data safety monitoring group on a biannual basis and it was registered with ClinicalTrials.gov (NCT02409680) and the Clinical Trials Registry-India (CTRI/2016/05/006970).

Role of the Funding Source:

Staff from the funder (NICHD) had input into the study design, data interpretation, and reviewed and approved this report. Nonetheless, the authors views do not necessarily represent those of the NICHD. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results:

From March 2016 through June 2018, a total of 14361 provided informed consent. A total of 2385 women were excluded or declined randomisation and the remaining 11976 were consented and randomised: 5990 were assigned to low-dose aspirin and 5986 were allocated to placebo (Figure 1). The low-dose aspirin group had 5787 women who were in the modified intent to treat (MITT) population and the placebo group contained 5771. Baseline characteristics and site of delivery were similar between the two groups (Table 1). Overall adherence to medication or placebo defined as taking ≥ 90% of the prescribed medications was high (MITT population overall 84.9%: aspirin 85.3% vs placebo 84.4%). The quality of the drug was evaluated upon manufacture and episodic assessments of stability by a masked third party demonstrated appropriate potency throughout the duration of the study (See the Supplementary Appendix).

The primary outcome of preterm delivery before 37 weeks occurred in 11.6% of women receiving aspirin and 13.1% of women in the placebo group (RR, 0.89; 95%CI, 0.81 to 0.98; RD, −0·02; 95% CI, −0·03, −0·01). In the per protocol population, the primary outcome occurred in 10.9% of women receiving aspirin and 12.3% of women in the placebo group (RR, 0.89; 95% CI, 0.80 to 0.99). No interaction between the study site and the primary outcome was seen in these analyses. Also, intent to treat outcomes are similar to the modified intent to treat analyses and are provided in the Web-table 1&2. With respect to secondary outcomes, early preterm delivery(< 34 weeks) was reduced in women who were randomised to aspirin compared to those randomised to placebo (3.3% vs. 4.0%; RR, 0.75; 95%CI, 0.61 to 0.93). The post-hoc outcome of extremely preterm delivery (< 28 weeks)

trended lower in women who received aspirin compared to placebo but with a confidence interval for the relative risk spanning 1 (0.9% vs. 1.3%; RR, 0.72; 95%CI, 0.51 to 1.02).

Perinatal mortality occurred less frequently among women randomised to aspirin compared to those who received placebo (aspirin 45.7/1000 vs placebo 53.6/1000; RR, 0.86; 95%CI, 0.73 to 1.00). The incidence of overall hypertensive disorders of pregnancy was not different between women randomised to aspirin (6.1%) and those who received placebo (5.6%) (RR, 1.08; 95%CI, 0.94 to 1.25); however, the incidence of women who were delivered before 34 weeks with hypertensive disorders of pregnancy was lower in women randomised to aspirin (0.1%) compared to women randomised to placebo (0.4%)(RR, 0.38; 95%CI, 0.17 to 0.85). No differences in the occurrence of foetal growth abnormalities defined as a birthweight <2500 g or <1500 g were noted between the two groups (Table 2). Foetal loss (stillbirth and abortion at or after 16 weeks) was also lower among women randomised to aspirin (52.1/1000) compared to women who received placebo (60.8/1000) (RR, 0.86; 95% CI, 0.74 to 1.00). Other maternal and foetal/neonatal outcomes were similar between groups.

Table 3 presents RR estimates by site for the primary and secondary outcomes. For the primary outcome of preterm delivery, there was no evidence of a site by treatment group interaction (p-value=0.16) The p-value for the interaction of site by treatment group was less than 0.05 for the outcomes of early pre-term birth and birth weight < 1500g. For early pre-term birth, results by site were consistent with overall findings in that RR estimates were less than 1 in most sites; however, the upper limit of the RR confidence interval was less than 1 only for Zambia and Nagpur (RR, 0.42; 95% CI, 0.21,0.83 and RR 0.42, 95% CI, 0.23, 0.75 respectively). DRC and Kenya had estimated RR greater than 1 but the associated confidence intervals were large and spanned 1. For birth weight < 1500 g, the entire span of the RR confidence interval is less than 1 for Nagpur (RR, 0.36, 95% CI, 0.17,0.77). DRC and Kenya again had estimated RR greater than 1 with the lower limit of confidence interval for DRC also greater than 1.

Overall serious adverse events were similar between groups in the safety population (women receiving any drug or placebo) (aspirin 14.0% vs placebo 14.4%-RR, 0.94; 95%CI, 0.84 to 1.05) (Table 4). Broad categories of adverse events are compared between groups and are shown in table 4A (maternal) and 4B (foetal/neonatal). No differences in maternal bleeding complications (antepartum haemorrhage, postpartum haemorrhage, or upper gastrointestinal bleeding) were detected between the groups. The proportion of women who had a second haemoglobin ≤ 7.0 g/dl or had a 3.5 g/dl drop also did not differ between groups. Maternal mortality was high (176/100000) compared to high-income countries, though no observable differences were seen between groups. Foetal/neonatal serious adverse events did not differ between women who received aspirin and those who received placebo. No differences were seen in the rates of overall anomalies, gastroschisis or neonatal death.

Discussion

In this randomised double-masked controlled trial, nulliparous women with a singleton pregnancy who were allocated to low-dose aspirin between 6 weeks and 0 days and 13 weeks and 6 days until 36 weeks gestation were 11% less likely to deliver before 37 weeks.

Similarly, the risk of early preterm birth was lowered by 25% and perinatal mortality was decreased by 16%. Importantly, we saw no increase in either maternal or foetal serious adverse events between women prescribed low-dose aspirin compared to women who received placebo.

These outcomes are consistent with several meta-analyses which suggested similar levels of reduction of preterm birth and perinatal mortality [11,12]. Because of the large sample size, this trial was able to demonstrate these benefits definitively in a diverse group of women in six low and middle-income countries. Additionally, this study was based on a long standing registry with high rates of community engagement resulting in both data consistency, high rates of recruitment and followup[21]. Our overall rate of preterm birth was higher than that of our sample size determination. It should be noted that accurate estimates of preterm birth informed by early ultrasound in our study areas are lacking and we therefore chose a very conservative estimate of the preterm birth rate (See Supplementary Appendix). Similarly, we did not achieve the projected rate of 20% reduction in the rate of preterm birth but did demonstrate a statistically significant reduction in the rate of preterm birth (11%) and important reductions in early preterm birth (25%) and perinatal mortality (16%). The simple eligibility criteria used as part of this trial allows the intervention to potentially be applied to diverse groups of pregnant women in multiple settings and may be particularly relevant in low- and middle-income countries. The low cost and demonstrated tolerability of aspirin in this population suggests that this intervention can be readily and safely adopted across a span of clinical sites.

Several limitations should be noted. First the applicability of this intervention to other groups of women beyond nulliparas with singleton gestations remains unclear. Secondly, prior meta-analyses have suggested that higher doses of aspirin (>100 mg) may further lower the incidence of preeclampsia[24]. The optimal dose and time of initiation for the prevention of preterm birth remains unclear., Though aspirin has been endorsed for the prevention of preeclampsia, we were only able to demonstrate a decrease in the incidence of early preterm (<34 weeks) hypertensive disorders of pregnancy. This failure to demonstrate a difference in overall preeclampsia may be related to both our definition of hypertensive disorders of pregnancy and the settings in which we performed this study. The diagnosis of preeclampsia most commonly occurs at the time of the birth admission. In the care settings for this trial, measurement of blood pressure and assessment of proteinuria does not routinely occur at the time of delivery, potentially leading to an ascertainment bias. Recognizing this challenge in our care settings, we chose to use an expansive diagnosis of hypertensive disorders (See the Supplementary Appendix) that may have led to imprecision in this outcome. Nonetheless, our trial of aspirin in pregnancy is similar to other large trials that have likewise failed to demonstrate a benefit in the decreasing in the incidence of preeclampsia at term but noted a reduction in preeclampsia earlier in pregnancy[25–27].

Finally, we did not differentiate spontaneous preterm birth from iatrogenic preterm birth. This decision was intentional, as we recognized that the majority of our births would occur in facilities which would not have the ability to differentiate these diagnoses. We speculate from the fact that we saw no differences in the rates of the principal drivers of iatrogenic preterm birth (maternal early preterm hypertensive disorders(<34weeks) and foetal growth

restriction), that the difference in the rate of preterm birth seen with aspirin therapy may be due to differences in the rates of spontaneous preterm birth. In the end, ultimately the differences shown in both preterm birth <37 weeks and perinatal mortality with low dose aspirin therapy are the most meaningful outcomes to women and their children, regardless of the causative mechanism.

In conclusion, this trial demonstrates that the administration of aspirin at a dose of 81 mg beginning between 6 weeks 0 days and 13 weeks 6 days through 36 weeks resulted in a lower incidence of preterm birth amongst women with a singleton pregnancy in low and middle-income countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

We searched PubMed for articles on low dose aspirin (LDA) use in pregnancy for improved birth outcomes, from 2000 to present using the search terms ‘aspirin’ AND ‘pregnancy’ OR ‘hypertensive disease’ OR ‘preterm birth’ OR ‘preeclampsia’. A secondary analysis of a trial of aspirin and a single trial of preconception aspirin (Effects of Aspirin in Gestation and Reproduction (EAGeR) suggested reduced risk of preterm birth among women who received LDA compared to control. Meta-analyses and systematic reviews of trials of LDA in pregnant women to prevent preeclampsia have suggested that women receiving aspirin have a lower occurrence of preterm birth, which may be greater when LDA is started early in pregnancy.

Added value of this study

This is the first large trial of low-dose aspirin initiated early in pregnancy with the prevention of preterm birth as the primary outcome. This trial was designed to test the hypothesis that LDA (81 mg) administered daily initiated in the first trimester reduces the incidence of preterm delivery amongst nulliparous women with a singleton pregnancy. Additionally, data suggested that the intervention is safe for women in the study.

Implications of all the available evidence

This trial confirms the earlier suggestion of benefit in reduction or risk of preterm birth with LDA. In this trial, nulliparous women with a singleton pregnancy who were allocated to low-dose aspirin between 6 weeks and 0 days and 13 weeks and 6 days until 36 weeks gestation were 11% less likely to deliver before 37 weeks. In addition, the risk of early preterm delivery (prior to 34 weeks) was reduced by 25% and perinatal mortality was decreased by 16%. These outcomes are consistent with several meta-analyses which had demonstrated similar levels of reduction of preterm birth and perinatal mortality. Because of the large sample size, this trial was able to demonstrate these benefits definitively in a diverse group of women in six low and middle-income countries. The low cost and demonstrated tolerability of aspirin in this population suggests that this intervention can be readily and safely adopted across a span of clinical sites.

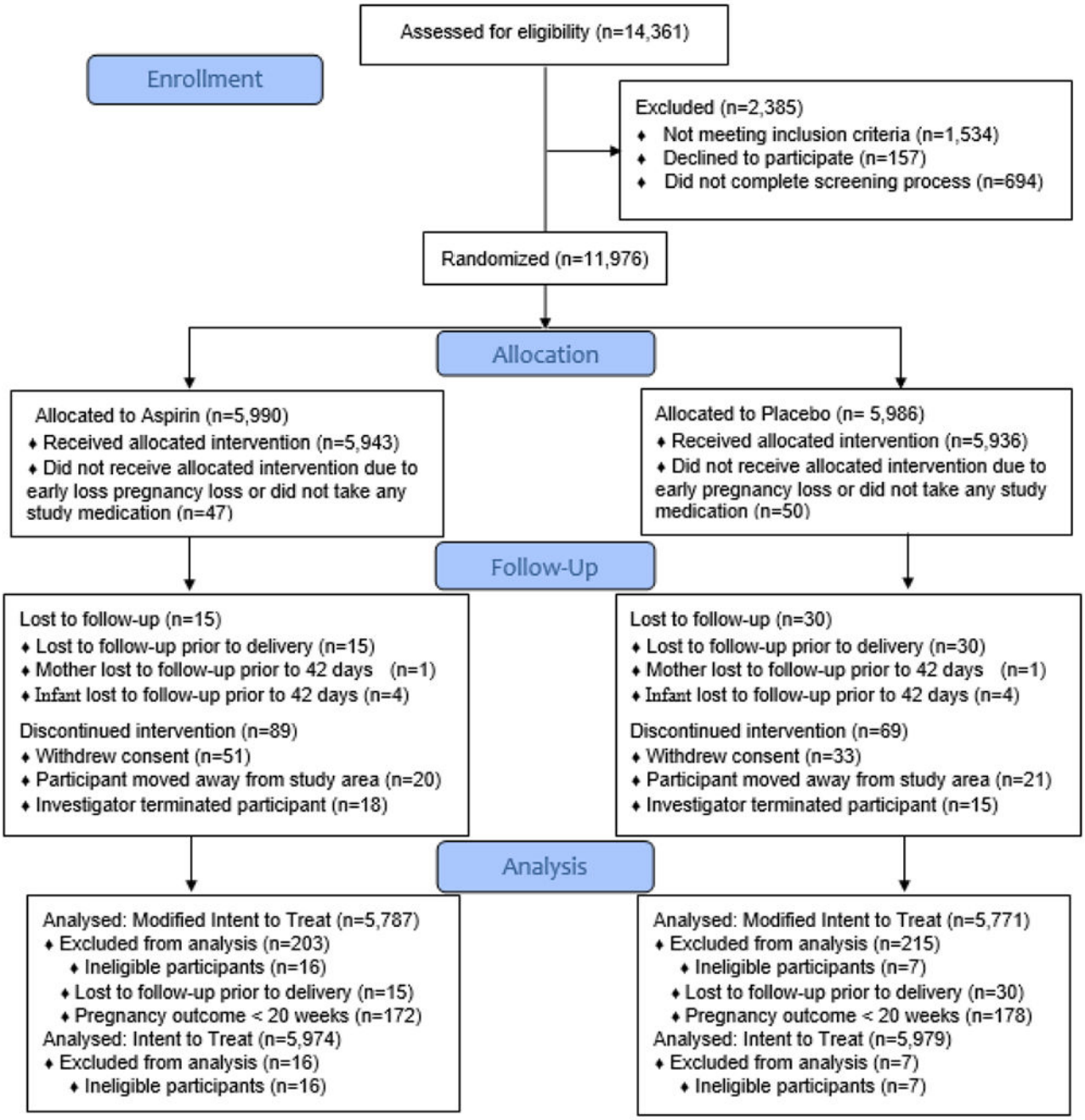

Figure 1.
Randomization and Follow-up in the ASPIRIN Trial

Table 1.

Baseline and Site of Delivery Characteristics (Modified Intent to Treat Population)

Characteristic	Aspirin (n=5,787)	Placebo (n=5,771)
Maternal age (years), n (%)		
< 20	2,233 (39%)	2,273 (39%)
20·29	3,429 (59%)	3,372 (58%)
> 29	125 (2%)	126 (2%)
Number of prior pregnancies, n (%)		
0	5,274 (91%)	5,226 (91%)
1	451 (8%)	469 (8%)
2	62 (1%)	76 (1%)
Projected gestational age at enrollment (weeks), Median (Q1, Q3)	10·1 (8·6, 120)	10·1 (8·6, 120)
Maternal education, n (%)		
No formal schooling	830 (14%)	828 (14%)
1 - 6 years of schooling	857 (15%)	856 (15%)
7 - 12 years of schooling	3,470 (60%)	3,454 (60%)
≥ 13 years of schooling	629 (11%)	632 (11%)
Maternal height (cm), Mean (StdDev)	153·1 (6·9)	153·1 (7·0)
Maternal weight (Kg), Mean (StdDev)	49·3 (8·9)	49·2 (8·7)
Maternal BMI (Kg/m^2), Mean (StdDev)	21·0 (3·8)	21·0 (3·6)
Antenatal care visits, Median (Q1, Q3)	5 (4, 6)	5 (4, 6)
Delivery attendant, n (%)		
Physician	2,938 (51%)	2,908 (50%)
Nurse/Nurse midwife	2,240 (39%)	2,239 (39%)
Traditional birth attendant	464 (8%)	473 (8%)
Family/Self/Other	142 (2%)	147 (3%)
Delivery location, n (%)		
Hospital	3,479 (60%)	3,494 (61%)
Clinic/Health center	1,818 (31%)	1,765 (31%)
Home/Other	488 (8%)	509 (9%)
Delivery mode, n (%)		
Vaginal	4,258 (74%)	4,326 (75%)
C-Section	1,523 (26%)	1,440 (25%)
Miscarriage	0	0
MTP	4 (< 1%)	2 (< 1%)
Site, n (%)		
DRC	655 (11%)	665 (12%)
Zambia	499 (9%)	511 (9%)
Guatemala	836 (14%)	835 (14%)
Belagavi, India	1,327 (23%)	1,323 (23%)

Characteristic	Aspirin (n=5,787)	Placebo (n=5,771)
Pakistan	771 (13%)	762 (13%)
Nagpur, India	1,026 (18%)	1,020 (18%)
Kenya	673 (12%)	655 (11%)

Characteristics were compared between study arms using chi-square tests for categorical measures, t-tests for continuous data, and Wilcoxon rank sum tests for ordinal data.

All p-values comparing treatment groups were greater than 0.05.

Table 2.

Primary and Secondary Outcomes

Variable	Aspirin	Placebo	RR (95% CI)	p-Value
Primary Outcome				
Preterm delivery[1], n/N (%)	668/5,780 (11·6%)	754/5,764 (13·1%)	0·89 (0·81, 0·98)	0·012
Secondary Maternal Outcomes				
Hypertensive disorders[1], n/N (%)	352/5,780 (6·1%)	325/5,764 (5·6%)	1·08 (0·94, 1·25)	0·299
Vaginal bleeding[2], n/N (%)	214/5,933 (3·6%)	246/5,940 (4·1%)	0·87 (0·73, 1·04)	0·125
Antepartum haemorrhage[1], n/N (%)	26/5,761 (0·5%)	25/5,746 (0·4%)	1·03 (0·60, 1·79)	0·900
Postpartum haemorrhage[3], n/N (%)	54/5,928 (0·9%)	43/5,907 (0·7%)	1·25 (0·84, 1·86)	0·274
Maternal mortality through 42 days[2], n/N (Rate/100,000 deliveries)	9/5,958 (151)	12/5,948 (202)	0·75 (0·32, 1·78)	0·512
Late abortion[2], n/N (Rate/1000)	23/5,819 (4·0)	30/5,808 (5·2)	0·77 (0·45, 1·31)	0·331
Early Preterm and hypertensive disorders[1], n/N (%)	8/5,780 (0·1%)	21/5,764 (0·4%)	0·38 (0·17, 0·85)	0·015
Secondary Foetal Outcomes				
Small for gestational age[1], n/N (%)	1,506/5,492 (27·4%)	1,564/5,467 (28·6%)	0·95 (0·90, 1·01)	0·171
Perinatal mortality[1], n/N (Rate/1000)	264/5,779 (45·7)	309/5,763 (53·6)	0·86 (0·73, 1·00)	0·048
Early Preterm (< 34 weeks) [1], n/N (%)	189/5,780 (3·3%)	230/5,764 (4·0%)	0·75 (0·61, 0·93)	0·039
Extremely Preterm (< 28 weeks)[1], n/N (%)	54/5,780 (0·9%)	75/5,764 (1·3%)	0·72 (0·51, 1·02)	0·062
Measured birth weight < 2500g[1], n/N (%)	1,078/5,628 (19·2%)	1,153/5,624 (20·5%)	0·93 (0·87, 1·01)	0·073
Birth weight < 2500g[1], n/N (%)	1,101/5,671 (19·4%)	1,178/5,671 (20·8%)	0·94 (0·87, 1·01)	0·071
Measured birth weight < 1500g[1], n/N (%)	78/5,628 (1·4%)	101/5,624 (1·8%)	0·87 (0·57, 1·33)	0·084
Birth weight < 1500g[1], n/N (%)	97/5,671 (1·7%)	118/5,671 (2·1%)	0·79 (0·58, 1·07)	0·152
Foetal loss[2], n/N (Rate/1000)	303/5,818 (52·1)	353/5,807 (60·8)	0·86 (0·74, 1·00)	0·039
Spontaneous abortion[2], n/N (Rate/1000)	134/5,956 (22·5)	152/5,946 (25·6)	0·88 (0·70, 1·10)	0·261
Stillbirth (macerated excluded)[1], n/N (Rate/1000)	105/5,744 (18·3)	119/5,717 (20·8)	0·88 (0·68, 1·14)	0·324
All stillbirth[1], n/N (Rate/1000)	141/5,780 (24·4)	166/5,764 (28·8)	0·85 (0·68, 1·06)	0·141
Medical termination of pregnancy (MTP) [2], n/N (Rate/1000)	42/5,956 (7·1)	30/5,946 (5·0)	1·40 (0·88, 2·23)	0·157
Postterm (≥ 42 weeks gestation)[1]	90/5,787 (1·6%)	105/5,771 (1·8%)	0·86 (0·65, 1·13)	0·266

The following superscripts indicate the analysis population for each outcome variables:

[1]Modified intent to treat (mITT),

[2]Intent to treat (ITT) and

[3]Safety.

Table 3:

Serious adverse events (safety population)

	Aspirin (n=5943)	Placebo (n=5936)	RR (95% CI)	p value
At least one serious adverse event	832 (14·0%)	857 (14·4%)	0·98 (0·89–1·06)	0·568
At least one other serious adverse event	495 (8·3%)	514 (8·7%)	0·97 (0·86–1·09)	0·579
Maternal events				
Maternal death	9 (0·2%)	12 (0·2%)	0·75 (0·32–1·78)	0·514
Upper gastrointestinal bleeding	4 (0·1%)	1 (<0·1%)	3·99 (0·45–35·72)	0·216
Vaginal spotting, bleeding, or leaking	10 (0·2%)	10 (0·2%)	1·00 (0·42–2·39)	0·997
Antepartum haemorrhage	35 (0·6%)	33 (0·6%)	1·06 (0·66–1·70)	0·815
Post-partum haemorrhage	50 (0·8%)	43 (0·7%)	1·16 (0·77–1·73)	0·481
Anaemia	24 (0·4%)	23 (0·4%)	1·04 (0·59–1·84)	0·893
Pre-eclampsia or eclampsia	150 (2·5%)	141 (2·4%)	1·06 (0·85–1·33)	0·591
Preterm labour or preterm birth evaluation before delivery	45 (0·8%)	56 (0·9%)	0·80 (0·54–1·19)	0·271
Hypertension admission or medical visit before delivery	120 (2·0%)	106 (1·8%)	1·14 (0·88–1·47)	0·325
Fever or infection	54 (0·9%)	46 (0·8%)	1·18 (0·80–1·73)	0·415
Other	57 (1·0%)	57 (1·0%)	1·00 (0·70–1·44)	0·995
Fetal and infant events				
Fetal loss	142 (2·4%)	162 (2·7%)	0·88 (0·70–1·09)	0·246
Neonatal death up to 28 days	163 (2·7%)	190 (3·2%)	0·86 (0·70–1·05)	0·138
Miscarriage, abortion, or medical termination of pregnancy	51 (0·9%)	54 (0·9%)	0·95 (0·65–1·38)	0·771
Congenital anomaly	32 (0·5%)	36 (0·6%)	0·89 (0·55–1·43)	0·626
Gastroschisis	2 (<0·1%)	1 (<0·1%)	2·01 (0·18–22·11)	0·569

Data are n (% of group), where n is participants with at least one serious adverse event form indicating the specified event.

Table 4.

Serious Adverse Events (Safety Population)

Variable	Aspirin (n=5,943)	Placebo (n=5,936)	RR (95% CI)	p-Value
Participants with at least one SAE, n (%)	832 (14·0%)	857 (14·4%)	0·98 (0·89, 1·06)	0·568
At least one other SAE, n (%)	495 (8·3%)	514 (8·7%)	0·97 (0·86, 1·09)	0·579
4A Maternal Events				
Maternal death, n (%)	9 (0·2%)	12 (0·2%)	0·75 (0·32, 1·78)	0·514
Upper GI bleeding, n (%)	4 (0·1%)	1 (0·0%)	3·99 (0·45, 35·72)	0·216
Vaginal spotting/Bleeding/Leaking pv, n (%)	10 (0·2%)	10 (0·2%)	1·00 (0·42, 2·39)	0·997
Antepartum haemorrhage, n (%)	35 (0·6%)	33 (0·6%)	1·06 (0·66, 1·70)	0·815
Postpartum haemorrhage, n (%)	50 (0·8%)	43 (0·7%)	1·16 (0·77, 1·73)	0·481
Anemia/Drop in Hb > 3.5 g/dl, n (%)	24 (0·4%)	23 (0·4%)	1·04 (0·59, 1·84)	0·893
Preeclampsia/Eclampsia, n (%)	150 (2·5%)	141 (2·4%)	1·06 (0·85, 1·33)	0·591
Preterm labor/Preterm birth evaluation prior to delivery, n (%)	45 (0·8%)	56 (0·9%)	0·80 (0·54, 1·19)	0·271
Hypertension admission/Medical visit prior to delivery, n (%)	120 (2·0%)	106 (1·8%)	1·14 (0·88, 1·47)	0·325
Fever/Infection, n (%)	54 (0·9%)	46 (0·8%)	1·18 (0·80, 1·73)	0·415
Other, n (%)	57 (1·0%)	57 (1·0%)	1·00 (0·70, 1·44)	0·995
4B Foetal/Infant Events				
Foetal loss after 20 weeks, n (%)	142 (2·4%)	162 (2·7%)	0·88 (0·70, 1·09)	0·246
Neonatal death, n (%)	163 (2·7%)	190 (3·2%)	0·86 (0·70, 1·05)	0·138
Miscarriage/Abortion/Medical termination of pregnancy (MTP), n (%)	51 (0·9%)	54 (0·9%)	0·95 (0·65, 1·38)	0·771
Other foetal anomaly, n (%)	32 (0·5%)	36 (0·6%)	0·89 (0·55, 1·43)	0·626
Gastroschisis, n (%)	2 (0·0%)	1 (0·0%)	2·01 (0·18, 22·11)	0·569

The denominator for each serious adverse event is any participant included in the safety population and the numerator is participants with at least one SAE form indicating the specified serious adverse event.