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Prevention of Preeclampsia with Aspirin Therapy in the Second Trimester and Pregnancy Outcome: A Meta-analysis

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Abstract

Background: Low-dose aspirin (LDA, range from 60-150 mg/d) therapy has been used to prevent preeclampsia (PE) for many years. However, whether LDA could positively affect pregnancy outcome remains unknown.

Purpose: We performed this meta-analysis to assess the effectiveness of LDA therapy in women at high risk for PE.

Methods: We searched studies published from January 1985 to February 2015. All the studies were search from the databases of PubMed, EMBASE, Cochrane, ScienceDirect, and Biosis Preview. The association between PE and pregnancy outcome with aspirin therapy was assessed by odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Thirteen articles involving 6735 participants were included in the final meta-analysis. When all studies were pooled into the meta-analysis, a statistically significant effect was found among pregnant women who underwent LDA therapy during their second trimester (14 to 28 weeks of gestation) to reduce PE (OR=0.72, 95% CI=0.54–0.95). Meanwhile, no difference was noted in the pregnancy outcomes including low birth weight (birth weight of 2,500 g or less in a live born infant) (OR=1.06, 95% CI=0.88–1.29), postpartum haemorrhage (blood loss more than 500 ml within 24 h after delivery) (OR=1.09, 95% CI=0.85–1.40), intrauterine growth restriction (IUGR, the fetal weight was below the 10th percentile for gestational and the neonatal birth weight fell below the 10th percentile) (OR=0.66, 95% CI=0.42–1.06), and pre-term delivery (diagnosed <37 + 0 weeks of gestation) (OR=0.78, 95% CI=0.57–1.05).

Conclusions: The present meta-analysis suggests that the incidence of PE was statistically significant between LDA therapy groups and placebo groups. Furthermore, LDA therapy was not associated with pregnancy outcome including fetal birth weight, postpartum haemorrhage, IUGR, and preterm delivery. Harm from aspirin therapy was not observed in our study.

Keywords: Aspirin; Preeclampsia; Pregnancy outcome; Second trimester; Meta-analysis

Introduction

According to statistics, hypertensive disorders complicating pregnancy are common, affecting about 10% of pregnant woman worldwide [1,2] and account for 14% of all maternal deaths [3]. Preeclampsia (PE), a pregnancy specific hypertensive disease, is defined as new-onset hypertension after 20 weeks of gestation often accompanied with positive proteinuria (urinary excretion of 0.3 g/24 h protein was defined as significant proteinuria [4] and confers significant maternal and fetal risks [5-7]. More than 100,000 pregnant women die from PE every year [8].

At present, the etiology of PE remains unclear. The theory about mechanistic placental dysfunction is widely accepted.

Placentation comprises trophoblast cell invasion of the spiral arteries, which results in reversible changes in the normal vascular wall structure. Under normal circumstances, trophoblastic invasion of the spiral arteries starts at 8 weeks of gestation and is completed at 16–20 weeks of gestation [9,10]. Meanwhile, PE is considered to be associated with excessive thromboxane synthesis. In normal pregnancy, a balance should be maintained between prostacyclin (PGI2) and thromboxane (TxA) [11,12]. Pregnant women who have obstetric one or more risk factors of following, such as age more than 40 years, previous history of pregnancy-induced hypertension other hypertensive disorders, chronic nephritis or diabetes, anti-phospholipid antibodies, nulliparity or multiparity, and early pregnancy systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg, abnormal uterine artery Doppler results, got a positive result in the angiotensive sensitivity test [13], are more likely to synthesize excess thromboxane and change the TxA2/PGI2 ratio [14].

Aspirin inhibits cyclooxygenase (COX) enzyme irreversibly and prevents excessive TxA synthesis [15,16]. Meanwhile, the development of placental vasculature may improve and the risk of PE may reduce. Over the past decades, aspirin has been used to prevent maternal and perinatal morbidity worldwide. American College of Obstetrics and Gynecology 2013 Guide proposes that pregnant women who have a previous history of pregnancy-induced hypertension before 34 weeks of gestation or repeated PE should begin low-dose aspirin (LDA) therapy in early pregnancy [17]. The US Preventive Services Task Force proposed that pregnant women at high risk of PE should begin LDA (60–150 mg/d) therapy before 12 weeks of gestation [18].

Over the past 30 years, considerable effort has been focused on determining whether LDA affects women at risk of PE. Different conclusions were proposed by various scholars.

Golding et al. proposed that no consistent benefit of LDA therapy during 12 to 32 weeks of gestation was found in primiparae. In addition, women under LDA therapy are more likely to suffer from bleeding disorders antenatally, intrapartum, and postpartum [19]. Authors did not show evidence that LDA change the incidence of PE in women with abnormal uterine artery Doppler [20-22], either for women in angiotensin-sensitive [23] and nulliparous women [24]. Moreover, the use of non-steroidal anti-inflammatory drugs during early pregnancy is deemed to be associated with increased risk of miscarriage [25].

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Martin et al. [26] showed that progressively increasing LDA doses in late pregnancy may increase bleeding time.

However, many studies have shown that pregnancy outcomes are not significantly affected by LDA [27-28]. Meta-analysis showed evidence that LDA therapy initiated in early pregnancy (≤ 16 weeks) may reduce PE incidence, preterm birth, and IUGR [29].

Roberge et al. reviewed relevant literature published from 1965 to October 2011 and selected randomized controlled trials involving participants treated with LDA (≤ 150 mg), with dipyridamole (≤ 300 mg) use considered. They concluded that LDA initiated at 16 weeks of gestation or less significantly reduces PE, perinatal death, and IUGR; however, participants who took dipyridamole may have affected the conclusion [28].

Recently, Ting-ting Xu et al. [30] make a report after taken 29 randomized controlled trials (RCT) into consideration. However, the dosage of aspirin were different between RCTs, which range from 50-150 mg/d. in these RCTs, patients initiated LDA therapy at any time before 32 weeks of gestation. Finally, evidence was show that LDA initiate before 16 weeks of gestation work better than after.

Therefore, whether LDA treatment reduces the risk of PE and affects pregnancy outcome in women at high risk initiating LDA therapy in second trimester is still unresolved [31,32]. This meta-analysis was performed to clarify this problem.

Materials and Methods

Literature search

Comprehensive computerized literature searches were conducted in PubMed, EMBASE, Cochrane database, ScienceDirect, and Biosis Preview. The following medical key words and headings were used: "aspirin," "acetylsalicylic acid," "preeclampsia," "hypertensive" and "hypertensive disorders complicating pregnancy." Studies were searched without restriction on sample size and population, and all searches were published up to February 2015. Relevant references cited in the articles were also explored and included. All RCTs evaluating the effect of aspirin were reviewed. In these studies, all pregnant women with PE risk started LDA (range from 60 to 150 mg/d) therapy during the second trimester (14 to 28 weeks of gestation).

Inclusion and exclusion criteria

Any published studies were included based on the following criteria: (i) studies that dedicated to probe associations among PE, pregnancy outcome, and LDA therapy started at second trimester; (ii) case–control design; and (iii) sufficient sample size presented to calculate the ORs and 95% CIs.

The criteria used to exclude literature were as follows: (i) meta-analysis, comments, letters, or reviews; (ii) participants who initiated LDA therapy before or after the second trimester, the dosage of aspirin pregnancy women accepted were more than 150 mg/d or less than 60 mg/d, and (iii) studies with more than 20% women lost to follow-up or excluded from analysis to prevent from attrition bias.

Data extraction

Two authors (Haifeng liang and Hongyan Chen) reviewed all the eligible studies and extracted data independently. Data were summarized as follows: the first author, year of publication, total number of participants, dose, and week of gestation when LDA therapy was started, and comparison (Table 1). To ensure accuracy of the extracted information, the two authors checked the extraction results and reached consensus on all of the collected data.

Statistical analysis

The association between PE and pregnancy outcome with aspirin therapy was assessed by odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity among studies was estimated by χ^2 tests and I2 statistic for evaluate the degree of heterogeneity. P values greater than 0.10 were considered heterogeneity was not statistically significant. I^2 less than 25%, no heterogeneity; I^2 rang from 25-50%, moderate heterogeneity; I^2 greater than 50%, large or extreme heterogeneity. Once heterogeneity was not statistically significant, fixed-effects model (the Mantel–Haenszel method) was used for the forest plot [33], on the other side, a random-effects model (the DerSimonian and Laird method) was used [34]. Galbraith plots analysis was performed to explore the source of heterogeneity. To estimate the potential publication bias, Both Egger's test and Begg's funnel plot were performed [35-36]. A sensitivity analysis was used to assess the robustness of the outcomes. All the data were analyzed by Stata 12.0 software. A P value < 0.05 was considered to be statistically and used to assess the significance of the pooled ORs.

Results

Characteristics of the studies

Research with selected key words yielded 695 potentially relevant records, with 405 records left after removal of duplicates. Initial reading was extensive and after screening titles, abstracts, and reviews, 118 relevant studies remained for full-text evaluation. 67 studies that participants initiated LDA therapy before or after the second trimester were excluded. 35 studies were remove because of the dosage of aspirin pregnancy women accepted more than 150 mg/d or less than 60 mg/d. 3 studies with more than 20% women lost to follow-up or excluded from analysis were excluded. After a second round of reading, 13 studies involving 6735 participants fulfilled the criteria for inclusion (Figure 1) [14,20-24,37-43]. The main characteristics of the eligible studies are listed in Table 1.

Among these articles, several studies were used to evaluate pregnancy outcome in women who took LDA during the second trimester (Table 2). Three studies with 435 cases were included for evaluation of IUGR among pregnant women under aspirin therapy during second trimester [38,39,41]. Five studies involving 4365 participants were included in the analysis of postpartum haemorrhage among pregnant women under aspirin therapy [20,24,33,40,43]. Five

Outcome	Number of trails	Number of Participants	Meta-analysis		I-squared
			OR (95% CI)	P Value	
IUGR	3 [41-43]	435	0.66(0.42,1.06)	0.38	0.00%
Postpartum hemorrhage	5 [21,25,37,44,43]	4365	1.09(0.85,1.40)	0.65	0.00%
Birth weight	5 [21,22,24,25,34]	3734	1.06(0.88,1.29)	0.752	0.00%
Preterm delivery	5 [22,23,37,41,43]	1125	0.78(0.57,1.05)	0.28	0.00%

Table 1: The result for pregnancy outcome of LDA therapy.

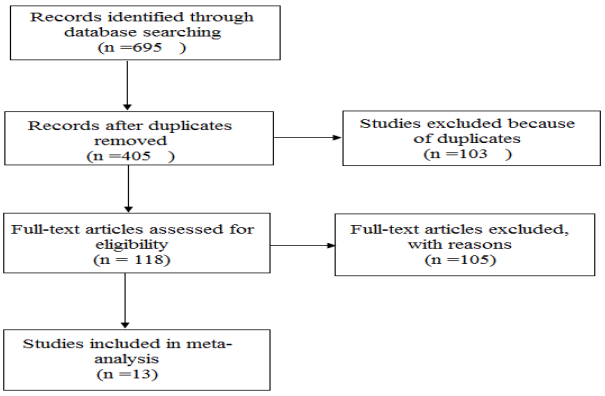

Figure 1: Flow diagram of included studies for this meta-analysis.

studies involving 3734 participants were included in the study of birth weight [20,21,23,24,30]. Five studies with 1125 pregnant women were included in the study of preterm delivery [21,22,33,41,43].

Meta-analysis

In the present study, a statistically significant effect was found among pregnant women who underwent LDA therapy during the second trimester to reduce PE (Figure 2) (13 studies, OR=0.72, 95% CI=0.54–0.95, heterogeneity χ^2: P=0.052, I^2=42.6%).

The overall results for pregnancy outcomes under LDA therapy measures are presented in Table 2. In this analysis, all P values are more than 0.05. The differences between the aspirin and placebo groups were not statistically significant (Figures 3-6). LDA therapy did not significantly affect pregnancy outcomes including preterm delivery, birth weight, postpartum haemorrhage, and IUGR.

Heterogeneity analysis

For the study among pregnant women who underwent LDA therapy during the second trimester, the I^2 value of heterogeneity was 42.6% and heterogeneity χ^2: P=0.052, showed that modarate heterogeneity was observed among the 13 studies. Galbraith plots analysis was performed to explore the source of heterogeneity. Our results showed that Ebrashy et al. [41] and Fan et al. [43] were outliers contributing to the study (Figure 7). By excluding the outliers Ebrashy et al. and Fan et al., I^2 value of heterogeneity decreased and heterogeneity χ^2 was greater than 0.10 (I^2=0.0%, heterogeneity χ^2: P=0.472).

Sensitivity analysis

Sensitivity analysis was conducted to investigate the stability of results by sequential omitting one article each time. The results indicating that no individual study significantly affected the pooled ORs and our outcomes were statistically robust.

Publication bias

Egger's test and Begg's funnel plot were used to evaluate publication bias in all studies including PE prevention and pregnancy outcome by using Stata 12.0 metabias (Figure 8). P values are more than 0.05. The results detected no evidence of publication bias in the analysis of PE prevention and pregnancy outcomes among women under LDA therapy.

Discussion

This meta-analysis review is to conduct a comprehensive survey of PE prevention and pregnancy outcomes under aspirin therapy during second trimester. Meta-analysis performed supports that a statistically significant effect existed among pregnant women who underwent LDA therapy during the second trimester for PE reduction.

Pregnancy outcomes including preterm delivery, birth weight, and IUGR among women who underwent LDA therapy during the second trimester showed no statistical significance between LDA therapy groups and placebo groups. In addition, the incidence of blood loss and bleeding events during delivery were not significantly changed by LDA use, which is contrary to the conclusion proposed by Golding [19].

As a potential problem when discussing the result of the meta-analysis, the sources of heterogeneity should be found [44]. Galbraith plots analysis was used to find the outliers which might contribute to the heterogeneity. The result show that Ebrashy et al. [41] and Fan et al. [43] were outliers contributing to the study about pregnant women who underwent LDA therapy during the second trimester. I^2 value of heterogeneity decreased and heterogeneity χ^2 was greater than 0.10 after excluding the outliers Ebrashy et al. and Fan et al. What's more, by omitting the studies of Ebrashy et al. and Fan et al. the result was not material changed, indicating that our result was robust and reliable. In addition, the result indicated that studies of Ebrashy et al. and Fan et al. were the major source of the heterogeneity.

Powerful searches have been included in the current study;

First author	Year	Number of Participants	Dosage of Aspirin (mg/d)	Comparison	Gestational age at entry (week)
Herabutya [14]	1996	1348	60	Placebo	18-22
Harrington [21]	2000	210	100	No treatment	17-23
Morris [22]	1996	102	100	Placebo	18
Speer [23]	2004	559	150	Placebo	22-24
Kyle [24]	1995	80	60	Placebo	28
Subtil [25]	2003	3271	100	Placebo	14-20
Chiaffarino [41]	2004	35	100	No treatment	14
Bower [42]	1996	61	60	Placebo	24
Byaruhanga [43]	1998	230	75	Placebo	20-28
Parra [44]	2003	554	150	Placebo	22-24
Ebrashy [41]	2005	139	75	No treatment	14-16
Wallenburg [42]	1986	46	60	Placebo	28
Fan [43]	2005	100	100	Vitamin E	18-20

Table 2: The main characteristics of the eligible studies for the meta-analysis.

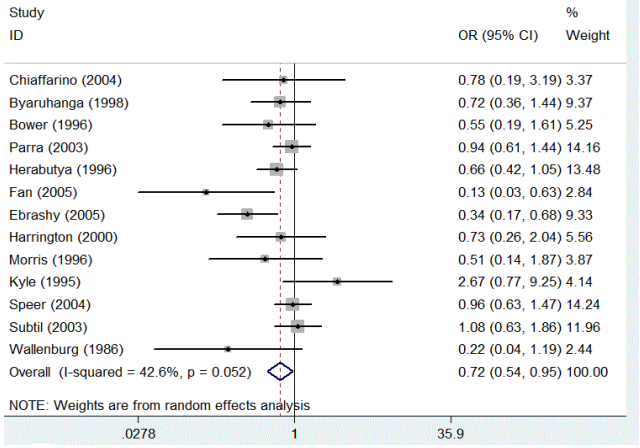

Figure 2: Forest plot for the effect of LDA therapy in reducing preeclampsia. CI: Confidence Interval; OR: Odds Ratio.

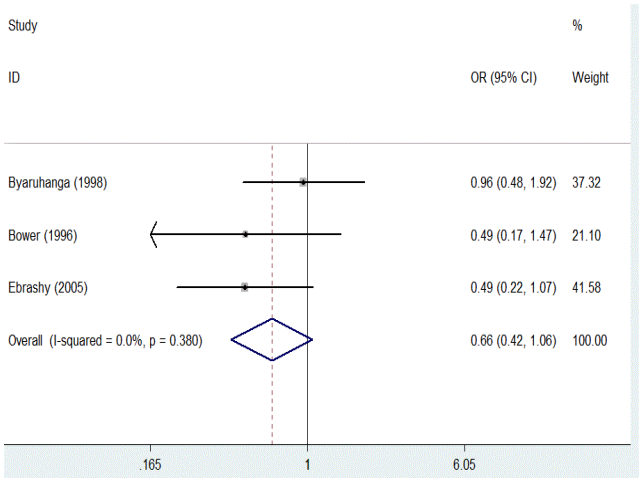

Figure 3: Forest plot to evaluate the association between LDA therapy with IUGR (Intrauterine growth restriction).

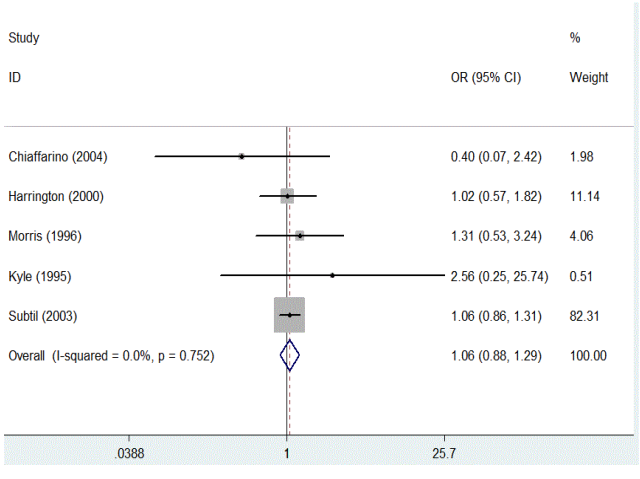

Figure 4: Forest plot to evaluate the association between LDA therapy with birth weight.

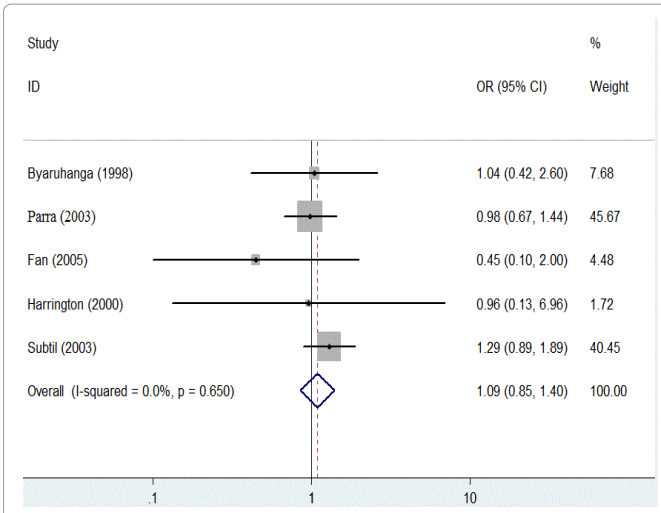

Figure 5: Forest plot to evaluate the association between LDA therapy with postpartum haemorrhage.

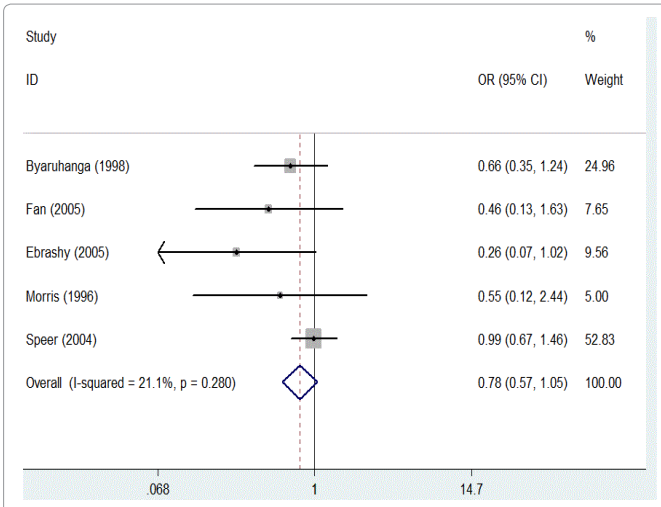

Figure 6: Forest plot to evaluate the association between LDA therapy with preterm delivery.

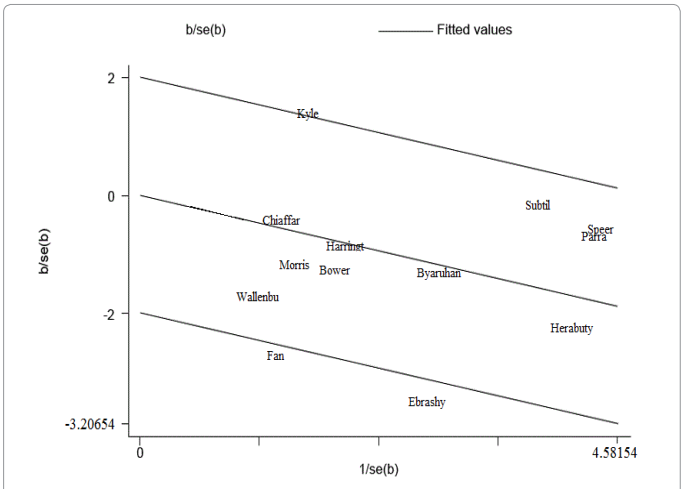

Figure 7: Galbraith plots analysis of LDA therapy in reducing PE. Studies of Ebrashy et al. and Fan et al. were spotted as outlier.

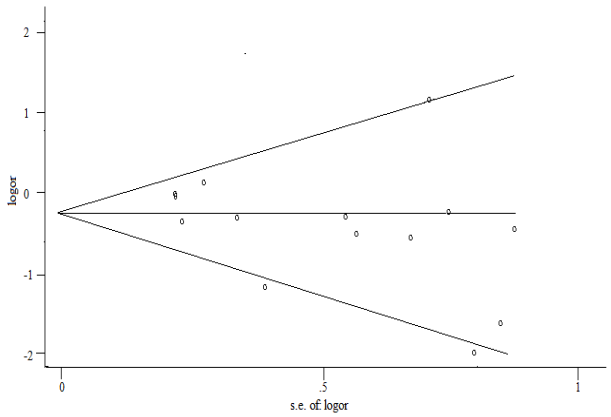

Figure 8: Funnel plot for publication bias prevention of preeclampsia with aspirin therapy in second trimester.

nonetheless, several potential limitations must be considered. First, unpublished data and papers published in languages other than Chinese and English may lead to publication bias, even though no statistical evidence was found. Second, the number of studies included in the analyses of pregnancy outcomes was relatively small. Third, the number of eligible studies was relatively small for the meta-analysis about the effect of LDA to pregnancy outcomes. Meta-analysis can detect small effects by increasing the sample size. Thus, further well-designed studies with large sample size are needed to confirm our findings.

In summary, this comprehensive meta-analysis provides evidence that LDA therapy during second trimester reduced PE incidence. Meanwhile, pregnancy outcomes among women who started LDA therapy during second trimester were not statistically significant. Therefore, we suggest that LDA should be given to women at high-risk women for PE.

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