Aspirin in the Prevention of Fetal Growth Restriction: Its Mechanisms and Clinical Outcomes

Dhanalakshmi Selvam [1], Shalini Sivadasan*

[1]Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore - 641048, Tamil Nadu, India.

*Professor, Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore - 641048, Tamil Nadu, India.

*Corresponding author:

Phone: +91-422-2369302

Email: shaliniravichandran11@gmail.com

ORCID: 0000-0002-4341-7063

ABSTRACT

Background: Foetal growth restriction (FGR) is a serious pregnancy complication associated with long-term adverse outcomes, neonatal morbidity, and stillbirth. Its primary causes include inadequate spiral arterial remodelling, endothelial dysfunction, and reduced placental perfusion. Low-dose aspirin (LDA) has been extensively studied for improving uteroplacental blood flow through its antiplatelet, anti-inflammatory, and vasodilatory effects. Initiating aspirin before 16 weeks of gestation significantly reduces FGR risk in high-risk pregnancies. **Main Body:** A literature review was conducted using PubMed and related databases to identify clinical trials, meta-analyses, and guideline statements assessing aspirin for FGR and preeclampsia prevention. Key search terms included low-dose aspirin, foetal growth restriction, preeclampsia, placental insufficiency, and pregnancy complications. Studies from India were reviewed separately to highlight regional evidence variations. **Results:** Randomized trials and meta-analyses indicate that aspirin enhances uteroplacental circulation, lowers preeclampsia risk, and reduces FGR incidence, particularly when started before 16 weeks at

100–150 mg daily. Safety outcomes are favourable, with minimal maternal or neonatal adverse effects at recommended doses. However, compliance and outcomes vary due to differences in healthcare access, antenatal care timing, and practices. In India, limited large-scale studies and inconsistent guidelines have hindered routine aspirin use in obstetric care. **Conclusion:** Low-dose aspirin is a safe, cost-effective intervention that reduces FGR and associated complications when initiated early in high-risk pregnancies. Despite global recommendations, its use remains suboptimal in some regions, including India. Population-specific trials and standardized national protocols are needed to optimize clinical benefits.

Keywords

Endothelial dysfunction, Uteroplacental circulation, Preeclampsia, Placental insufficiency, Low-dose aspirin, Foetal growth restriction

1.INTRODUCTION

Fetal growth restriction (FGR), which affects 5–10% of pregnancies globally, is still a major problem in obstetric care. It's a condition where the fetus doesn't reach its genetically set growth potential, which frequently results in higher risks of perinatal morbidity and death. The main cause of FGR is known to be placental insufficiency, however the pathogenesis is complex. Reduced placental function causes the growing fetus to receive insufficient oxygen and nutrients, which restricts growth and can lead to a number of negative consequences, such as preterm birth, stillbirth, and long-term neurodevelopmental damage.[1,2]

One of the most studied prophylactic interventions for preventing FGR is low-dose aspirin (LDA), a widely available and cost-effective antiplatelet agent. Aspirin is commonly prescribed during pregnancy to mitigate the risk of preeclampsia, a hypertensive disorder characterized by endothelial dysfunction and placental hypoperfusion, both of which contribute to

FGR.[3] Its use in obstetrics is primarily based on its ability to inhibit platelet aggregation and reduce systemic inflammation, thereby improving placental perfusion and fetal growth. The mechanism of aspirin in preventing pre-eclampsia is shown in figure 1. However, the precise mechanisms by which aspirin exerts its protective effects against FGR remain as an area of active research.[4]

Several clinical trials and meta-analyses have evaluated the efficacy of aspirin in preventing FGR, with varying results. Studies indicate that the timing, dosage, and patient selection significantly influence aspirin's effectiveness.[4] Early initiation of aspirin therapy, particularly before 16 weeks of gestation, has been associated with greater benefits in reducing the incidence of FGR and related complications. Furthermore, emerging evidence suggests that personalized risk stratification, incorporating maternal risk factors and biomarkers, can optimize aspirin therapy and enhance clinical outcomes. Despite its potential benefits, concerns remain regarding aspirin's safety and effectiveness in diverse populations. While most studies report minimal adverse effects, questions persist about the ideal dosage, duration of therapy, and its impact on neonatal health. Additionally, certain subgroups of pregnant women may not respond adequately to aspirin, possibly due to genetic variations affecting drug metabolism and response.[5]

These uncertainties highlight the need for further research to refine aspirin's role in preventing FGR and to develop targeted therapeutic strategies for at-risk pregnancies. This review explores the mechanistic pathways through which aspirin may prevent FGR, summarizes the key clinical findings regarding its efficacy and safety, and discusses the potential future directions in optimizing aspirin therapy for fetal growth restriction prevention. Understanding these aspects is crucial for improving maternal-fetal health and reducing the burden of FGR-related complications worldwide.[6]

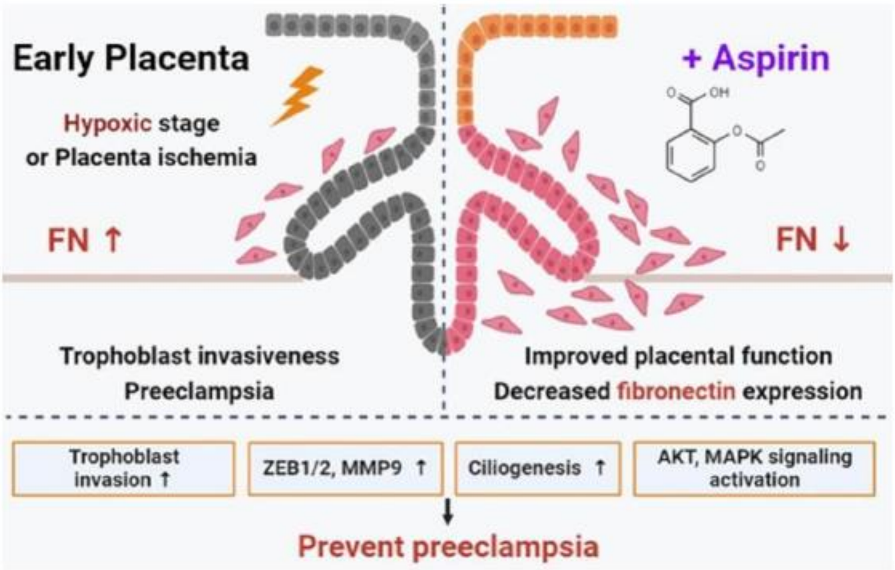

Figure 1. Aspirin's Mechanism in preventing pre-eclampsia.[7]

2. MAIN BODY

2.1 METHODS

2.1.1 Data Sources

A comprehensive literature search was conducted using PubMed, scopus, google scholar, and cochrane library databases to identify studies published between 2000 and 2025. Additional resources such as national and international obstetrics guidelines (e.g., ACOG, WHO, NICE) and reference lists of selected articles were also screened.[8]

2.1.2 Search Strategy

The following keywords and MeSH terms were applied in different combinations: 'low-dose aspirin", "fetal growth restriction", "intrauterine growth restriction", "placental insufficiency", "preeclampsia", "pregnanc y complications", and "uteroplacental circulation". Boolean operators (AND/OR) were used to refine results.

2.1.3 Inclusion Criteria

- Clinical trials (randomized or observational), meta-analyses, systematic reviews, and relevant narrative reviews

- Studies focusing on the prevention of FGR or preeclampsia with aspirin therapy
- Studies in both singleton and multiple pregnancies

2.1.4 Exclusion Criteria

- Case reports, editorials, and conference abstracts without sufficient data.[9,10]

2.1.5 Data Extraction

From each eligible study, information regarding population characteristics, aspirin dosage, timing of initiation, duration of therapy, outcomes (incidence of FGR, preeclampsia, perinatal morbidity and mortality), and safety endpoints were extracted. Where available, region-specific evidence (particularly from India and other low- and middle-income countries) was highlighted to address contextual differences.[11]

2.2 CLASSIFICATION OF FGR

FGR is classified into two major types: Early-onset FGR and Late-onset FGR

2.2.1 Early-onset FGR (before 32 weeks): Usually linked to maternal vascular problems, preeclampsia, or placental insufficiency. It frequently manifests as increased perinatal mortality and aberrant uterine artery Doppler findings.

2.2.2 Late-onset FGR (beyond 32 weeks): More common, less severe in appearance, and frequently linked to a small placental malfunction and an increased chance of stillbirth.[12,13]

2.3 IMPORTANCE FOR OBSTETRICS

FGR has a significant role in long-term neurodevelopmental problems, neonatal difficulties, and stillbirths. Later in life, it is linked to cardiovascular disorders, metabolic abnormalities, and hypoxia. Early detection and intervention, including the use of low-dose aspirin, are necessary to improve foetal outcomes.[14]

2.3.1. Fetal Growth Restriction Epidemiology (FGR)

A major public health concern, foetal growth restriction (FGR) affects 5–10% of babies worldwide. It is particularly prevalent in low- and middle-income countries (LMICs) due to poor nutrition, access to healthcare, and maternal health. FGR is a major cause of infant fatalities worldwide, contributing considerably to perinatal morbidity, stillbirths, and long-term problems.[15] Maternal, foetal, placental, and environmental variables are among the multifactorial risk factors for FGR. Hypertensive disorders, preeclampsia, diabetes, chronic renal disease, anaemia, and malnutrition are among the maternal risk factors. Furthermore, because of the decreased oxygen availability, smoking, substance misuse, and high-altitude pregnancies raise the risk of FGR.[16]

Limited foetal growth is caused by placental failure, inadequate trophoblast invasion, and vascular insufficiency, whereas foetal causes include chromosomal abnormalities, congenital infections and multiple gestations.[17]Additionally important are socioeconomic factors such mother stress, poverty, and poor prenatal care. Early detection, maternal dietary interventions, aspirin prophylaxis, and better prenatal care especially in high-risk populations, are the main focuses of efforts to lower FGR.[18]

2.4 PATHOPHYSIOLOGY

Maternal risk factors such as hypertension, preeclampsia, malnutrition, and smoking play a crucial role in compromising normal placental development. These factors contribute to poor trophoblast invasion, resulting in the failure of proper placental implantation. Consequently, impaired spiral artery remodelling occurs, leading to high-resistance uteroplacental circulation. This inadequate blood flow causes placental hypoxia and oxidative stress, triggering inflammatory responses, apoptosis, and placental dysfunction. The ensuing vascular insufficiency further reduces maternal-foetal blood exchange, increasing placental resistance. As a result, endothelial dysfunction develops due to an imbalance between vasodilators and vasoconstrictors, ultimately reducing oxygen and nutrient transport to the foetus. This cascade of events culminates in foetal growth restriction, characterized by chronic hypoxia, metabolic disturbances, and neurodevelopmental impairment.[19,20]

2.5 ASPIRIN IN PREGNANCY

Aspirin's antiplatelet, anti-inflammatory, and vasodilatory actions on the placenta are important in preventing foetal growth restriction (FGR).[12] It improves uteroplacental circulation and stops excessive platelet aggregation by inhibiting cyclooxygenase-1 (COX-1) and lowering thromboxane A2 levels. In addition, aspirin inhibits oxidative stress and inflammatory cytokines, preventing vascular damage to the placenta.[21] It also increases the generation of prostacyclin and nitric oxide, which causes vasodilation and better blood flow, which improves foetal growth and oxygenation. When combined, these strategies reduce the risk of FGR and preeclampsia.[22]

2.5.1 The effect of aspirin on uteroplacental blood flow

By blocking the powerful vasoconstrictor thromboxane A2, aspirin increases the generation of prostacyclin and nitric oxide, which causes vasodilation and lowers vascular resistance, hence improving uteroplacental perfusion. This promotes placental blood flow, improves spiral artery remodelling, and guarantees optimum foetal oxygenation.[23] Aspirin prevents placental ischemia by lowering micro thrombosis and endothelial dysfunction, which in turn lowers the risk of preeclampsia and foetal growth restriction (FGR).[24]

2.5.2 Aspirin during high-risk pregnancy

Women who have a history of FGR, preeclampsia, thrombophilia, or other conditions that increase their risk of FGR are advised to take aspirin. Aspirin decreases the incidence of hypertension, enhances placental blood flow, and lessens endothelial dysfunction in preeclampsia.[25] It improves uteroplacental circulation in thrombophilia by preventing placental micro thrombosis. The vasodilatory properties of aspirin help women with a history of FGR by maximizing foetal oxygenation and nutrition supply. A dose of 100–150 mg per day and early beginning (12–16 weeks) decrease the risk of unfavourable pregnancy outcomes.[26] The timing and dosage of aspirin to be administered for the prevention of FGR is shown in table 1.

Table 1. Dosing of aspirin for FGR prevention[27]

PARAMETER	RECOMMENDATION	JUSTIFICATION
Ideal Start-Up Time	Prior to 16 weeks of pregnancy, ideally between 12 and 16 weeks	Aspirin can enhance spiral artery remodelling and placental implantation with early beginning, lowering the risk of FGR and preeclampsia.
Advice Regarding Dosage	75–150 mg daily, usually 100–150 mg before bed	Preventing preeclampsia and lowering placental vascular resistance are better achieved with higher dosages (≥100 mg).
Therapy Duration	Up to 36 weeks before delivery or gestation	Aspirin's protective effects on placental blood flow are maintained when it is stopped prior to labour, lowering the risk of haemorrhage.

2.5.3 Safety profile of aspirin in pregnancy

Low-dose aspirin is considered safe during pregnancy, especially for preventing preeclampsia and foetal growth restriction. Doses between 75–150 mg per day, started early (12–16 weeks) and continued until 36–37 weeks, have shown significant benefits without major risks to the mother or baby. Studies confirm that low-dose aspirin does not increase the risk of bleeding or birth defects and is recommended by major health organizations like WHO and ACOG for high-risk pregnancies.[28] As part of the safety profile of aspirin in pregnancy, the potential maternal and foetal risks must be considered**.**

Maternal Hazards: The risk of postpartum haemorrhage (PPH) is increased by aspirin's inhibition of platelet aggregation, especially when anticoagulants are used along. With continuous treatment, some women may develop peptic ulcers, reflux, or gastritis.

Foetal Risks: This includes complications related to neonatal bleeding. Aspirin may change the haemostasis of newborns, which raises the risk of brain haemorrhage if taken shortly before delivery, however this is uncommon. Ductus arteriosus constriction: Excessive dosages (>150 mg) may result in the ductus arteriosus closing too soon, which could harm the foetus's cardiovascular system.[29,30]

2.5.4 Aspirin use in multiple pregnancies: effectiveness in twin and higher-order gestations.[31]

The preventive pathway and clinical benefits of using low-dose aspirin in multiple pregnancies, such as twins or triplets, to reduce the risk of preeclampsia and foetal growth restriction (FGR). The process begins with the identification of multiple gestations, which are associated with an increased risk of preeclampsia and FGR due to heightened placental demand, vascular dysfunction, and endothelial stress. To counteract these complications, low-dose aspirin (100–150 mg/day) is recommended to be initiated between 12 and 16 weeks of gestation. Early initiation is vital because it supports placental development and improves blood flow during the critical early stages of pregnancy.

The mechanism of action of aspirin includes inhibition of platelet aggregation through its antiplatelet effect, reduction of inflammation due to its anti-inflammatory property, and enhancement of uteroplacental blood flow via vasodilation. These effects together help in maintaining better placental perfusion and reducing oxidative stress. Continuous use of aspirin therapy until 36–37 weeks or until delivery has been shown to decrease the risk of preeclampsia by approximately 30%, reduce the incidence of foetal growth restriction, and improve birth weight and neonatal outcomes. Overall, the use of low-dose aspirin in multiple pregnancies contributes to a safer pregnancy with reduced maternal and foetal adverse outcomes, ensuring a healthier outcome for both mother and baby.[31]

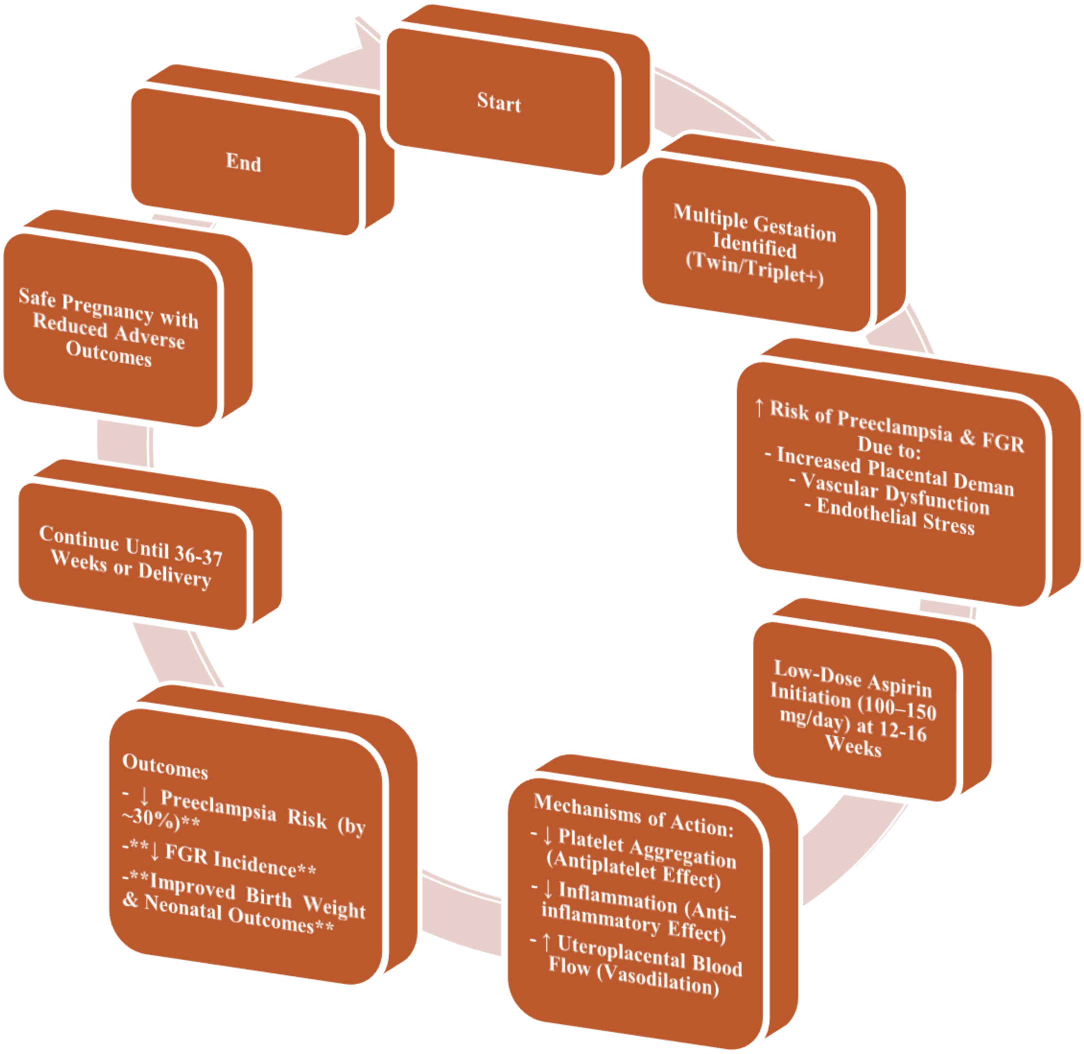

Figure 1. Aspirin use in multiple pregnancies: effectiveness in twin and higher-order gestations

2.6 ASPIRIN AND LONG-TERM FETAL OUTCOMES

The health and neurodevelopment of the unborn child have not been significantly harmed by low-dose aspirin use during pregnancy. Research shows no rise in cerebral palsy, congenital defects, or cognitive impairment. In fact, by enhancing placental perfusion and lowering foetal hypoxia, aspirin may have neuroprotective advantages. According to long-term follow-ups, children exposed to aspirin during pregnancy appear to reach typical developmental milestones.[32] Table 2 shows the aspirin resistance in pregnancy.

Table 2. Aspirin resistance in pregnancy

FACTOR	EFFECT ON ASPIRIN EFFICACY	POTENTIAL SOLUTIONS
Obesity	Increased platelet activation and reduced aspirin bioavailability	Higher aspirin dose (150 mg/day)
Genetic variants (e.g., cox-1 polymorphisms)	Altered aspirin metabolism leads to incomplete platelet inhibition	Genetic screening; alternative antiplatelet therapy
Delayed absorption	Reduced efficacy when taken in the morning due to circadian platelet activation	Nighttime dosing enhances platelet inhibition
Inadequate dosage	Standard 75 mg dose may not be sufficient in high-risk pregnancies	Increase to 100–150 mg/day
Medication interactions	NSAIDs compete with aspirin for COX-1 binding, reducing its effect	Avoid NSAID co-administration
Gastrointestinal PH variability	Gastric acidity affects aspirin dissolution and absorption	Use enteric-coated formulations or buffered aspirin
Pre-Existing Platelet Hyperactivity	Certain pregnancy conditions (e.g., preeclampsia, APS) cause persistent platelet activation	Combination therapy (e.g., aspirin + LMWH).[33,34]

2.7 THE FUTURE OF ASPIRIN IN OBSTETRICS

Recent studies propose that aspirin's benefits extend beyond foetal growth restriction (FGR) and preeclampsia. Its potential to lower stillbirth rates, improve IVF results, and avoid recurrent pregnancy loss is being investigated.[35] The anti-inflammatory and vascular properties of aspirin are also being studied for placenta-mediated problems and gestational diabetes. Effectiveness may be improved by using customized dosage plans and novel biomarkers. Optimal timing, patient selection, and combination therapy are being refined in ongoing trials to optimize benefits and minimize hazards.[36]

2.8 ETHICAL CONSIDERATIONS IN ASPIRIN USE DURING PREGNANCY

The Ethical issues of informed consent, mother autonomy, and risk-benefit balance are brought up by the prescription of aspirin during pregnancy. In order to ensure shared decision-making, clinicians must give patients clear, fact-based information regarding the advantages and possible hazards of aspirin. Particular attention must be paid to situations when access to prenatal care is restricted or health literacy is low. Patient autonomy is emphasized by ethical frameworks, which call for voluntary acceptance free from coercion.[37] Additionally, continuing research and open communication are required due to concerns regarding long-term foetal consequences. In the end, aspirin use ought to be consistent with maternal values and individual risk assessments.[38]

3. CONCLUSION AND FUTURE DIRECTIONS

Preventing foetal growth restriction (FGR) and preeclampsia, enhancing uteroplacental blood flow, and lowering unfavourable pregnancy outcomes are all made possible by low-dose aspirin. Its safety and effectiveness are currently supported by research, especially when started early (12–16 weeks) at 100–150 mg/day. Aspirin resistance, the best dosage for obese women, and its function in multiple gestations are still being studied, though. Large-scale randomized studies can be carried out to improve international standards and broaden the use of aspirin in placental dysfunction disorders beyond its existing indications. Long-term foetal outcomes, genetic factors determining responsiveness, and customized aspirin therapy should be the main topics of future research.

4. REFERENCES

1. Saxena U, Lachyan A, Goyal C, Kapoor G, Agarwal K, Prasad S. Comparison of 75 mg versus 150 mg aspirin for the prevention of preterm preeclampsia in high-risk women at a tertiary level hospital: study protocol for a randomized double-blind clinical trial. Trials. 2024; 25(1):679. Available from https://doi.org/10.1186/s13063-024-08520-z
2. Chaemsaithong P, Appiah K, Sahota D, Leung Ty, Poon Lcy. Screening and prevention of pre-eclampsia: a review. Hong Kong J Gynaecol Obstet Midwifery 2019;19(1):56-72 Available from https://doi.org/10.12809/hkjgom.19.1.07
3. Society for Maternal-Fetal Medicine (SMFM). Electronic address: smfm@smfm.org; Combs CA, Kumar NR, Morgan JL; SMFM Patient Safety and Quality Committee. Society for Maternal-Fetal Medicine Special Statement: Prophylactic low-dose aspirin for preeclampsia prevention-quality metric and opportunities for quality improvement. Am J Obstet Gynecol. 2023; 229(2):B2-B9. doi: 10.1016/j.ajog.2023.04.039. Epub 2023 May 4. PMID: 37146704.
4. Rottenstreich A. Controversies and Clarifications Regarding the Role of Aspirin in Preeclampsia Prevention: A Focused Review. J Clin Med. 2024;13(15):4427. doi: 10.3390/jcm13154427. PMID: 39124694; PMCID: PMC11312818.
5. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016; 164(12):826-35. doi: 10.7326/M15-2112. Epub 2016 Apr 12. PMID: 27064261.
6. LeFevre ML; U.S. Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and

mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Annals of internal medicine. 2014; 161(11):819-26. doi: 10.7326/M14-1884. PMID: 25200125.

7. Firdaus T, Ilyas S. The Role of Aspirin in the Prevention of Preeclampsia (A Mini Review). International Journal of Ecophysiology. 2025; 7(1):79-84. Available from https://doi.org/10.32734/ijoep.v7i1.20227

8. Mollard E, Cottrell C. Lifestyle and the hypertensive disorders of pregnancy in nulliparous women in the United States: a secondary data analysis of the nuMom2b. BMC Pregnancy and Childbirth. 2023; 23(1):201. doi: 10.1186/s12884-023-05522-8. PMID: 36959650; PMCID: PMC10035211.

9. Sutton EF, Rogan SC, Lopa S, Sharbaugh D, Muldoon MF, Catov JM. Early Pregnancy Blood Pressure Elevations and Risk for Maternal and Neonatal Morbidity. Obstet Gynecol. 2020;136(1):129-139. doi: 10.1097/AOG.0000000000003885. PMID: 32541286; PMCID: PMC7321869.

10. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016; 48(3):333-9. doi: 10.1002/uog.15884. PMID: 26909664.

11. Kupka E, Roberts JM, Mahdy ZA, Escudero C, Bergman L, De Oliveira L; Global Pregnancy Collaboration. Aspirin for preeclampsia prevention in low- and middle-income countries: mind the gaps. AJOG Glob Rep. 2024;4(2):100352. doi: 10.1016/j.xagr.2024.100352. PMID: 38694484; PMCID: PMC11061325.

12. Figueras F, Gratacos E. An integrated approach to fetal growth restriction. Best Pract Res Clin Obstet Gynaecol.

2017; 38:48-58. doi: 10.1016/j.bpobgyn.2016.10.006. Epub 2016 Oct 20. PMID: 27940123.

13. Baschat AA. Fetal growth restriction - from observation to intervention. J Perinat Med. 2010; 38(3):239-46. doi: 10.1515/jpm.2010.041. PMID: 20205623.
14. Tsikouras P, Antsaklis P, Nikolettos K, Kotanidou S, Kritsotaki N, Bothou A, Andreou S, Nalmpanti T, Chalkia K, Spanakis V, Iatrakis G, Nikolettos N. Diagnosis, Prevention, and Management of Fetal Growth Restriction (FGR). J Pers Med. 2024; 14(7):698. doi: 10.3390/jpm14070698. PMID: 39063953; PMCID: PMC11278205.
15. Colella M, Frérot A, Novais ARB, Baud O. Neonatal and Long-Term Consequences of Fetal Growth Restriction. Curr Pediatr Rev. 2018;14(4):212-218. doi: 10.2174/1573396314666180712114531. PMID: 29998808; PMCID: PMC6416241.
16. Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Cheikh Ismail L, Lambert A, Jaffer YA, Bertino E, Gravett MG, Purwar M, Noble JA, Pang R, Victora CG, Barros FC, Carvalho M, Salomon LJ, Bhutta ZA, Kennedy SH, Villar J; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet. 2014; 384(9946):869-79. doi: 10.1016/S0140-6736(14)61490-2. Erratum in: Lancet. 2014 Oct 4;384(9950):1264. PMID: 25209488.
17. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol. 2018;218(2S): S745-S761.

doi: 10.1016/j.ajog.2017.11.577. PMID: 29422210.

18. Janaki S, Prabakar S. Examining the impact of poverty on maternal health: Adverse pregnancy outcomes, contributing factors, and strategies for improvement. Multidiscip Sci J. 2025;7(5):2025209. Available from https://doi.org/10.31893/multiscience.2025209
19. Ortega MA, Fraile-Martínez O, García-Montero C, Sáez MA, Álvarez-Mon MA, Torres-Carranza D, Álvarez-Mon M, Bujan J, García-Honduvilla N, Bravo C, Guijarro LG, De León-Luis JA. The Pivotal Role of the Placenta in Normal and Pathological Pregnancies: A Focus on Preeclampsia, Fetal Growth Restriction, and Maternal Chronic Venous Disease. Cells. 2022;11(3):568. doi: 10.3390/cells11030568. PMID: 35159377; PMCID: PMC8833914.
20. Rizi S, Wiens E, Hunt J, Ducas R. Cardiac physiology and pathophysiology in pregnancy. Can J Physiol Pharmacol. 2024; 102(10):552-571. doi: 10.1139/cjpp-2024-0010. Epub 2024 May 30. PMID: 38815593.
21. low-dose aspirin use during pregnancy. ACOG Committee Opinion No. 743. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2018;132(1): e44-52. Available from https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2018/07/low-dose-aspirin-use-during-pregnancy
22. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi JM. Pre-eclampsia: pathophysiology, diagnosis, and management. Vasc Health Risk Manag. 2011; 7:467-74. doi: 10.2147/VHRM.S20181. Epub 2011 Jul 19. PMID: 21822394; PMCID: PMC3148420.
23. Bernardes TP, Mol BW, Ravelli AC, van den Berg P, Boezen HM, Groen H. Early and late onset pre-eclampsia and

small for gestational age risk in subsequent pregnancies. PloS one. 2020;15(3):e0230483. doi: 10.1371/journal.pone.0230483. PMID: 32218582; PMCID: PMC7100959.

24. Bujold E, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin: A meta-analysis. Obstet Gynecol. 2010; 116(2 Pt 1):402-14. doi: 10.1097/AOG.0b013e3181e9322a. PMID: 20664402.
25. Vanda R, Aramesh S, Sadeghian M, Ghatee MA, Ghaffari P. Effect of aspirin on pre-eclampsia and fetal growth restriction in obese pregnant women: a randomized controlled clinical trial. J Clin Care Skills. 2020;1(4):159–64. Available from http://jccs.yums.ac.ir/article-1-77-en.html
26. Groom KM, David AL. 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. doi: 10.1016/j.ajog.2017.11.565. Epub 2017 Dec 8. PMID: 29229321.
27. Ren Y, Zhao Y, Yang X, Shen C, Luo H. Application of low dose aspirin in pre-eclampsia. Front Med (Lausanne). 2023; 10:1111371. doi: 10.3389/fmed.2023.1111371. PMID: 36968826; PMCID: PMC10030847.
28. Asiimwe P, Nambozi G, Brennaman L, Ngonzi J, Ruzaaza G. Effectiveness of low-dose aspirin in reducing the risk of preeclampsia in women with chronic hypertension: an integrative literature review. BMC Cardiovasc Disord. 2025; 25(1):554. doi: 10.1186/s12872-025-04941-z. PMID: 40739172; PMCID: PMC12309040.
29. Jiang Y, Chen Z, Chen Y, Wei L, Gao P, Zhang J, Zhou X, Zhu S, Zhang H, Du Y, Fang C, Su R, Wang S, Yu J, He M, Ding W, Feng L. Low-dose aspirin use during pregnancy may be a potential risk for postpartum hemorrhage and

increased blood loss: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2023;5(4):100878. doi: 10.1016/j.ajogmf.2023.100878. Epub 2023 Jan 25. PMID: 36706919.

30. Knol HM, Schultinge L, Veeger NJ, Kluin-Nelemans HC, Erwich JJ, Meijer K. The risk of postpartum hemorrhage in women using high dose of low-molecular-weight heparins during pregnancy. Thromb Res. 2012; 130(3):334-8. doi: 10.1016/j.thromres.2012.03.007. Epub 2012 Apr 3. PMID: 22475315.
31. Multiple gestation pregnancy. The ESHRE Capri Workshop Group. Hum Reprod. 2000 Aug;15(8):1856-64. PMID: 10920117.
32. Hoffman MK, Goudar S, Dhaded S, Figueroa L, Mazariegos M, Krebs NF, Westcott J, Tikmani SS, Karim F, Saleem S, Goldenberg RL, Lokangaka A, Tshefu A, Bauserman M, Patel A, Das P, Hibberd P, Chomba E, Mwenchanya M, Carlo WA, Trotta M, Williams A, Moore J, Nolen T, Goco N, McClure EM, Lobo MA, Cunha AB, Derman RJ. Neurodevelopment of Children Whose Mothers Were Randomized to Low-Dose Aspirin During Pregnancy. Obstet Gynecol. 2024; 143(4):554-561. doi: 10.1097/AOG.0000000000005514. Epub 2024 Jan 23. PMID: 38262066; PMCID: PMC10953679.
33. Goodman T, Ferro A, Sharma P. Pharmacogenetics of aspirin resistance: a comprehensive systematic review. Br J Clin Pharmacol. 2008; 66(2):222-32. doi: 10.1111/j.1365-2125.2008.03183.x. Epub 2008 Apr 22. PMID: 18429969; PMCID: PMC2492913.
34. Siddiqui MA, Jain C, Usmani A, Hafeez A, Khalid M, Mujahid M. Pharmacogenetics and pharmacogenomics impact on aspirin response. Pharmacogenomics Pharmacogenet Drug Ther. IntechOpen; 2024. DOI:

10.5772/intechopen.113026 Available from https://www.intechopen.com/chapters/88235

35. Abdi N, Rozrokh A, Alavi A, Zare S, Vafaei H, Asadi N, Kasraeian M, Hessami K. The effect of aspirin on preeclampsia, intrauterine growth restriction and preterm delivery among healthy pregnancies with a history of preeclampsia. J Chin Med Assoc. 2020; 83(9):852-857. doi: 10.1097/JCMA.0000000000000400. PMID: 32773581; PMCID: PMC7478204.
36. Araganji R, Somannavar MS, Vernekar SS, Kavi A, Hoffman MK, Goudar SS. The impact of low-dose aspirin on markers of inflammation and placental function: an ancillary study of the ASPIRIN trial. J Matern Fetal Neonatal Med. 2022; 35(25):6901-6905. doi: 10.1080/14767058.2021.1929160. Epub 2021 May 20. PMID: 34016022; PMCID: PMC11287008.
37. Allesee L, Gallagher CM. Pregnancy and Protection: The Ethics of Limiting a Pregnant Woman's Participation in Clinical Trials. J Clin Res Bioeth. 2011; 2(108):1000108. doi: 10.4172/2155-9627.1000108. PMID: 21863146; PMCID: PMC3158978.
38. Sheiner E, Kapur A, Retnakaran R, Hadar E, Poon LC, McIntyre HD, Divakar H, Staff AC, Narula J, Kihara AB, Hod M. FIGO (International Federation of Gynecology and Obstetrics) Post pregnancy Initiative: Long-term Maternal Implications of Pregnancy Complications-Follow-up Considerations. Int J Gynaecol Obstet. 2019; 147(Suppl 1):1-31. doi: 10.1002/ijgo.12926. PMID: 32323876.