

An Overview of Prophylactic Acetylsalicylic Acid for the Prevention of Intra-uterine Growth Restriction (IUGR) in Women at Risk for Preeclampsia

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Abstract

Background: Preeclampsia is a major global cause of maternal, neonatal and perinatal mortality. The aim of this review was to summarize all reviews on Acetylsalicylic Acid for the prevention of Intra-uterine Growth Restriction (IUGR) in women at risk for Preeclampsia.

Materials and Methods: In this overview we searched databases following Medline, Scopus, EMBASE, Central Records Central Register Cochrane and the Web of Science databases for finding related articles regarding Acetylsalicylic Acid on the prevention of IUGR in women at high risk for Preeclampsia. Search was conducted from 1996 to 5 April 2019 with English keywords. Any meta-analysis (published or unpublished), was eligible for inclusion. No language restriction was imposed.

Results: Finally eight meta-analysis were included in the review. Acetylsalicylic acid begun at 16≤weeks significantly reduced IUGR in women; but it was not effective in the subgroups of women who took acetylsalicylic acid when they had gestational age of more than 16 weeks. One meta-analysis showed that acetylsalicylic acid was superior to control group in decreasing of IUGR in East Asians (OR=0.36); while no significant effectiveness was observed in non-East Asians (OR = 0.85). According to one meta-analysis, a dose-response effect of acetylsalicylic acid (p=0.04) on IUGR was observed if it was begun at 16≤ weeks. However, a dose-response effect (p= 0.95) was not seen if women started acetylsalicylic acid when they were in gestational age more than 16 weeks.

Conclusion: Acetylsalicylic acid has decreased the incidence of IUGR if administrated before or at 16 weeks. Acetylsalicylic acid was superior to control group in decreasing IUGR risk in East Asians but not in non-East Asians.

Key Words: Acetylsalicylic Acid, Intra-uterine Growth Restriction, Preeclampsia, Women.

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1- INTRODUCTION

Preeclampsia is a pregnancy specific form of hypertension that presents a major health problem worldwide. Preeclampsia complicates 5 to 8% of all pregnancies and increases both maternal and neonatal morbidity and mortality (1). Blood pressure disorder during pregnancy is known to be the main death cause of fetuses, neonates, and mothers. Pregnant women with hypertension are at high risk of acute complications such as stroke, cerebral edema, liver infarction, preterm birth, eclampsia, placental abruption, placenta intrauterine growth retardation (2, 3). In patients who have a new blood pressure of 140/90 mmHg, the control and management of hypertension are important during the admission and scheduling process for delivery (2, 4, 5).

Nevertheless, disordered trophoblast invasion of the maternal spiral arteries in early pregnancy is known to lead to under perfusion of the placenta and, ultimately, placental ischaemia and infarction. The resultant placental damage is thought to lead to activation of platelets and the clotting system and to an imbalance between prostacyclin, a vasodilator, and thromboxane, a vasoconstrictor and stimulant of platelet aggregation (6). In general, stresses, as well as placenta development disorder, followed by oxidative stress, inordinate production of free radicals and increased sensitivity to angiotensin II ultimately lead to vascular constriction and hypertension in Preeclampsia (2, 4, 5).

Treatment of eclamptic seizures in patients with hypertensive pregnancy is magnesium sulfate (MgSO₄), it must not be initially administered as a first line treatment against the hypertension. Hydralazine, Nifedipine or Labetalol, which are known as the most important alternatives for the anti-hypertensive medicines, have lately been suggested to treat severe gestational hypertension (7). Its complications are still

inevitable. The labetalol has been reported to enhance the risk of neonatal bradycardia (8). The hydralazine is also associated with reflux tachycardia, lupus-like syndrome, vasculitis, hemolytic anemia, and glomerulonephritis (7). Indeed, numerous studies have suggested that antiplatelet agents such as aspirin can prevent gestational hypertension and preeclampsia in patients with high-risk pregnancies (9). As far as we know, seven meta-analyses have been done to assess the effect of Acetylsalicylic acid on IUGR. Each meta-analysis reported different subgroups such as country, dosage and administration time of acetylsalicylic acid. The aim of this review was to address all subgroups in a review to provide enough information to both patients and health care providers.

2- MATERIALS AND METHODS

2-1 Search Strategy

In this overview study, we searched databases including Medline, Scopus, EMBASE, the Cochrane Central Register of Controlled Trials, and the Web of Science databases for finding related articles on Acetylsalicylic acid on the Prevention of Intra-uterine Growth Restriction in women at risk for Preeclampsia.

We used a combination of key words and Medical Subject Headings terms: "aspirin", "antiplatelet", "acetylsalicylic acid", "ASA", "pregnancy-complication", "pregnancy", "preeclampsia", "preeclampsia", "hypertension", "blood pressure", "eclampsia", "PIH", "toxemia", and "Meta-analysis". No language restriction was imposed. Meta-analysis included in review was detected using a search of studies published from January 1966 through April 2019. Process of selecting the meta-analysis studies is shown in **Figure.1**.

2-2. Data extraction

Table.1 shows the characteristics of studies included in our systematic review such as publication year, the name of first author, number of studies including meta-analysis and type of treatment in intervention/control (9-16). Two authors who were blinded to the authors of meta-analysis extracted information on the study.

2-3. Quality assessment

The assessment of quality of meta-analysis followed by PRISMA Statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (17). The assessment of bias followed the criteria appraisal tool from the Center for Evidence Based Medicine (CEBM) are shown in **Table.1**. Also, quality of each of articles assessed by two authors based on the Critical Appraisal Tool from the Center for Evidence Based Medicines (18).

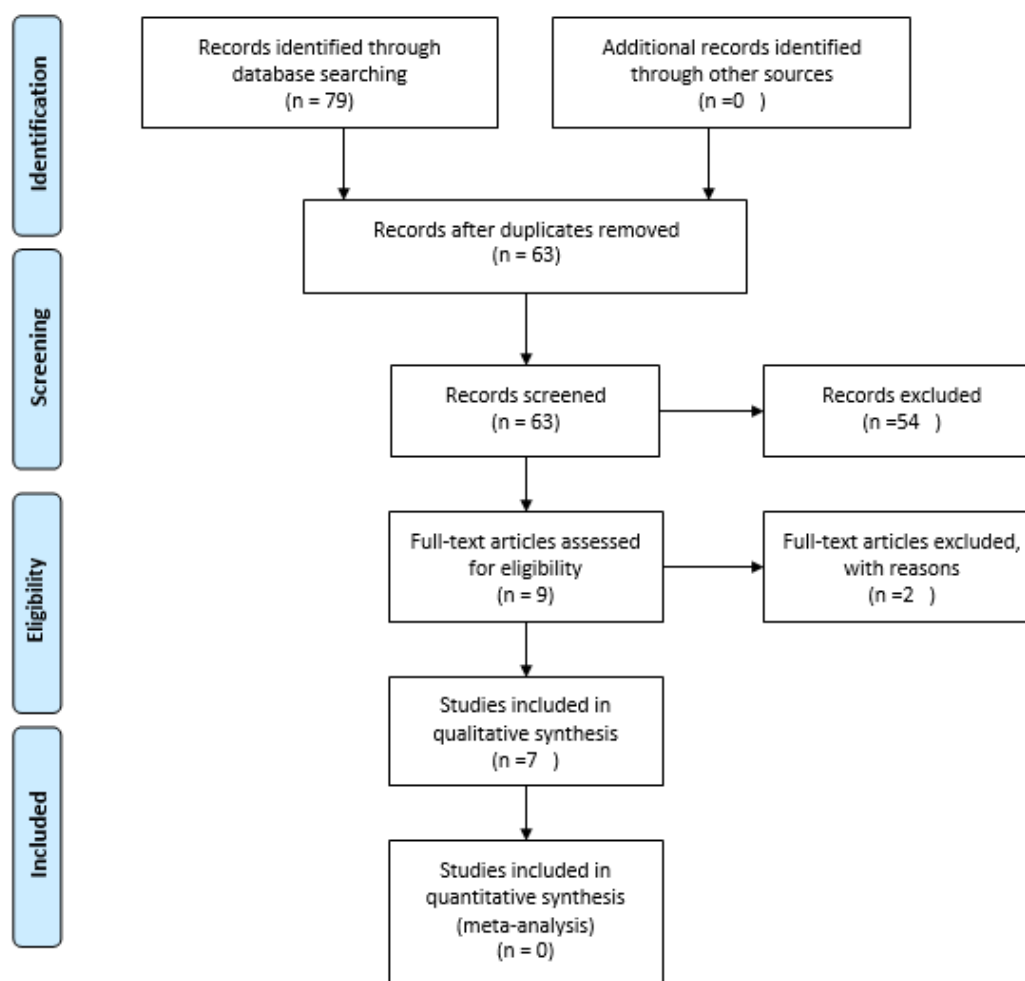


Fig.1: PRISMA flochart.

3- RESULTS

3-1. The effect of Acetylsalicylic Acid on IUGR

We found eight meta-analyses in our search on the effect of Acetylsalicylic acid on IUGR. In the first meta-analysis,

Acetylsalicylic acid was begun at 16 \leq weeks and significantly reduced (Relative risk [RR]: 0.44). But it was not effective in the subgroup of women who took it when they were at more than 16 weeks of gestational age (RR: 0.98) (10). In second meta-analysis, if Acetylsalicylic acid was

begun at $16 \leq$ weeks, it could significantly decrease the incidence of IUGR (RR: 0.44). But it was not effective if started after 16 weeks (RR: 0.98). There was not any significant difference between two subgroups (9). In third meta-analysis, subgroup who took Acetylsalicylic acid in ≤ 16 weeks gestation showed better effect in reducing IUGR than subgroup (>16 weeks gestation) ($p < 0.001$) (11). In fourth meta-analysis, receiving Aspirin at 16 weeks or less was linked with a significant decrease in incidence of IUGR (RR: 0.56; $p < 0.001$), and also a dose-response effect of acetylsalicylic acid ($p = 0.04$) was observed. However, if women started Aspirin when they were in gestational age more than 16 weeks, a non-significant reduction was seen in incidence of preeclampsia (RR: 0.95), a dose-response effect (0.95) was not seen (12). In fifth meta-analysis, authors conducted a subgroup based on type of country. Acetylsalicylic Acid was superior to control group in decreasing IUGR risk in East Asians (OR: 0.36); while, no significant effect was observed in non-East Asians (OR: 0.85) (13).

In 6th meta-analysis, no significant difference was observed between two groups of aspirin and control group incidence of IUGR in high risk group (OR: 0.96; 95% confidence interval [CI]: 0.83–1.11; $p = 0.60$) (14). In 7th meta-analysis, in the high-risk group, risk of IUGR decreased by 11% after administration of low dose acetylsalicylic acid and low dose acetylsalicylic acid failed to produce significant reduction in the risk of IUGR in the low-risk group (16). In 8th meta-analysis, 60 mg of Acetylsalicylic acid started before 17 weeks gestation showed no benefits for SGA (RR: 0.84; 95% CI: 0.56–1.26), when only Large Randomized Trials were included into Meta-analysis (15). In 9th meta-analysis, no heterogeneity was identified ($I^2 = 0\%$). Meta-analysis with fixed-effects model

with 7 RCTs suggested the acetylsalicylic acid reduced the risk of IUGR or SGA (RR: 0.71; 95% CI: 0.58-0.89; $p = 0.004$) (15).

4- DISCUSSION

The aim of this review was to summarize all reviews on Acetylsalicylic acid for the prevention of Intra-uterine Growth Restriction (IUGR) in women at risk for Preeclampsia. Crandon and Isherwood (1979) highlighted for the first time that the administration of Aspirin may impede the female preeclampsia. The first randomized controlled trial (1985) documented that the administration of Acetylsalicylic acid could be useful to inhibit the fetal growth retardation, fetal death and preeclampsia (9). Afterwards, numerous meta-analyses were done in this field (19-28).

IUGR is defined as birth weight below the 10th percentile. Acetylsalicylic acid if begun at $16 \leq$ weeks significantly reduced IUGR. In a meta-analysis, authors conducted a subgroup based on type of country. Acetylsalicylic acid was superior to control group in decreasing risk of IUGR risk in East Asians. Whereas no significant effect was observed in non-East Asians. The attained results can be influenced by various standards of prenatal care, diet, and exercise among patient populations of East Asian and non-East Asian (10).

4-1. Action mechanism of Acetylsalicylic Acid

The activation of clotting and platelet systems can result in endothelial dysfunction due to inappropriate perfusion and placental ischemia. Therefore, the hypothesis is that preeclampsia may be inhibited by antiplatelet agents, and there has been special attention to IUGR in the past 30 years. The thromboxane-mediated vasoconstriction could be prevented by Acetylsalicylic acid, resulting in protection

against placental vasoconstriction and pathological blood coagulation. Accordingly the failure of physiological spiral artery transformation is expected, thereby increasing the risk of preeclampsia and IUGR (13). The clinical consequences of our results are significant. To avoid these results, low-dose aspirin should be begun early in pregnancy.

4-2. Study Limitations

One of the limitations of our review article was English-limited meta-analysis, so that English articles published the effectiveness of intervention, whereas the articles in language other than English reported less significant outcomes, meaning language bias (16).

5- CONCLUSION

Acetylsalicylic acid decreased the incidence of IUGR if administered before or at 16 weeks. Acetylsalicylic acid was superior to control group in decreasing the IUGR risk in East Asians but not in non-East Asians. Low-dose aspirin (LDA) has been used as a strategy for secondary prevention of preeclampsia. However, as observed in the present analysis, low-dose aspirin exhibits only a small effect in the prevention of preeclampsia and this benefit is restricted to the high-risk group, showing that we still need to study and better understand the pathophysiology of preeclampsia.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Quitterer U, Lothar H, Abdalla S, editors. AT1 receptor heterodimers and angiotensin II responsiveness in preeclampsia. *Seminars in nephrology*; 2004: Elsevier.
2. Brennan LJ, Morton JS, Davidge ST. Vascular dysfunction in preeclampsia. *Microcirculation*. 2014;21(1):4-14.
3. Helewa ME, Burrows RF, Smith J, Williams K, Brain P, Rabkin SW. Report of the Canadian Hypertension Society Consensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. *Canadian Medical Association Journal*. 1997;157(6):715-25.
4. Gasperin D, Netuveli G, Dias-da-Costa JS, Pattussi MP. Effect of psychological stress on blood pressure increase: a meta-analysis of cohort studies. *Cadernos de Saúde Pública*. 2009;25:715-26.
5. Cunningham FG, MacDonald PC, Gant NF. *Williams obstetrics*: McGraw-Hill Professional New York, NY; 2018.
6. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *The Lancet*. 2007;369(9575):1791-8.
7. Abdelrahman TN, Youssry MA, Radwan AM, Ahmed A. Impact of intravenous infusion of labetalol combined with magnesium sulfate versus hydralazine combined with magnesium sulfate on fetomaternal hemodynamics in severe preeclampsia. *Ain-Shams Journal of Anesthesiology*. 2019;11(1):5.
8. Vigil-De Gracia P, Lasso M, Ruiz E, Vega-Malek JC, de Mena FT, López JC. Severe hypertension in pregnancy: hydralazine or labetalol: a randomized clinical trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2006;128(1-2):157-62.
9. Xu Tt, Zhou F, Deng Cy, Huang Gq, Li Jk, Wang Xd. Low-Dose aspirin for preventing preeclampsia and its complications: a meta-analysis. *The Journal of Clinical Hypertension*. 2015;17(7):567-73.
10. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstetrics & Gynecology*. 2010;116(2):402-14.
11. Roberge S, Nicolaidis K, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. *Ultrasound in obstetrics & gynecology*. 2013;41(5):491-9.

12. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. *American journal of obstetrics and gynecology*. 2017;216(2):110-20. e6.
13. Gan J, He H, Qi H. Preventing preeclampsia and its fetal complications with low-dose aspirin in East Asians and non-East Asians: a systematic review and meta-analysis. *Hypertension in pregnancy*. 2016;35(3):426-35.
14. Rossi AC, Mullin PM. Prevention of pre-eclampsia with low-dose aspirin or vitamins C and E in women at high or low risk: a systematic review with meta-analysis. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2011;158(1):9-16.
15. Cui Y, Zhu B, Zheng F. Low-dose aspirin at \leq 16 weeks of gestation for preventing preeclampsia and its maternal and neonatal adverse outcomes: A systematic review and meta-analysis. *Experimental and therapeutic medicine*. 2018;15(5):4361-9.
16. Trivedi N. A meta-analysis of low-dose aspirin for prevention of preeclampsia. *Journal of postgraduate medicine*. 2011;57(2):91.
17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP & et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *Ann Intern Med*. 2009; 151(4):W65-94.
18. Center for Evidence Based Medicine (CEBM). Critical Appraisal tools. Available at: <https://www.cebm.net/2014/06/critical-appraisal/>.
19. Groom, Katie M. *Francog, Cmf*. The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction. *Am J Obstet Gynecol*. 2018; 218(2S):S829-S840.
20. Leitich H, Egarter C, Husslein P, Kaidler A, Schemper M. A meta-analysis of low dose aspirin for the prevention of intrauterine growth retardation. *Br J Obstet Gynaecol*. 1997;104(4):450-9.
21. Golding J. A randomised trial of low dose aspirin for primiparae in pregnancy. The Jamaica Low Dose Aspirin Study Group. *Br J Obstet Gynaecol*. 1998;105(3):293-9.
22. Vainio M, Kujansuu E, Iso-Mustajärvi M, Mäenpää J. Low dose acetylsalicylic acid in prevention of pregnancy-induced hypertension and intrauterine growth retardation in women with bilateral uterine artery notches. *BJOG*. 2002; 109(2):161-7.
23. Lin L, Zhu Y, Li B, Yang H. APPEC Study Group. Low-dose aspirin in the prevention of pre-eclampsia in China (APPEC study): protocol for a multicentre randomized controlled trial. *Trials*. 2018;19(1):608.
24. Mone F, Mulcahy C, McParland P, Stanton A, Culliton M, Downey P, et al. An open-label randomized-controlled trial of low dose aspirin with an early screening test for pre-eclampsia and growth restriction (TEST): Trial protocol. *Contemp Clin Trials*. 2016;49:143-8.
25. Yu CK, Papageorgiou AT, Parra M, Palma Dias R, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Randomized controlled trial using low-dose aspirin in the prevention of pre-eclampsia in women with abnormal uterine artery Doppler at 23 weeks' gestation. *Ultrasound Obstet Gynecol*. 2003;22(3):233-9.
26. Villa PM, Kajantie E, Räikkönen K, Pesonen AK, Hämäläinen E, Vainio M, et al. Aspirin in the prevention of pre-eclampsia in high-risk women: a randomised placebo-controlled PREDO Trial and a meta-analysis of randomised trials. *BJOG*. 2013;120(1): 64-74.
27. Huang J, Chen X, Xing H, Chen L, Xie Z, He S, et al. Aspirin and heparin for the prevention of pre-eclampsia: protocol for a systematic review and network meta-analysis. *BMJ Open*. 2019;9(2):e026920.
28. Henderson JT, Whitlock EP1, O'Conner E1, Senger CA1, Thompson JH1, Rowland MG1. Low-Dose Aspirin for the Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force [Internet]. Evidence Syntheses, No. 112. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK196392/>.