Mini-CAT Draft **Name Anthony Guan**

Brief description of patient problem/setting:

Previous studies have showed the use of antiplatelet's like aspirin had a moderate reduction in the risk of preeclampsia, and quite possibly preterm births. However preterm birth remains one of the most common causes of death of infants worldwide even with medical advances. I questioned whether low dose aspirin would lead to a reduction in the rate of preterm birth.

Search Question:

In pregnant patients does taking low dose aspirin reduce the rate of preterm birth?

PICO search terms:

P	I	C	O
Pregnancy	Aspirin		Preterm Birth
Pregnant women	Antiplatelets		Spontaneous preterm birth
	Low dose aspirin		Pregnancy outcome

Search tools and strategy used:

PubMed:

- Pregnancy, aspirin, preterm birth (Best Match) – 229
- Pregnancy, aspirin, preterm birth (Best Match, 10 yr range) – 140
- Pregnancy, aspirin, preterm birth (Best Match, 10 yr range, Meta-analysis, Systematic reviews, RCT) – 38

Cochrane Library:

- Pregnancy, aspirin, preterm birth (10 yr range)
    - Reviews – 5
    - Trials – 53

Trip Database

- Pregnancy, aspirin, preterm birth – 15

Google Scholar

- Pregnancy, aspirin, preterm birth (10 yr range) – 10,800
- Pregnancy, aspirin, preterm birth (5 yr range) – 3,640

I was looking for articles that gave pregnant patients antiplatelet, like aspirin and measured their birth outcome. So I wanted to find articles that related to my PICO questions and were of the highest level of evidence available, so either a systematic review or a meta-analysis or combined. If the highest level of evidence such as a meta-analysis or systematic review were not available, randomized control trials (RCT) would be useful to determine if a different technique is as effective or better than previously established standards. A RCT can provide evidence as to the efficacy and efficiency while minimizing or eliminating any bias. A RCT is well structured, detailed, and planned experiments that allows for comparisons, and control over many variables. I also felt it was important to use studies that were conducted recently, therefore I narrowed my search to articles that were published within the last 10 years (2010-2020) and was glad to have found recent articles published in in the last five years. I searched through four different databases, and ended up choosing articles from PubMed and Google Scholar.

Articles chosen:

1)

Citation: van Vliet EO, Askie LA, Mol BW, Oudijk MA. Antiplatelet Agents and the Prevention of Spontaneous Preterm Birth: A Systematic Review and Meta-analysis. *Obstet Gynecol*. 2017;129(2):327-336. doi:10.1097/AOG.0000000000001848

Type of article: A Systematic Review and Meta-analysis

Abstract

Objective: Spontaneous preterm birth is an important cause of neonatal mortality and morbidity. An increasing body of evidence suggests that uteroplacental ischemia plays an important role in the etiology of spontaneous preterm birth. We aimed to study whether antiplatelet agents reduce the risk of spontaneous preterm birth.

Data sources: We included data from an individual participant data meta-analysis of studies that had evaluated the effect of antiplatelet agents to reduce preeclampsia (Perinatal Antiplatelet Review of International Studies Individual Participant Data).

Methods of study selection: The meta-analysis included 31 studies that randomized women to low-dose aspirin-dipyridamole or placebo-no treatment as a primary preventive strategy for preeclampsia. For the current study we analyzed data from 17 trials (28,797 women) that supplied data on type of delivery (spontaneous compared with indicated birth).

Tabulation, integration, and results: Primary endpoints were spontaneous preterm birth at less than 37 weeks, less than 34 weeks, and less than 28 weeks of gestation. We analyzed outcomes for each trial separately using χ statistics and combined in an individual participant data meta-analysis using a binary logistic regression model. Women assigned to antiplatelet treatment compared with placebo or no treatment had a lower risk of spontaneous preterm birth at less than 37 weeks (relative risk [RR] 0.93, 95% confidence interval [CI] 0.86-0.996) and less than 34 weeks of gestation (RR 0.86, 95% CI 0.76-0.99). The RR of having a spontaneous preterm birth at less than 37 weeks of gestation was 0.83 (95% CI 0.73-0.95) for women who have had a previous pregnancy and 0.98 (95% CI 0.89-1.09) for women in their first pregnancy. The treatment effect was stable in all other prespecified subgroups.

Conclusion: Antiplatelet agents reduce spontaneous preterm birth in pregnant women

at risk for preeclampsia.

Hyperlink:
https://journals.lww.com/greenjournal/Fulltext/2017/02000/Antiplatelet_Agents_and_the_Prevention_of.13.aspx

2)

Citation: Hoffman MK, Goudar SS, Kodkany BS, et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial [published correction appears in Lancet. 2020 Mar 21;395(10228):e53]. *Lancet*. 2020;395(10220):285-293. doi:10.1016/S0140-6736(19)32973-3

Type of article: A randomized controlled trial

Abstract

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

Methods: ASPIRIN was a randomised, multicountry, double-masked, placebo-controlled trial of low-dose aspirin (81 mg daily) initiated between 6 weeks and 0 days of pregnancy, and 13 weeks and 6 days of pregnancy, in nulliparous women with an ultrasound confirming gestational age and a singleton viable pregnancy. Participants were enrolled at seven community sites in six countries (two sites in India and one site each in the Democratic Republic of the Congo, Guatemala, Kenya, Pakistan, and Zambia). Participants were randomly assigned (1:1, stratified by site) to receive aspirin or placebo tablets of identical appearance, via a sequence generated centrally by the data coordinating centre at Research Triangle Institute International (Research Triangle Park, NC, USA). Treatment was masked to research staff, health providers, and patients, and continued until 36 weeks and 7 days of gestation or delivery. The primary outcome of incidence of preterm birth, defined as the number of deliveries before 37 weeks' gestational age, was analysed in randomly assigned women with pregnancy outcomes at or after 20 weeks, according to a modified intention-to-treat (mITT) protocol. Analyses of our binary primary outcome involved a Cochran-Mantel-Haenszel test stratified by site, and generalised linear models to obtain relative risk (RR) estimates and associated confidence intervals. Serious adverse events were assessed in all women who received at least one dose of drug or placebo. This study is registered with ClinicalTrials.gov, NCT02409680, and the Clinical Trial Registry-India, CTRI/2016/05/006970.

Findings: From March 23, 2016 to June 30, 2018, 14 361 women were screened for inclusion and 11 976 women aged 14-40 years were randomly assigned to receive low-dose aspirin (5990 women) or placebo (5986 women). 5780 women in the aspirin group and 5764 in the placebo group were evaluable for the primary outcome. Preterm birth before 37 weeks occurred in 668 (11·6%) of the women who took aspirin and 754 (13·1%) of those who took placebo (RR 0·89 [95% CI 0·81 to 0·98], p=0·012). In women taking aspirin, we also observed significant reductions in perinatal mortality (0·86 [0·73-1·00], p=0·048), fetal loss (infant death after 16 weeks' gestation and before 7 days post partum; 0·86 [0·74-1·00], p=0·039), early preterm delivery (<34 weeks; 0·75 [0·61-0·93], p=0·039), and the incidence of women who delivered before 34 weeks with hypertensive disorders of pregnancy (0·38 [0·17-0·85], p=0·015). Other adverse maternal and neonatal events were similar between the two groups.

Interpretation: In populations of nulliparous women with singleton pregnancies from low-income and middle-income countries, low-dose aspirin initiated between 6 weeks and 0 days of gestation and 13 weeks and 6 days of gestation resulted in a reduced incidence of preterm delivery before 37 weeks, and reduced perinatal mortality.

Hyperlink: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32973-3/fulltext

3)

Citation: Andrikopoulou M, Purisch SE, Handal-Orefice R, Gyamfi-Bannerman C. Low-dose aspirin is associated with reduced spontaneous preterm birth in nulliparous women. *Am J Obstet Gynecol*. 2018;219(4):399.e1-399.e6. doi:10.1016/j.ajog.2018.06.011

Type of article: A Randomized controlled trial

Abstract

Background: Preterm birth is one of the leading causes of perinatal morbidity and mortality. Clinical data suggest that low-dose aspirin may decrease the rate of overall preterm birth, but investigators have speculated that this is likely due to a decrease in medically indicated preterm birth through its effect on the incidence of preeclampsia and other placental disease. We hypothesized that low-dose aspirin may also have an impact on the mechanism of spontaneous preterm labor.

Objective: Our objective was to determine whether low-dose aspirin reduces the rate of spontaneous preterm birth in nulliparous women without medical comorbidities.

Study design: This is a secondary analysis of a randomized, placebo-controlled trial of low-dose aspirin for the prevention of preeclampsia in healthy, low-risk, nulliparous women. Low-risk women were defined by the absence of hypertension, renal disease, diabetes, other endocrine disorders, seizures, heart disease, or collagen vascular disease. Our study was limited to singleton, nonanomalous gestations. Women were eligible if they had prior pregnancy terminations but not prior spontaneous pregnancy loss <20 weeks. Current pregnancies that resulted in a loss or termination <20 weeks or antepartum stillbirth or had missing follow-up data were excluded. The treatment intervention was 60 mg of aspirin, initiated at 13-25 weeks' gestation or matching placebo. The primary outcome was spontaneous preterm birth <34 weeks' gestation. Secondary outcomes included spontaneous preterm birth <37 weeks and overall preterm birth <37 and <34 weeks. Baseline demographics and primary and secondary outcomes were compared between treatment groups. A logistic regression model was used to adjust for confounders related to spontaneous preterm birth.

Results: Of 2543 included women, 1262 (49.6%) received low-dose aspirin and 1281 (50.4%) placebo. Baseline characteristics were similar between groups, except for marital status. The rate of spontaneous preterm birth <34 weeks was 1.03% (n = 13) and 2.34% (n = 30) in the low-dose aspirin and placebo group, respectively (odds ratio, 0.43, 95% confidence interval, 0.26-0.84). Additionally, the rate of spontaneous preterm birth <37 weeks was 6.58% (n = 83) in the low-dose aspirin group and 7.03% (n = 90) in the placebo group (odds ratio, 0.97, 95% confidence interval, 0.71-1.33), and the rate of overall preterm birth <37 weeks was 7.84% (n = 99) in the low-dose aspirin group and 8.2% (n = 105) in the placebo group (odds ratio, 0.97, 95% confidence interval, 0.72-1.31). After adjustment for variables that were clinically relevant or statistically significant, including body mass index, race, tobacco use, marital status, and education level, there was a significant reduction in spontaneous preterm birth <34 weeks in the low-dose aspirin group (adjusted odds ratio, 0.46, 95% confidence interval, 0.23-0.89). The rates of overall preterm birth <34 and <37 weeks and spontaneous preterm birth

<37 weeks were similar in women who received low-dose aspirin compared with placebo. **Conclusion:** Low-dose aspirin is associated with a substantial decrease in spontaneous preterm birth <34 weeks in healthy nulliparous women without comorbidities. These findings suggest a new therapeutic option for preterm birth prevention that requires further study.
Hyperlink: https://pubmed.ncbi.nlm.nih.gov/29913174/

4)

Citation: Silver RM, Ahrens K, Wong LF, et al. Low-dose aspirin and preterm birth: a randomized controlled trial. Obstet Gynecol. 2015;125(4):876-884. doi:10.1097/AOG.0000000000000736
Type of article: A Randomized controlled trial
Abstract **Objective:** To evaluate the association between low-dose aspirin initiated before conception and the risk of preterm birth. **Methods:** This was a secondary analysis of the Effects of Aspirin in Gestation and Reproduction trial. Women with a history of pregnancy loss (original stratum: one loss less than 20 weeks of gestation during the previous year; expanded stratum: one or two losses with no restrictions on timing or gestational age of the losses) were randomized to either daily low-dose aspirin (81 mg, n=615) and folic acid or folic acid alone (placebo; n=613). Preterm birth was compared between groups using intent-to-treat analysis. **Results:** Preterm birth rates were 4.1% (22/535 low-dose aspirin) and 5.7% (31/543 placebo) (relative risk [RR] 0.72, 95% confidence interval [CI] 0.42-1.23); spontaneous preterm birth rates were 1.1% (6/535 low-dose aspirin) and 2.2% (12/543 placebo) (RR 0.51, 95% CI 0.19-1.34); medically indicated preterm birth rates were 2.6% (14/535 low-dose aspirin) and 2.9% (16/543 placebo) (RR 0.89, 95% CI 0.44-1.80). After restriction to confirmed pregnancies using inverse probability weighting, preterm birth rates were 5.7% and 9.0% (RR 0.63, 95% CI 0.37-1.09) and spontaneous preterm birth rates were 1.4% and 3.2% (RR 0.44, 95% CI 0.17-1.18). In confirmed pregnancies in the original stratum, preterm birth occurred in 3.8% and 9.7% of the low-dose aspirin and placebo groups, respectively (RR 0.39, 95% CI 0.16-0.94). **Conclusion:** Preconception low-dose aspirin was not significantly associated with the overall rate of preterm birth. Although the study was underpowered for this secondary analysis, numeric trends in favor of benefit, particularly in the women with a recent, single early pregnancy loss, warrant further investigation.
Hyperlink: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6152923/pdf/nihms-656729.pdf

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
van Vliet EO, Askie LA, Mol BW, Oudijk MA. (2017)	A Systematic Review and Meta-analysis	• The authors analyzed 17 studies that randomized women to low-	• They looked at three main outcome measures which were	• The results were that 2,670 (9.7%) of women	• Limitations to this study include that the analysis was based

		dose aspirin or placebo/no treatment groups as a primary prevention for preeclampsia. The studies were found through extensive searches of databases like MEDLINE. • The 17 studies comprised of 28,797 women with known delivery type/method. However only 27,510 women were included because 1,287 were excluded from analysis since gestational age was unknown. • 13,825 were randomly assigned to antiplatelet treatment and 13,685 to a placebo or no treatment. Of the 17 trials, 15 of them used Aspirin (60 – 150mg/day). One trial used a combo of aspirin and dipyridamole, and the other only gave dipyridamole.	spontaneous preterm birth of a live born neonate: 1) between 20 and 37 weeks of gestation; 2) between 20 and 34 weeks of gestation; and 3) between 20 and 28 weeks of gestation.	had a preterm birth before 37 weeks, 773 (2.8%) before 34 weeks, and 151 (0.5%) before 28 weeks. This demonstrates that antiplatelet agents are associated with a significant reduction in the risk of preterm birth before 37 and 34 weeks. However it was not statistically significant before 28 weeks, although the relative risk is reduced.	on a previous study/analysis, the risk of a type I error or significant results due to chance was addressed. However the authors feel that the new analysis focused on antiplatelet benefit and thus had clinical relevance. Also since the data was based on the Perinatal Antiplatelet Review of International Studies Individual Participant Data meta-analysis that was published in 2007, studies that were published after 2005 were not included in this article. The authors did find that six relevant trials have been published but all with small samples totaling 569 women and

					feel that it would not affect results. Inconsistenc y in the definition of spontaneous preterm birth may exist it the analyzed studies, but the bias was minimized.
Hoffman MK, Goudar SS, Kodkany BS, Metgud M, Somannav ar M, Okitawutsh u J, Lokangaka A, Tshefu A, Bose CL, Mwapule A, Mwenecha nya M, Chomba E, Carlo WA, Chicuy J, Figueroa L, Garces A, Krebs NF, Jessani S, Zehra F, Saleem S, Goldenberg RL, Kurhe K, Das P, Patel A, Hibberd PL Achieng E, Nyongesa P, Esamai F, Liechty EA, Goco N, Hemingway	A randomize d controlled trial	• This study was labeled the ASPIRIN (Aspirin Supplementation for Pregnancy Indicated risk Reduction In Nulliparous) trial, which was a double blinded randomized placebo controlled trial. It took place in six different countries, India, Pakistan, Zambia, the Democratic Republic of the Congo, Guatemala, and Kenya. • Screening was established by each site/country that was most effective to find study participants. Participants included nulliparous pregnant women aged 18-40 years and 14 years or older in	• The primary outcome was to find the incidence of preterm birth from after 20 weeks of gestation to before 37 weeks of gestation. Secondary outcomes included hypertensive disorders like pre-eclampsia, gestational hypertension; also vaginal bleeding; antepartum and post-partum hemorrhage; maternal mortality; and late abortion. Secondary fetal and neonatal outcomes included perinatal mortality, small for gestational age, low birth weight,	• A total of 14,361 women were screened, 2385 were excluded due to not meeting inclusion criteria, declined participation, or incomplete screening. Thus the study had 11,976 participants, of which 5990 were in the aspirin group and 5986 in the placebo group. However only 5787 from the aspirin and 5771 in the placebo group were included in analysis. Some participants did not receive intervention, discontinued intervention, withdrew consent, investigator	• Limitations of the study are that it only looked at nulliparous women with singleton gestation, so results are unclear for other groups. This study only used 81 mg aspirin, while other studies have indicated higher doses to be more effected to reduce incidence of pre-eclampsia. The study failed to differentiate spontaneous and iatrogenic preterm birth, but was done so purposefully as most sites cannot differentiate them.

-Foday J, Moore J, Nolen TL, McClure EM, Koso-Thomas M, Miodovnik M, Silver R, Derman RJ, and the ASPIRIN Study Group* (2020)		countries of Kenya, Zambia, and Congo with parental consent. • Nulliparous women were selected because they have a higher rate of preterm birth compared to multiparous women. Women were to be pregnant for at least 6 weeks and no longer than 13 weeks and 6 days, confirmed by ultrasound. Women who were allergic or had some contraindication to aspirin were excluded. Other exclusion criteria were previous use of aspirin during pregnancy, multiple gestations, more than two miscarriages, history of hypertension and diabetes, and such. Participants were also required to have a blood pressure lower than 140/90 mm HG, hemoglobin >7.0g/dL, a fetal heartbeat on US, single gestation,	spontaneous abortion, stillbirth, and fetal loss.	terminated treatment, lost to follow up, or with a pregnancy outcome less than 20 weeks. • Primary outcome results were 668 out of 5780 taking aspirin had a preterm delivery, about 11.6% and 754 out of 5764 taking the placebo, about 13.1 % delivered preterm. As for secondary outcomes in women taking aspirin compared to the placebo group perinatal mortality, fetal loss, early preterm delivery, and the incidence of women who delivered before 34 weeks with hypertensive disorders of pregnancy were also significantly reduced in women taking aspirin. Other adverse maternal and neonatal events were similar	

		and no fetal anomaly during screening. • Women were randomly assigned in a 1:1 ratio of aspirin and placebo group. Manufacturing, packaging, testing, and distribution were all controlled so that everyone was masked to treatment. No unmasking was required. • All the women were asked to take the daily regimen of aspirin or placebo until 36 weeks and 7 days of gestation or delivery. Medication was prepacked for 2 weeks with basic instructions., and then replenished at bi-weekly visits for compliance and adverse events.		between the groups. • The study found that in nulliparous women with a singleton pregnancy, those who took low dose aspirin early on were 11% less likely to deliver preterm than the placebo group. The outcomes were comparable to systematic reviews and meta analysis that suggest fewer preterm births when taking low dose aspirin. • Since this was a large, diverse, wide spread study, the authors believe the interventions may be generally applied to diverse groups in various clinical settings especially in low/middle income countries.	
Andrikopoulou M, Purisch SE, Handal-Orefice R, Gyamfi-Bannerman	A randomized controlled trial	• Women were divided into 2 groups, low-dose aspirin and placebo group. • From the original 3171	• The primary outcome was a spontaneous preterm birth before	• They found that spontaneous preterm birth <34 weeks was significantl	• The main weakness or limitation was that this was a secondary analysis of

C. (2018)		patients in the RCT, 678 were excluded due to multiple gestations, congenital malformations, missing data, voluntary termination of pregnancy, and history of spontaneous pregnancy loss. Thus a total of 2543 women were included and 1262 received low dose aspirin (60mg) while 1281 received a placebo.	34 weeks gestation. Secondary outcomes looked at preterm birth <37 weeks, blood loss during delivery, postpartum hemorrhage, and placental abruption rates.	y lower in women who received low-dose aspirin. However the rate for <37 weeks was similar between the two groups. Several sensitivity analyses were done such as time of aspirin initiation (before or after 16 weeks), still yielded a statistically significant reduction in preterm births <34 weeks. When excluding patients with preeclampsia there was still a statistically significant reduction in preterm births <34 weeks. • Looking at the secondary outcomes, placental abruption	an old data set. The result may only be generalized to nulliparous women without comorbidities. Also the study participants had a low BMI, which may differ from the general pregnant population.

				was more common in the low-dose aspirin group, but was relatively low in both groups. As for the blood loss and hemorrhage rates, they were similar in both groups.	
Silver RM, Ahrens K, Wong LF, Perkins NJ, Galai N, Lesher LL, Faraggi D, Wactawski-Wende J, Townsend JM, Lynch AM, Mumford SL, Sjaarda L, Schisterman EF. (2015)	A randomized controlled trial	• The Effects of Aspirin in Gestation and Reproduction (EAGeR) trial was a multi-center, block-randomized, double-blinded, placebo-controlled trial of 1,228 women in the U.S. • It consisted of women 18-40, and patients were stratified into two groups: either 1 documented pregnancy loss <20 wks in past 12 months, or 102 prior	• This was a secondary analysis of the EAGeR, the primary outcome was live birth (13) and a planned secondary outcome was preterm birth. • Preterm birth was defined as delivery between 20 weeks and zero days and 36 weeks and six days' gestation. • Information on	• Participant characteristics were similar between groups. • About 88% (1078) of particiants of completed the study. • The study found 53 preterm births resulting in a 4.9% occurrence. Of the preterm births, 18 (34.0%) were classified as spontaneous, 30 (56.6%) as medically	• The study likely biased participants towards high education and socioeconomic status, reducing the risk of preterm birth. • The rates of preterm birth were relatively low compared to the overall US. • Limitations of the study included only women with 1 or 2 prior pregnancy losses, and their age was relatively high, further limiting the generalizabili

		pregnancy losses regardless of gestational length or time since the loss. • They were also randomized to receive either the intervention (81 mg low-dose aspirin daily plus 400 mcg of folic acid) (n=615) or an identical looking placebo containing only 400 mcg of folic acid (n=613).	preeclampsia/gestational hypertension, birth weight, mode of delivery (vaginal vs. cesarean), multifetal gestation, Apgar score (1 and 5 minutes), neonatal sex, and any events of neonatal death were abstracted from delivery records by Effects of Aspirin in Gestation and Reproduction trial research staff. Fetal growth restriction was defined as birth weight less than 10% for gestational age (15). Stillbirth was defined as death of the fetus at ≥ 20 weeks of gestation.	indicated, and 5 (9.4%) as elective/unknown. • Of the 1078 patients, 4.1% (22/535) of women treated with low-dose aspirin and 5.7% (31/543) treated with placebo had preterm birth. The occurrence of spontaneous preterm birth was 1.1% (6/535) in women treated with low-dose aspirin compared to 2.2% (12/543) in the placebo group. • Though the occurrence of preterm birth tended to be lower in the low-dose aspirin group,	ty of the current data.

				overall none of the compariso ns were statistically significant.	

Conclusion(s):

van Vliet EO, Askie LA, Mol BW, Oudijk MA stated that preterm birth can occur in 5-12% of all deliveries and accounts for 70% of perinatal mortality. This article sought to evaluate the efficacy of low-dose aspirin for prevention of preterm birth. It included data from the Perinatal Antiplatelet Review of International Studies Individual Participant Data meta-analysis. Their analysis showed that antiplatelet agents like aspirin reduces the relative risk of spontaneous preterm birth by about 7%. This is especially true in patients at risk for preeclampsia. When looking at preterm birth of <34 weeks the relative risk is reduced by 14%. Also for preterm birth <37 weeks the risk reduction is about 17% in women with a second or subsequent pregnancy.

Hoffman MK, Goudar SS, Kodkany BS, et al. discovered that aspirin has been investigated to reduce the risk of recurrent early onset pre-eclampsia, but it is the first to look at its protective effects for prevention of preterm birth. This RCT demonstrated that the use of daily low dose aspirin initiated early in pregnancy reduced the incidence of preterm births before 37 week in women who have not given birth and birthing of only one child. The study established that in nulliparous women with a singleton pregnancy, those who took low dose aspirin early on were 11% less likely to deliver preterm than the placebo group.

Andrikopoulou M, Purisch SE, Handal-Orefice R, Gyamfi-Bannerman C. focused on preterm birth but was based off the Eunice Kennedy Shriver National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units' randomized placebo-controlled trial of low-dose aspirin (60 mg) for the prevention of preeclampsia in women at low risk. Furthermore this article and RCT looked at whether low dose aspirin reduces spontaneous preterm birth in nulliparous women without comorbidities and found that taking low-dose aspirin is linked with a greater than 50% reduction in the odds of spontaneous preterm birth <34 weeks, which is a considerable decrease.

Silver RM, Ahrens K, Wong LF, et al. had completed the Effects of Aspirin in Gestation and Reproduction trial (EAGeR), which compared the association with live birth rates in women with prior pregnancy loss treated pre-conception with low-dose aspirin and placebo. Thus for this analysis they evaluated the association between low-dose aspirin initiated prior to conception and the risk of preterm birth. They discovered that low-dose aspirin did not significantly reduce the risk of preterm birth overall. Also, there was a non-significant reduction in the risk of preterm birth among women taking low-dose aspirin preconception.

However, there was a suggestion of a reduction in spontaneous preterm birth and a reduction in preterm birth in women with a single early pregnancy loss within a year.

Thus in conclusion the articles demonstrate a promising use of aspirin to decrease spontaneous preterm birth, and expanding its use in pregnant patients other than for preeclampsia. This may indicate the generalizability across diverse populations, being that aspirin is relatively safe, cost-effective, long shelf life, and easily stored. Even a small reduction in preterm birth would have tremendous medical, social and financial benefit. However further research is needed to examine the intervention of aspirin in multiparous women and those with multiple gestations.

Clinical Bottom Line:
From the articles I have chosen, the highest quality of evidence available, the systematic reviews and meta-analyses referenced here, suggest that in pregnant patients taking low dose aspirin may reduce the rate of preterm birth. As their study displayed significant decreases of preterm birth with use of antiplatelet agents like aspirin. Aspirin in pregnancy are a low-cost and safe intervention, which may also be a promising intervention for women at high risk for a spontaneous preterm birth, especially in high-risk women with a previous pregnancy.

Weight of the Evidence:
van Vliet EO, Askie LA, Mol BW, Oudijk MA. Weighs the most because it was the highest level of evidence that addresses my PICO question being a meta-analysis and systematic review that was published in March 2018. The journal, Obstetrics and gynecology is Medline indexed and the study analyzed data from 17 trials with a total sample of 28,797 women. This is a large sample size, which looked at the incidence of preterm birth at different endpoints while taking an antiplatelet drug.

Hoffman MK, Goudar SS, Kodkany BS, et al. would be weighed 2nd since it was a randomized control trial that was published in the Lancet this year, in 2020. The study was conducted in multiple countries and had a large sample size with 11,976 women. Examining how low-dose aspirin, which is usually used to prevent pre-eclampsia, also suggested that the incidence of preterm birth might also be decreased, particularly if initiated before 16 weeks of gestation.

Andrikopoulou M, Purisch SE, Handal-Orefice R, Gyamfi-Bannerman C. is weighed 3rd because it was a secondary analysis of an RCT and was published within the last 5 years in October 2018. This study included 2543 women, although less than the other articles, it still represents a good sample size. Additionally this review closely examines whether low-dose aspirin reduces the rate of spontaneous preterm birth in nulliparous women without medical comorbidities.

Silver RM, Ahrens K, Wong LF, et al., I weighed last since it was an RCT so the level of evidence was not higher than that of a systematic review or meta-analysis. It was also published in 2015 so not as recent as my other articles. Although it evaluated the association between low-dose aspirin and the risk of preterm birth, it was given before conception and not during pregnancy like my other articles.

Magnitude of any effects:

Being that all studies showed that the degree of the association with preterm birth and low-dose aspirin was clinically important, although Silver RM, et al. showed no significant results, the beneficial results of using low dose aspirin to decrease risk of preterm births, early preterm birth and perinatal mortality is encouraging. Aspirin is safe, cost-effective and a promising intervention that may decrease spontaneous preterm birth in an even broader population than previously reported, independent of preeclampsia.

Clinical significance (not just statistical significance):

Despite advances in perinatal medicine, preterm birth remains one of the most common causes of death of infants worldwide. Preterm means any birth before 37 weeks of pregnancy are completed. In high-income countries prenatal and neonatal care has improved mortality of infants born prematurely, however in low/middle income countries resources may be limited or unavailable. Secondary preventions such as detecting, timely delivery, and calcium supplementation along with tocolytics to suppress labor can be obscure and resource heavy when used in large at risk populations. Previous studies have suggested that pregnant women receiving low dose aspirin have a reduced rate of preeclampsia and possibly preterm birth.

Given the challenges of preterm birth in obstetrics and being a major cause or perinatal morbidity and mortality, the articles demonstrate a promising use of aspirin to decrease spontaneous preterm birth, and expanding its use in pregnant patients other than for preeclampsia. This may indicate the generalizability across diverse populations, being that aspirin is relatively safe, cost-effective, long shelf life, and easily stored. Additionally it may have an impact on global public health in resource-limited settings. It may also be a promising intervention for women at high risk for a spontaneous preterm birth, especially in high-risk women with a previous pregnancy.

Therefore, the current findings might be applicable to a broader population of pregnant women. Since there is a scarcity of preventive strategies for spontaneous preterm birth, it may be suggested that the use of antiplatelet agents may be a promising intervention for women who have a history of spontaneous preterm birth.

Any other considerations important in weighing this evidence to guide practice:

Silver RM, Ahrens K, Wong LF, et al., found a large, but nonsignificant reduction in spontaneous preterm birth in women with prior pregnancy loss, which laid groundwork for future studies, as the level of the association of aspirin with preterm birth was clinically important. It is uncertain whether the association is due to an increased benefit from treatment initiated prior to conception and/or very early in pregnancy. However, their data justified further appropriately designed clinical trials to assess the potential benefits of low-dose aspirin on preterm birth. Van Vliet et al. found a reduction in spontaneous preterm birth, but this was limited to women at risk for preeclampsia. Andrikopoulou M, et al., included nulliparous women without medical comorbidities or previous poor obstetrical history, and determined a benefit to low-dose aspirin. Nonetheless further research is needed to examine the intervention of aspirin in multiparous women and those with multiple gestations. Because of the accumulating evidence of a possible benefit, there are ongoing clinical trials to further investigate the impact of low-dose aspirin in the reduction of indicated as well as spontaneous preterm birth. Current research has provided clinicians with the best available evidence to counsel women regarding who may benefit from utilizing aspirin.