

REVIEW

Aspirin for prevention of preeclampsia and fetal growth restriction

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Abstract

For the past decades, growing attention has been given to aspirin use during pregnancy. It favors placentation by its proangiogenic, antithrombotic, and anti-inflammatory effects. Therefore, low doses of aspirin are prescribed in the prevention of placenta-mediated complications, mainly preeclampsia and fetal growth restriction. However, questions regarding its clinical application are still debated. Aspirin is effective in preventing preeclampsia in a high-risk population. Most guidelines recommend that risk stratification should rely on medical history. Nevertheless, screening performances dramatically improve if biochemical and biophysical markers are included. Concerning the appropriate timing and dose, latest studies suggest aspirin should be started before 16 weeks of pregnancy and at a daily dose of 100 mg or more. Further studies are needed to improve the identification of patients likely to benefit from prophylactic aspirin. Besides, the role of aspirin in the prevention of fetal growth restriction is still questioned.

1 | INTRODUCTION

Preeclampsia (PE) occurs in 3% to 5% of all pregnancies and is responsible for 70 000 maternal deaths worldwide each year.¹ It is a placenta-mediated complication causing a multisystem disorder. PE is defined as hypertension accompanied by one of the following after the 20th week of pregnancy: proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and new onset cerebral or visual symptoms.² Over the past decade, substantial advances have been made in understanding the pathophysiology of PE.³ However, no curative treatment of PE has been found. Hence, to date, delivery of the placenta is the only treatment. Current management of preterm PE consists in balancing the risks of continuing pregnancy and iatrogenic prematurity. Given its major repercussions and the lack of curative treatment, predicting and preventing PE appear to be a major issue of modern obstetrics.⁴

Fetal growth restriction (FGR) complicates 5% to 10% of pregnancies.⁵ It is a leading cause of premature birth and intrapartum hypoxia. Utero-placental insufficiency is the most common cause of FGR.⁵⁻⁷

As with PE, there is no treatment to reverse placental-related fetal restriction.⁸

Aspirin has been used for its anti-inflammatory properties since time immemorial. For the last 70 years, it has been widely prescribed in the prevention of coronary and cerebrovascular complications. Early descriptions of PE refer to extensive placental thrombotic lesions.⁹ Aspirin was therefore prescribed for its antithrombotic properties. The first evidence of aspirin efficacy in preventing PE was published in 1985.¹⁰ Since then, numerous trials have assessed the efficacy of aspirin in preventing placenta-mediated complications.¹¹ Nevertheless, its mechanism of action has not been fully elucidated, and questions regarding its clinical application remain unanswered.

2 | BASIS OF PATHOPHYSIOLOGY

PE originates in early stages of placentation. Placentation starts with extravillous trophoblast (EVT) cell invasion. The cells invade the decidual stroma, before reaching the myometrium and spiral arteries.¹² In normal pregnancies, invasion of the spiral arteries eradicates their

layer of muscle, and maternal endothelial cells are replaced with EVT. Consequently, these vessels dilate and lose their ability to constrict. This remodelling of the spiral arteries is a key feature of placentation since it creates a low-resistance, high-flow vascular system, essential to ensure adequate perfusion of the intervillous space.¹³

Recent findings suggest that cytotrophoblasts produce cytokines and factors responsible for adequate placentation and vascular remodelling. For instance, growth factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) promote remodelling of spiral arteries and utero-placental angiogenesis.¹⁴ In addition, nitric oxide (NO) is involved in the remodelling of uterine arteries and placentation. Other cytokines are thought to play a major role and are currently being investigated: Activated leukocyte cell adhesion molecule (ALCAM)¹⁵ is involved in blastocyst implantation and the placental differentiation process while CXCL-16 promotes trophoblast proliferation, invasion, and interaction with maternal lymphocytes.¹⁶

In PE, early cytotrophoblast secretion of cytokines and related factors is altered.¹⁷ Preeclamptic patients have significantly reduced PIGF, pregnancy-associated plasma protein A (PAPP-A), ALCAM, and CXCL-16 serum levels.¹⁸ Increased trophoblast apoptosis and premature trophoblast differentiation are also observed in PE.¹⁷ As a result, trophoblast invasion is less extensive, and remodelling of the spiral arteries is impaired. It leads to reduced utero-placental blood flow and episodes of ischemia-reperfusion. Reactive oxygen species (ROS) are generated. It results in the release of inflammatory mediators,¹⁹ anti-angiogenic agents²⁰ such as sFlt-1 and syncytiotrophoblast microfragments into the maternal circulation.^{21,22} sFlt-1 is a soluble receptor of VEGF and PIGF and prevents them from binding to their proper receptor. In PE, sFlt-1 expression is increased, leading to anti-angiogenic effects.

PAPP-A also participates in the mechanism of placentation. It is synthesized in the syncytiotrophoblast. Its concentration increases throughout pregnancy, with maximum levels at term.²³ PAPP-A increases local bioavailability of insulin-like growth factor (IGF) by cleaving the inhibitors IGFBP-4 and IGFBP-5 (IGF-binding protein 4 and 5).²⁴ IGF has mitogenic and antiapoptotic activities.²⁵ Therefore, PAPP-A favors placentation and regulates fetal growth. Studies show

What's already known about this topic?

- Low doses of aspirin are prescribed in the prevention of placenta-mediated complications.
- Aspirin is effective in preventing preterm preeclampsia in a high-risk population.

What does this study add?

- Risk stratification for preeclampsia should include clinical history and biochemical and biophysical factors
- Aspirin should be started before 16 weeks of pregnancy and at a daily dose of 100 mg or more.

that preeclamptic patients had decreased PAPP-A levels in the first trimester.^{26,27}

The defective trophoblastic invasion to the spiral arteries results in abnormal placentation and disturbed maternal uteroplacental blood flow with abnormal conditions of hypoxia/oxygenation.²⁸ These events generate excessive ROS and oxidative stress, as well as inflammation, contributing to endothelium dysfunction.²⁹ The causes of defective placentation also involve a reduced bioavailability of NO associated with the dysfunction of endothelial nitric oxide synthase (eNOS). A close relationship has been established between oxidative stress and the decreased NO bioavailability, which are thought to play a critical role in the maternal-placental circulation, poor placentation, and endothelial dysfunction.³⁰⁻³³

The hypoxic placenta releases soluble antiangiogenic agents and trophoblast-derived fragments.^{34,35} These substances also trigger systemic endothelial dysfunction in the mother.³⁶ It results in ischemic injury in maternal organ systems, leading to systemic symptoms of PE: hypertension, proteinuria, renal insufficiency, impaired liver function, pulmonary edema, and cerebral or visual symptoms. In addition, reduced utero-placental blood supply prevents adequate fetal development and leads to FGR. An overview of PE pathophysiology is presented in Figure 1.

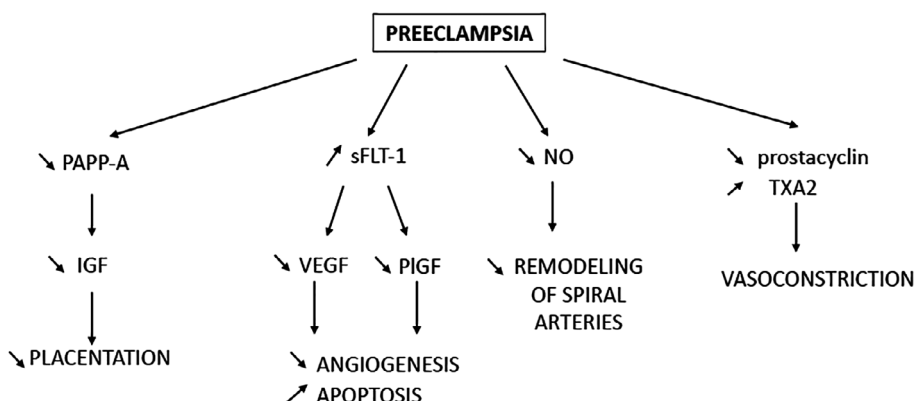


FIGURE 1 Biomarkers and preeclampsia pathophysiology. IGF, insulin growth factor; NO, nitric oxide; PAPP-A, pregnancy associated plasma protein A; PIGF, placenta growth factor; sFLT-1, soluble fms-like tyrosine kinase 1; TXA2, thromboxane A2; VEGF, vascular endothelial growth factor

3 | MECHANISM OF ACTION OF ASPIRIN IN PREVENTING PE

Aspirin is the trade name for acetylsalicylic acid. It comprises a benzene ring, a carboxyl radical, and an acetyl group.

The main mechanism of action of aspirin is an irreversible inactivation of the cyclo-oxygenase (COX) through acetylation of its catalytic site.³⁷ COX is a key enzyme in the production of prostanoids. It converts arachidonic acid (AA) into prostaglandin G2 and then into prostaglandin H2 (PGH2).³⁸ The action of prostacyclin synthases on PGH2 subsequently leads to the synthesis of various prostaglandins depending on cell type. COX exists in two isoforms: COX-1 and COX-2. Aspirin inhibits COX-1 more selectively. COX-1 is expressed constitutively in most cells. It regulates basal levels of prostaglandins, such as thromboxane A2 (TX-A2) and prostacyclin, both of which have opposite effects on endothelium and platelet function. TX-A2 is mostly synthesized in platelets and promotes vasoconstriction and platelet aggregation. On the opposite, prostacyclin is synthesized in endothelial cells. It promotes vasodilatation and inhibits platelet aggregation.³⁹ Therefore, the biological effect depends on the ratio of endothelial prostacyclin to platelet thromboxane. On the contrary, COX-2 is inducible and responsible for releasing prostaglandins in the case of inflammation or hypoxia. Aspirin has a dose-dependent effect on prostaglandin synthesis.³⁹ Low doses (75-150 mg/d) have an anti-thrombotic effect with no teratogenic risk while higher doses (>1000 mg/d) have anti-inflammatory properties and are responsible for teratogenicity. Recent findings demonstrate that low doses of aspirin also have anti-inflammatory properties.⁴⁰ The half-life of low-dose aspirin (LDA) is less than 30 minutes.⁴¹ Thus, the neo-synthesis of COX allows prostaglandin production to restart rapidly after aspirin intake. The endothelium produces de novo COX, ensuring basal secretion of prostacyclin. However, the platelets are anuclear. COX inhibition therefore lasts for the entire life of the platelet and TX-A2 levels decrease. Thus, the balance between prostacyclin and thromboxane A2 promotes vasodilatation and an antithrombotic effect. This concept is particularly interesting in the case of PE since preeclamptic patients present increased thromboxane and decreased prostacyclin production. Low doses of aspirin allow the thromboxane A2/prostacyclin ratio to be reversed.⁴² An overview of COX mechanism of action is presented in Figure 2.

Recent studies indicate that COX-1 is also involved in sFlt-1 synthesis⁴³; sFlt-1 is a circulating antiangiogenic factor that plays a key role in the pathogenesis of PE. Early stages of trophoblast invasion require growth factors, such as VEGF and placental growth factor (PlGF). sFlt-1 binds with high affinity to VEGF and PlGF and prevents them from binding to their proper receptor. It therefore interferes with normal angiogenesis, and the elevated sFlt-1 levels observed in PE may play a role in its development. Recent data suggest that aspirin inhibits sFlt-1 production via the inactivation of COX-1.⁴³ Thus, aspirin may exert its beneficial properties partly by inhibiting sFlt-1 synthesis.

Aspirin also interferes with trophoblastic cytokine production.¹⁸ To support this hypothesis, *in vitro* trophoblasts were supplemented

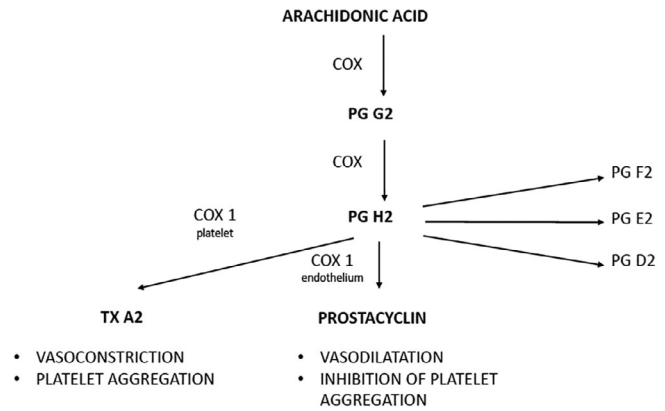


FIGURE 2 Cyclooxygenase mechanism of action. COX, cyclooxygenase; PG, prostaglandin; TXA2, thromboxane A2

with the serum of preeclamptic patients, with or without aspirin, or with the serum of normotensive patients.¹⁸ In this experiment, aspirin significantly increased the trophoblast production of PlGF. Moreover, CXL-16 and ALCAM levels increased and came close to those observed in non-preeclamptic trophoblasts. In addition, apoptotic and differentiation markers decreased in trophoblasts supplemented with aspirin. Thus, the possible mechanisms of action are modulation of cytokine secretion, reduction of apoptosis, and reduction of premature trophoblast differentiation.

Aspirin also acts by inducing aspirin-triggered lipoxins (ATLs), which are the epimeric form of endogenous lipoxin A4 (a potent immunomodulator and antioxidant). Acetylation of the active site of COX 2 redirects its activity, leading to the production of 15-R-HETE from AA. 15-R-HETE is then converted into ATLs by the 5-Lipoxygenase (5-LO) of leukocytes. ATLs act as antioxidant, immunomodulator, and anti-inflammatory factors. They interfere in various pathways: They inhibit nuclear factor (NF)- κ B activation and tumor necrosis factor (TNF) secretion in activated T cells and inhibit leukocyte-endothelial interaction.⁴⁴⁻⁴⁸ They also activate NO production by inducing eNOS. Recent studies suggest that ATLs prevent the plasma-induced inflammatory response on endothelial cells in preeclamptic women^{49,50}: Exogenous ATL has the potential to reverse the inflammatory process observed in PE by upregulating interleukin-10 (IL10) and NO, and downregulating the generation of TNF- α . ATL exerts its action by binding to a G-protein-coupled receptor called ALXR. During the first trimester of pregnancy, ALXR expression is increased in the decidua,⁵¹ suggesting that ATLs could be a key feature in the use of aspirin in preventing PE.

Aspirin could also inhibit NF- κ B-mediated inflammation⁵² and prevent TNF- α -mediated microRNA (miR)-155 biogenesis and eNOS downregulation.⁵³ Aspirin restored TNF- α - and ROS-mediated downregulation of eNOS expression and NO production in human umbilical vein endothelial cells (HUVECs) by inhibiting redox-sensitive NF- κ B-responsive miR-155 expression. Finally, some authors have pointed out the impact of aspirin on transcription factors such as STOX1 in PE-like syndromes in mice,⁵⁴ and on regulation of hepatocyte nuclear factor (HNF) expression in preeclamptic placentas from mice and

humans.⁵⁵ An overview of aspirin mechanism of action in preventing PE is presented in Figure 3.

4 | OPTIMAL GESTATIONAL AGE FOR INITIATION OF ASPIRIN AND APPROPRIATE DOSE

Physiological considerations suggest aspirin should be started early in the pregnancy in order to facilitate placentation. However, the optimal timing is unclear. Bujold et al published a meta-analysis of randomized trials on this issue.⁵⁶ They found that initiation of aspirin at 16 weeks of gestation or before was associated with a significant reduction in the incidence of PE (relative risk [RR] 0.47, 95% confidence interval [CI], 0.34-0.65) and FGR (RR 0.44, 95% CI, 0.30-0.65). When aspirin was initiated after 16 weeks of gestation, no significant benefit was observed on PE (RR 0.81, 95% CI, 0.63-1.03) nor FGR (RR 0.98, 95% CI, 0.87-1.10). Similarly, the optimal gestational age for interrupting aspirin is unclear. The FIGO guidelines of March 2019 recommend to stop aspirin at 37 weeks of pregnancy or 2 weeks before a planned early delivery,⁵⁷ but we could speculate that aspirin could be stopped at the end of placentation.

Regarding the appropriate dose of aspirin, recommendations vary from 60 to 150 mg/d. Roberge et al conducted a meta-analysis to estimate the impact of aspirin dosage on the prevention of PE and FGR.⁵⁸ When aspirin was initiated before 16 weeks of gestation, they showed a dose-response effect for the prevention of PE and FGR. Aspirin 100 mg was significantly more effective than 60 mg in reducing PE (RR 0.48, 95% CI, 0.31-0.74 vs RR 0.93, 95% CI, 0.74-1.15, $P < .001$) and FGR (RR 0.45, 95% CI, 0.28-0.71 vs RR = 0.78, 95% CI, 0.53-1.16, $P = .006$). This dose-response effect might be due to aspirin resistance or maternal BMI. In an observational cohort study, 30% of pregnant women were nonresponsive to a daily dose of 81 mg.⁵⁹ This resistance was overcome with higher doses in most cases.

Indeed, pharmacokinetics of aspirin is altered during pregnancy. A recent study demonstrated a reduction of approximately 40% in drug metabolite concentration of aspirin in pregnant women compared with nonpregnant women.⁶⁰

A recent meta-analysis of 16 randomized trials, including several recently published trials, investigated the effect of aspirin in the prevention of preterm and term PE, in relation to gestational age at onset of treatment and dosage. It concluded that aspirin reduces the risk of preterm PE when it is initiated before 16 weeks of gestation and at a daily dose greater than 100 mg.⁶¹

Placentation occurs during the end of the first trimester of pregnancy.²⁹ Therefore, we could hypothesize that aspirin could improve placentation; it would be greater if started during the first trimester. Chaemsainthong et al⁶² performed a meta-analysis to estimate the effect of LDA initiated before 11 weeks on the risk of PE and gestational hypertension. They included eight randomized controlled trials (1426 participants). They found no significant reduction of PE or gestational hypertension. However, the included studies have several limitations. First, aspirin dose was not appropriate (lower than 100 mg) in five of the eight studies included. In addition, in one of the studies included, aspirin was stopped at 12 weeks of gestation. Moreover, the primary objective of the trials included was to improve the rate of live births in women at high risk for miscarriage. Without evident data before 11 weeks, we hypothesize that aspirin should be prescribed at the end of the first-trimester for optimal timing (between 9 and 14 wk).

5 | PATIENTS WHO COULD BENEFIT FROM PROPHYLACTIC ASPIRIN

Identifying women who may benefit from prophylactic aspirin is also controversial. Current guidelines recommend targeting high-risk women, but different strategies have been suggested to identify these women. The most widespread strategy bases risk stratification on

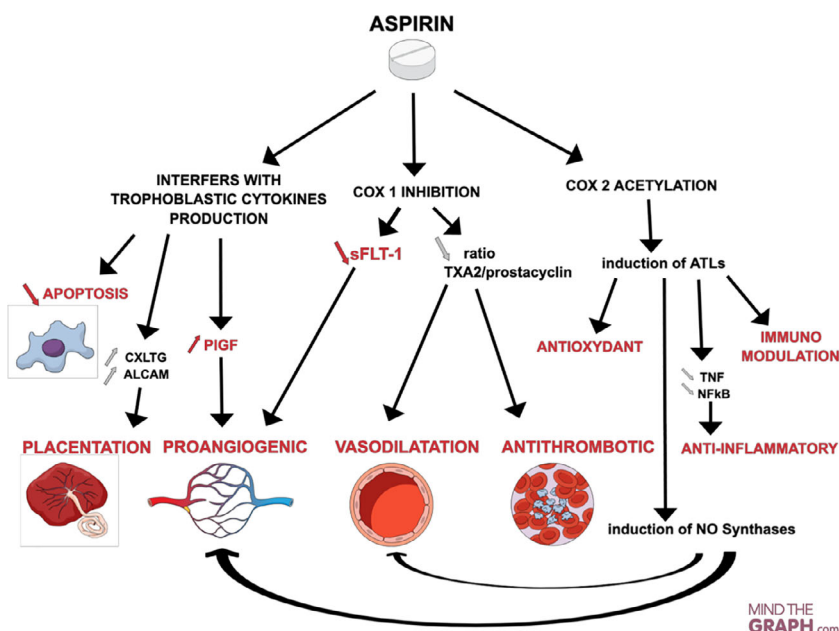


FIGURE 3 Aspirin mechanisms of action in preventing preeclampsia. ALCAM, activated leukocyte cell adhesion molecule; ATLs, aspirin triggered lipoxin; NO, nitric oxide; PIGF, placenta growth factor; sFLT-1, soluble fms-like tyrosine kinase-1; TNF, tumor necrosis factor; TXA2, thromboxane A2

clinical history. Women with a history of PE or presenting risk factors are considered to be high risk. For instance, the National Institute for Health and Care Excellence (NICE) recommends the prescription of LDA for patients with one high risk factor or more than one moderate risk factors⁶³ (Table 1). The outcome of this type of screening strategy is poor: detection rate of 30.4% for all PE and 40.8% for preterm PE with a positive screening rate of 10.3%.⁶⁴ The American College of Obstetricians and Gynecologists (ACOG) recommends treating patients with history of at least two PE or with history of PE requiring delivery before 34 weeks of gestation.² This screening strategy detects only 5% of preterm PE and 2% of full-term PE. Therefore, risk factors alone are not sufficiently effective for identifying women at high risk of PE.

Numerous markers of impaired placentation⁶⁵ have been tested for prediction of PE in the first trimester. The Fetal Medicine Foundation (FMF) developed an algorithm, based on maternal characteristics, pulsatility of uterine arteries, mean blood pressure and maternal serum levels of PIGF, and pregnancy-associated plasma protein A (PAPP-A) between 11 and 13 weeks of gestation.⁶⁶ A recent prospective study involving 8775 singleton pregnancies examined the diagnostic accuracy of this prediction model.⁶⁷ It reported a detection rate of 75% for preterm PE and 100% PE before 32 weeks of gestation, with a 10% false detection rate.⁶⁴ A multicenter, double-blind, randomized controlled trial was designed to evaluate the FMF algorithm in clinical practice: ASPRE trial.⁶⁸ One thousand seven hundred seventy-six women at high risk (>1/100) for preterm PE according to the FMF algorithm were randomly assigned to 150-mg aspirin per day

or placebo. Treatment was started at 11 to 14 weeks of gestation and discontinued at 36 weeks. The incidence of preterm PE was 60% lower in the aspirin group compared with the placebo group (OR 0.38, 95% CI, 0.20-0.74). According to the subgroup analysis, the beneficial properties of aspirin were particularly important for nulliparous women (OR 0.27, 95% CI, 0.11-0.64), whereas no significant difference was found for multiparous women, with (OR 0.50, 95% CI, 0.08-2.93) or without a history of PE (OR 0.79, 95% CI, 0.22-2.90).

Interestingly, the ASPRE trial found no significant reduction in full-term PE. Exploratory analysis suggests that aspirin acts by delaying delivery in women with PE.⁶⁹ In a population at high risk of preterm PE, the "conversion" of preterm PE into full-term PE by aspirin could explain the absence of any reduction in full-term-PE. The results are consistent with this hypothesis.

Screening strategy, leading to an individualized care, is presented in Figure 4. Recent data therefore indicate that LDA could reduce PE in high-risk patients by more than 50%. However, it is important to consider the high number of women to be screened in order to prevent preterm PE: 333 in the ASPRE trial.⁷⁰ It questions the cost-effectiveness of this strategy, and the optimal risk threshold for treatment is probably yet to be determined.

Besides PE, defective placentation also occurs in intrauterine growth restriction, preterm labor, preterm premature rupture of membranes, abruptio placentae, and late spontaneous abortion.⁷¹ These are referred to as "great obstetrical syndromes."⁷² As aspirin favors placentation in early stages of pregnancy, it might help preventing this spectrum of obstetrical complications.

TABLE 1 Preeclampsia risk factors

High-risk Factors	Moderate-risk Factors
<ul style="list-style-type: none"> Hypertensive disease in previous pregnancy Chronic kidney disease Autoimmune disease, eg, SLE and antiphospholipid Type 1 or type 2 diabetes Chronic hypertension 	<ul style="list-style-type: none"> First pregnancy Age 40 or older Pregnancy interval >10 y BMI > 35 at first visit Family history of PE Multifetal pregnancy

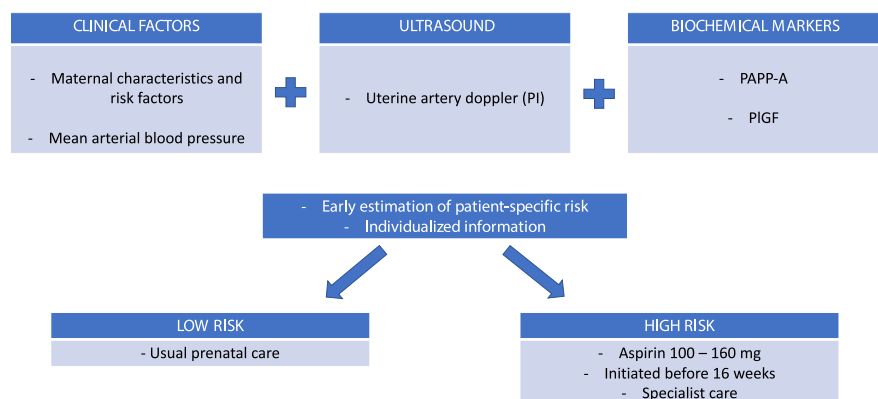
Abbreviations: BMI, body mass index; SLE, systemic lupus erythematosus.

6 | ASPIRIN AND FGR

FGR complicates 5% to 10% of pregnancies.⁵ It causes premature birth and neonatal morbidity and is mainly associated with utero-placental insufficiency.⁵⁻⁷ To date, there is no treatment to reverse placental-related FGR.⁸

Pathophysiology of placental-related FGR and PE are very similar.⁷³ Therefore, aspirin could also prevent placental-related FGR. Regrettably, scientific evidence is weaker since fewer trials specifically target FGR.

FIGURE 4 Preeclampsia screening and individualized care during pregnancy. PAPP-A, pregnancy associated plasma protein A; PI, pulsatility index; PIGF, placenta growth factor [Colour figure can be viewed at wileyonlinelibrary.com]



Optimal timing and aspirin dose are probably similar. Bujold et al meta-analysis⁵⁶ found that initiation of aspirin at 16 weeks of gestation or before was associated with a significant reduction in the incidence of FGR (RR 0.44, 95% CI, 0.30-0.65). When aspirin was initiated after 16 weeks of gestation, no significant benefit was observed on FGR (RR 0.98, IC 95%, 0.87-1.10). Roberge et al meta-analysis⁵⁸ showed aspirin 100 mg was significantly more effective than 60 mg in reducing FGR (RR 0.45, 95% CI, 0.28-0.71 vs RR = 0.78, 95% CI, 0.53-1.16, $P = .006$). Therefore, aspirin reduces the risk of placental-related FGR when it is initiated before 16 weeks of gestation and at a daily dose greater than 100 mg.

Identifying patients likely to benefit from LDA in prevention of placental-related FGR is challenging. In ASPRE trial,⁶⁸ no significant difference in full-term FGR was found between the aspirin and placebo groups (OR 0.53, 95% CI, 0.16-1.77). However, FGR was a secondary outcome so the trial was not powered to demonstrate a difference. Stanescu et al⁷⁴ published a randomized, placebo-controlled study including 150 patients who screened positive using the FMF early pregnancy screening test for PE.⁶⁶ They found a significant reduction of FGR in the aspirin group.

The French CNGOF recommends prescription of LDA for women with a history of severe FGR (<5th percentile). Conversely, ACOG and NICE guidelines do not support the use of LDA for FGR prophylaxis in the absence of other PE-related risk factors.^{5,75} Indeed, evidence supporting a reduction of FGR from LDA comes from studies including women at high risk of PE, not with history of FGR alone.

7 | IATROGENIC EFFECTS OF ASPIRIN

The safety of aspirin during pregnancy has been documented in large cohort studies.

The widespread use of aspirin in cardiovascular diseases provides sound evidence of its iatrogenic effects.⁷⁶ The most common adverse event is gastrointestinal discomfort. In most studies involving pregnant women, the iatrogenic effects do not differ between the aspirin and placebo groups and do not lead to treatment withdrawal. In terms of pregnancy-specific risks, a US Preventive Services Task Force meta-analysis⁷⁷ did not highlight any difference in terms of placental abruption (RR 1.12, 95% CI, 0.86-1.46) and postpartum hemorrhage (RR 1.02, 95% CI, 0.96-1.09).

Aspirin diffuses through the utero-placental circulation. Therefore, it might theoretically affect fetal development and impair neonatal platelet function, causing neonatal bleeding. Leonhardt et al determined neonatal plasma levels of acetylsalicylic acid, its metabolism, and effect on neonatal prostaglandin formation.⁷⁸ Thromboxane A2 formation was significantly decreased in neonates whose mothers received aspirin during pregnancy but recovered 2 to 3 days after discontinuation of aspirin. As aspirin is usually stopped in the 36th or 37th week of pregnancy, there is a theoretical risk of intracranial bleeding before then. However, no increase in neonatal intracranial hemorrhage was reported in a large-scale meta-analysis (RR 0.84,

95% CI, 0.61-1.16).⁷⁷ Likewise, there are no published reports of a significant link between LDA and congenital abnormalities such as heart defects, developmental anomalies,⁷⁹ or premature closure of the arterial canal.⁸⁰

A randomized controlled trial involving 1228 patients examined the safety of LDA started before conception and continued throughout pregnancy.⁸¹ The authors found no increased risk of adverse fetal or neonatal outcomes associated with LDA exposure. Likewise, a cohort of 15 000 women who reported aspirin use during the first trimester found no increased risk of congenital abnormalities.⁸²

Potential perinatal damage from LDA exposure during pregnancy has been studied, and results are reassuring. However, these data should be interpreted with extreme caution. The large cohorts published are probably underpowered to detect rare side effects, so we should remain cautious about their interpretation. Promising results obtained in recent trials could lead to broader aspirin indications during pregnancy. Close monitoring of potential iatrogenic effects is essential.

8 | BENEFIT OF ADDING HEPARIN TO ASPIRIN

Low-molecular-weight heparin (LMWH) can be prescribed concomitantly with aspirin during pregnancy in some indications, such as unexplained recurrent miscarriages. Its beneficial effect is commonly attributed to its anticoagulant action within the placenta. LMWH also improves endothelial function through different properties: anti-inflammatory action and increase in NO bioavailability.⁸³ In addition, LMWH treatment is associated with a significant increase in PIGF plasma levels and a decrease in the sFIT1/PIGF ratio, prompting a pro-angiogenic state.⁸⁴ LMWH could therefore potentiate the action of aspirin in preventing placenta-mediated complications.

A meta-analysis⁸⁵ compared the effect of adding LMWH to aspirin versus aspirin alone on the incidence of PE and FGR. A significant reduction in PE (OR 0.54, 95% CI, 0.32-0.91) and FGR (RR 0.56, 95% CI, 0.32-0.97) was observed in the group treated with LMWH. However, this meta-analysis shows important limitations: small number of studies included and heterogeneity in the inclusion criteria since five out of the eight studies included in the meta-analysis enrolled women with a history of >2 consecutive miscarriages. Furthermore, we note a potential selection bias as 57% of patients presented thrombophilia. Haddad et al recently published a well-designed randomized controlled trial on the addition of heparin to aspirin for reducing placenta-mediated complications in women with a history of severe PE.⁸⁶ They found no benefit of adding LMWH to aspirin. Groom et al reached the same conclusion in their multicenter randomized controlled trial.⁸⁷

On the basis of these latest publications, we believe that LMWH should not be combined with aspirin in the prevention of PE. Nevertheless, a well-designed trial evaluating this treatment in nulliparous women at high risk of PE would provide clearer evidence.

9 | CONCLUSION

Recent studies confirm that aspirin is effective in preventing preterm PE in a high-risk population. As with FGR, the scientific evidence is weaker since fewer trials specifically target FGR. It is commonly analyzed as a secondary outcome; hence, results are less reliable. Nonetheless, aspirin appears to reduce placenta-mediated FGR.

The traditional approach that defines a high-risk population based on maternal characteristics has been proven inadequate. However, a combination of maternal characteristics with biochemical and biophysical markers dramatically improves screening performance. While combined screening is the optimum strategy for identifying patients likely to benefit from prophylactic aspirin, it is currently not available in routine clinical practice in European countries. Moreover, the optimal risk threshold for treatment has yet to be defined. However, this strategy could be used extensively in the years to come. In March 2019, FIGO was the first institution to recommend combined PE screening for all pregnant women followed by aspirin prophylaxis in the case of high risk.⁵⁷

Growing evidence suggests that maternal organ dysfunction persists after pregnancy. A history of PE seems to be an independent cardiovascular risk factor.^{88,89} It can be assumed that aspirin could reduce long-term cardiovascular morbi-mortality rates by preventing preterm PE.

CONFLICT OF INTEREST

All the authors report no disclosure nor conflict of interest.

AUTHOR CONTRIBUTIONS

L.L. and P.G. had the idea for the review article and, with F.V., O.P., C.V., and S.H., carried out the design of the study. L.L. and P.G. produced the first draft. All authors read, revised, and approved the submitted version of the manuscript.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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