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REVIEW ARTICLE

Aspirin in the prevention of preeclampsia: the conundrum of how, who and when

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Abstract

Aspirin is widely used in preventing early onset preeclampsia in women who are identified as being high risk. Although the benefit of aspirin is increasingly evident and acknowledged, there remains many unanswered questions with regards to its optimal application in pregnancy. The issues mainly centre around the relatively modest risk reduction that is observed with the use of aspirin prophylactically. We aim to explore the reasons behind the conservative rate of benefit and aim to explore factors that are likely to influence the outcomes with the use of aspirin.

Introduction

Preeclampsia is a pregnancy related disorder with a global annual incidence of 2–8% of all pregnancies [1]. Although the general incidence of preeclampsia remains static, the incidence of maternal and fetal morbidity, particularly in developing countries, is increasing and remains the second commonest cause of maternal mortality internationally [1–3]. It is widely accepted that impaired placental invasion in the first trimester has a key role in the pathophysiology of early-onset preeclampsia [4, 5]. This is best summarized in a two-stage model (Fig. 1). Stage one describes impaired cytotrophoblast invasion and pseudovasculogenesis of the maternal uterine artery which subsequently leads to impaired utero-placental arterial flow. Stage two of the disease process occurs in the second or third trimester where there is ischaemic and oxidative stress of the hypoxic placenta. The resulting oxidative stress and angiogenic imbalance leads to maternal endothelial dysfunction. This is resultant from an increase in soluble fms-like tyrosine kinase-1 production and reduction in placental growth factor (PlGF) (Fig. 1) [4, 6].

The current strategy in managing established preeclampsia focuses on expectant management of the pregnancy—where clinician attempt to balance the risks to the mother, while minimizing the fetus's risk of iatrogenic prematurity. Although there is no targeted therapy that addresses the pathophysiology of established preeclampsia at present, current research suggest that this will be an option in the near future [7–10]. Until then, the emphasis is placed on the prevention of preeclampsia, which involves early identification and administration of prophylactic interventions in high-risk women.

The evidence on the benefit of aspirin in preventing preeclampsia continues to grow; however, many unanswered questions remain regarding its clinical application [11–13]. To begin with, risk stratification and selection of women who will benefit from prophylactic aspirin remains an area of ongoing debate with varying recommendations [14–16]. In addition, the optimal timing of initiating aspirin remains unclear. Previous data indicated a 17–20% risk reduction of early-onset preeclampsia with commencement of low-dose aspirin before 16 weeks of gestation, with a lack of benefit if started later in gestation [13, 17]. There are, however, contradictory data, suggesting benefit even when commenced after 16 weeks of gestation [12]. More recently, a risk reduction of ~60% (odds ratio 0.38; 95% confidence interval (CI), 0.20–0.74, $p < 0.004$) of preeclampsia was demonstrated when 150 mg of aspirin was commenced between 11 and 14 weeks of gestation [11]. Potential explanations for the observed heterogenous effects include aspirin non-adherence or resistance, varying doses and gestations at which aspirin has been used. The evidence

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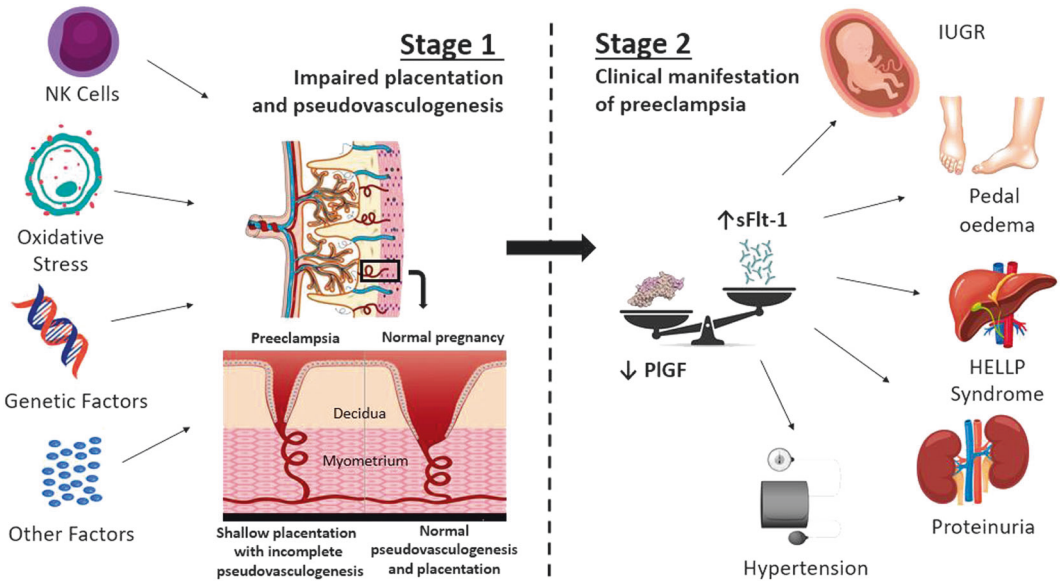

Fig. 1 Illustration of the two-stage pathophysiology of preeclampsia. Legends for Fig. 1: HELLP syndrome haemolysis, elevated liver enzymes, low platelet count syndrome, IUGR intrauterine growth retardation, NK cells natural killer cells, PlGF placental growth factor, sFlt-1 soluble fms-like tyrosine kinase-1

on aspirin non-adherence and resistance is increasingly prominent in cardiology studies, however, has not been adequately examined in pregnant women [18, 19]. There also remains a difference of opinion amongst clinicians on the potential chronotherapeutic effect of aspirin [20]. These variations result in inconsistencies with clinical application of the evidence and therefore needs further exploration to provide clinicians with clarity on the optimal use of aspirin.

The why: the beginning of the use of aspirin in preeclampsia

Almost 40 years ago, aspirin was avoided in pregnancy. Shortly after, however, aspirin's inhibitory action on cyclooxygenase and its effect on thromboxane (TXA2) and prostacyclin (PGI2) was discovered [21]. The understanding of the TXA2/PGI2 imbalance in the pathophysiology of preeclampsia led to the use of aspirin in managing preeclampsia, for the first time, in 1978 [22–24]. Subsequently, aspirin was shown to have a prophylactic role in preventing preeclampsia. In 1985, when Beaufils et al. [25] used a combination of aspirin (150 mg) and dipyridamole (300 mg) in the first trimester, a significant reduction in the rate of preeclampsia in the treatment group compared to controls (0/48 vs 6/45 $p < 0.05$) was observed. This was further noted in 1991 when the EPREDA trial proposed an added benefit of aspirin (150 mg daily) in reducing the rate of fetal growth retardation in comparison with placebo (20 [13%] vs. 19 [26%]; $p < 0.02$) [26]. Following this, however, the evidence for the use of prophylactic aspirin had been contradictory, with studies demonstrating equivocal or a lack of benefit in preventing preeclampsia [27–29]. These studies were confounded by usage of varying doses of aspirin, heterogenous inclusion criteria and different timing of aspirin initiation. More recently, aspirin has once again re-emerged as a promising prophylactic agent [11, 13, 30]. Between 2007 and 2010, Bujold et al. [13] and Askie et al. [30] demonstrated a benefit in the use of aspirin when commenced before 16 weeks of gestation (Risk reduction 0.47: 95% CI 0.34–0.65). These studies led to more recent studies that have supported the use of aspirin [11, 12, 16]. Although these studies have demonstrated variable outcomes, they have, collectively, provided useful safety data by demonstrating a lack of association between aspirin and complications in both the mother and fetus [13, 27, 28, 31].

The how: mechanism of aspirin as a prophylactic therapy in preeclampsia

Aspirin is a non-selective, irreversible cyclooxygenase (COX) inhibitor (Fig. 2). It prevents the production of TXA2 in platelets by acetylating a serine residue at position 529 of the COX-1 isoform. This results in an antithrombotic effect with a decrease in the TXA2/PGI2 ratio [21]. Early studies on the mechanism of aspirin's action in preeclampsia demonstrated an aspirin-induced decrease of TXA2 concentration and mediation of the unbalanced TXA/PGI2 ratio [32, 33]. Roberts et al. [34] noted a dose-mediated response with prostacyclin production in non-pregnant female and male volunteers. Their study demonstrated that 50 mg of aspirin daily reduced TXA2

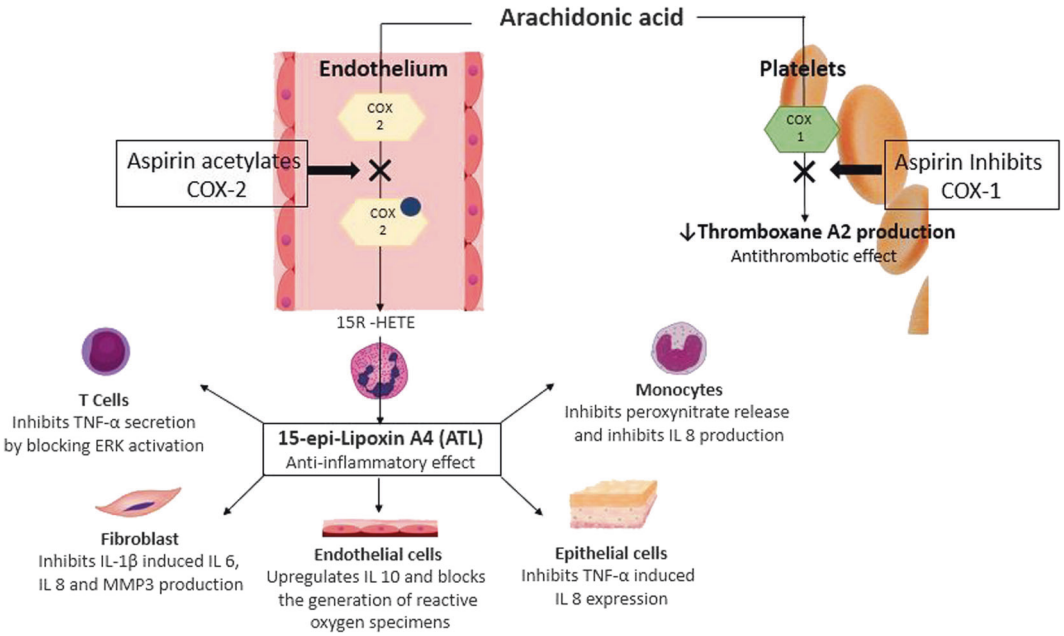

Fig. 2 Mechanism of action of aspirin and aspirin-triggered lipoxin (ATL). Legends for Fig. 2: 15 (R) HETE 15-hydroxyeicosatetraenoic acid, COX cyclooxygenase, ERK extracellular-signal-regulated kinase, IL 10 interleukin 10, IL8 interleukin 8, IL 6 interleukin 6, IL 1β interleukin 1β, MMP 3 matrix metalloproteinase-3, TNF-α tumour necrosis factor α

production in 95% of their volunteers without an alteration in prostacyclin production. The use of 100–300 mg of aspirin a day, however, completely inhibited TXA2 production and partially inhibited prostacyclin production [34]. When examined in pregnant women, Sibai et al. [35] demonstrated a dose response inhibition of TXA2 production with a 98% reduction after 1 week of 80 mg aspirin therapy. It was then hypothesized that aspirin improves placental blood flow and minimizes risk of placental thrombosis by reducing TXA2 and PGI2. Studies that examined the correlation between TXA2/PGI2 levels and maternal uterine artery pulsatile indexes (PI) demonstrated that aspirin reduced platelet aggregation and inhibited vasoconstriction when an enhanced uterine blood flow was noted [36]. Aspirin, however, has only demonstrated a modest benefit in the prevention of preeclampsia despite the postulated modulation of the TXA2/PGI2 imbalance [37, 38]. One explanation for this variation is that the TXA2/PGI2 imbalance is not the only pathologic pathway of preeclampsia. There may also be a wide inter-patient variation in the degree of aspirin effect in addition to a gestation specific effect. This is partially answered in the observation that the preventative effect of aspirin with early onset preeclampsia is greater than late onset preeclampsia. This suggests that the effect of aspirin may be on placental development and less so on maternal biochemical dysregulation [16, 17].

In 1989, Claria et al. [39] described the generation of a 15-epi-Lipoxin A4, better known as aspirin-triggered lipoxins (ATLs). ATLs are the epimeric form of endogenous lipoxin A4, which is a potent immunomodulator and antioxidant. It can block the generation of reactive oxygen species in endothelial cells, inhibit nuclear factor-κB cells (NF-κB) activation and tumour necrosis factor-α (TNF-α) secretion in activated T cells (Fig. 2) [40–43]. Use of exogenous ATL has demonstrated positive outcomes in experimental models of inflammatory conditions such as peritonitis [44], colitis [45], ischaemic reperfusion injury [44], and angiogenesis [46]. The generation of endogenous ATL with aspirin consumption was first confirmed by Fiorucci et al. [47]. This was further demonstrated by Chiang et al. [48] who showed a rise in ATL levels with low-dose aspirin (81 mg aspirin group (0.25 ± 0.63 ng/ml, $P = 0.04$). No effect on ATL was noted with the use of high dose aspirin (325 mg group (0.16 ± 0.71 ng/ml) and 650 mg group (0.01 ± 0.75 ng/ml, $P = 0.96$) [48].

More recently, ATL has been shown to have a role in reproductive medicine. Cell culture studies have demonstrated that exogenous ATL has the potential to reverse the inflammatory process observed in preeclampsia by upregulating interleukin-10 (IL10) and nitric oxide, whereas downregulating the generation of TNF-α [49, 50]. Zhangye Xu et al. [51] demonstrated that lipoxin A4, an endogenous lipoxin, is reduced by twofold in women with established preeclampsia. This was also demonstrated in a lipopolysaccharide induced preeclampsia rat model [51]. Furthermore, low first trimester lipoxin A4 has also been proposed as a potential screening biomarker in identifying women who are at risk of intrauterine growth dysregulation [52]. Lipa et al. [52] demonstrated decreased values of lipoxin A4

Table 1 Risk stratification based on clinical history

Major risk factors	Moderate risk factors
Previous hypertensive disorder of pregnancy	Primigravidity
Chronic hypertension	Age > 40 years
Pre-existing renal disease (persistent proteinuria or haematuria for more than 3 months)	Body mass index > 35 at the beginning of pregnancy
Autoimmune conditions	Pregnancy interval of > 10 years
Type 1 or Type 2 diabetes mellitus	Maternal family history of preeclampsia
	Multiple pregnancy

concentrations, both in small for gestational age and large for gestational age groups, when compared with average gestation for age (68.91 ± 33.72 and 68.30 ± 23.49 vs. 102.13 ± 121.9, respectively) [52]. Given the lipoxin A4 dysregulation in high-risk women, increasing understanding of ATL may provide an alternative mechanism by which aspirin modulates preeclampsia risk.

The who: risk stratifying women for prophylactic aspirin therapy

Identifying women who will benefit from the use of prophylactic aspirin is challenging. The current clinical guidelines suggest risk stratifying women based on clinical history (Table 1) [23, 24]. A recent meta-analysis demonstrated that clinical history alone has a detection rate of 37% for early-onset preeclampsia and 28.9% of late-onset preeclampsia [53]. In nulliparous women, clinical history alone detects 37% of preeclampsia for a false positive rate of 5% [54]. Prior history of preeclampsia was the second strongest predictor factor, which is not applicable to nulliparous women [55]. Mean arterial pressure (MAP) compared with systolic or diastolic reading alone has been discussed as another clinical predictor of preeclampsia. A prospective screening study utilising MAP (expressed as log multiple of the median) measured between $11 + 0$ and $13 + 6$ weeks gestation and maternal variables demonstrated a detection rate of preeclampsia of 62.5% for a false-positive rate of 10% [56, 57]. A predictive testing model incorporating maternal factors and second trimester uterine artery pulsitivity index (PI) demonstrated a detection rate of early and late preeclampsia 100% and 56.4%, respectively, for a false-positive rate of 10% [56]. More recently, the combined utility of pregnancy associated plasma protein A, PlGF, MAP, and clinical history has been shown to be sensitive, when used in combination, detecting 96% of cases of preeclampsia requiring delivery before 34 weeks and 54% of all cases of preeclampsia with a false-positive rate of 10% [58].

Although the utility of screening algorithms has shown to be effective in identifying women at risk, particularly nulliparous women, its use is often limited by accessibility to the required resources. Therefore, many centres rely on clinical history for this purpose. In keeping with this, the current guidelines recommend the use of clinical history in risk stratifying women [14, 15, 59]. This, however, may change based on the accessibility and cost- benefit analysis of the new screening markers.

The when: does timing of intervention and chronotherapy matter?

The optimal timing of the initiation of aspirin therapy is still unclear. Some studies have suggested greater benefit with prophylactic aspirin when initiated before 16 weeks of gestation [13, 17]. Meta-analysis by Bujold et al. [13] demonstrated that commencing low-dose aspirin before 16 weeks of gestation significantly reduced the rate of preeclampsia (RR 0.47, 95% CI 0.34–0.65), intrauterine growth retardation (IUGR) (RR 0.44, 95% CI 0.30–0.65) and severe preeclampsia (RR 0.09, 95% CI 0.02–0.37) [13]. The observed benefit was lost when aspirin was commenced after 16 weeks of gestation (preeclampsia: RR 0.81, 95% CI 0.63–1.03; IUGR: RR 0.98, 95% CI 0.87–1.10) [13]. Contrary to this, another meta-analysis suggested that the 16 weeks gestation cutoff was not as relevant [12]. Meher et al. [12] conducted an individual participant dataset analysis of the PARIS Collaboration dataset and suggested the outcomes with the use of aspirin was consistent when commenced before or after 16 weeks of gestation (RR) 0.90 (95% CI 0.79–1.03) for < 16 weeks and RR 0.90 (95% CI 0.83–0.98) for ≥ 16 weeks (interaction test $p = 0.98$) [12, 30]. Their analysis of the PARIS Collaboration data, however, only demonstrated a very modest overall preeclampsia reduction of ~10% with the use of prophylactic aspirin [12]. The current guidelines suggest initiating aspirin before 16 weeks of gestation [14, 15, 59]; however, recent studies suggest that a greater benefit maybe observed with earlier initiation of aspirin [11, 16, 60]. This, however, has not been assessed with a prospective randomized trial.

A similarly controversial issue is the chronotherapy of aspirin. Cardiology studies have demonstrated greater nocturnal blood pressure regulation with the use of nocturnal aspirin [61–63]. Hermida et al. [63] noted that a significant

blood pressure reduction was observed in males and non-pregnant females with untreated grade 1 hypertension (systolic blood pressure (SBP) 140–159 mm Hg, diastolic blood pressure (DBP) 80–99 mm Hg), who received nocturnal aspirin in comparison with daytime aspirin (decrease of 7.2/4.9 mm Hg in SBP/DBP; $p = 0.001$). The reduction in nocturnal blood pressure mean was double in non-dippers (11.0/7.1 mm Hg) compared with dippers (5.5/3.3 mm Hg; $p = 0.001$) [63]. Although the exact mechanism for this is unclear, some studies have suggested that a decrease in the renin and aldosterone pressor system could constitute a biologically plausible explanation for better blood pressure regulation when aspirin is ingested at bedtime [64–66]. Snoep et al. [65] found that low-dose aspirin (100 mg) when ingested at bedtime, compared with awakening, significantly diminished not only the 24 h level of plasma renin activity (RR 14% (95% CI 5–22) $p = 0.003$) but also the 24 h urine excretion of cortisol (RR 16% (95% CI 5–30) $p = 0.05$), dopamine (RR 14% (95% CI 1–28) $p = 0.04$) and norepinephrine (RR of 40% (95% CI − 1 to 88) $p = 0.02$) [65].This study was undertaken in non-pregnant females and males with a two of three male predominance. The clinical effect of chronotherapy of aspirin on primary and secondary cardiovascular outcomes is still unknown and is subject to ongoing research (CARING) ClinicalTrials.gov Identifier: NCT00725127.

Translating this to high-risk pregnant women, some studies have suggested a chronotherapeutic role of aspirin in preventing preeclampsia [20, 67]. In a prospective, randomized, double-blind, placebo-controlled, chronotherapy trial, 350 high-risk pregnant women were randomly assigned to 1 of the 6 groups defined according to treatment (placebo or aspirin, 100 mg/day) and time of treatment: upon awakening, 8 h after awakening, or at bedtime [20]. Ayala et al. [20] noted that ingesting 100 mg of aspirin daily at bedtime starting at ≤ 16 weeks of gestation decreased SBP on an average of 12.4/8.1 mm Hg (measured in 24 h SBP/DBP midline estimating statistics of rhythm) compared with ingesting aspirin upon awakening ($p < 0.001$) [20]. In addition, a lower rate of preeclampsia and IUGR was observed in the group of women who ingested aspirin at bedtime and in the group who ingested aspirin 8 h after awakening in comparison with those who ingested aspirin upon awakening (hazard ratio 0.19, 95% CI 0.10–0.39 $p < 0.001$) [20]. Although significant, this was not the primary outcome of the study. The mechanism for this, however, remains unclear, as it has not been adequately studied in pregnancy.

In keeping with this, more recent studies have utilised nocturnal aspirin in their studies [11, 16]. Although the current guidelines do not specify the utility of chronotherapy, this is likely to change as the evidence for this strengthens.

Aspirin resistance vs non-adherence

In 2009, the Working Group on Thrombosis of European Society of Cardiology categorized aspirin resistance as either clinical resistance or laboratory resistance [18]. Clinical resistance was described as the occurrence of a cardiovascular event despite aspirin therapy, whereas laboratory resistance or non-responsiveness was described as insufficient platelet inhibition activity. The relatively modest benefit of prophylactic aspirin in some studies in preventing preeclampsia has raised the question of clinical aspirin resistance among high-risk pregnant women. The actual incidence of clinical aspirin resistance in the pregnant cohort is unknown. Approximately 30% of pregnant women demonstrate a lack of laboratory response to aspirin at doses < 100 mg based on platelet function analyser (PFA-100) [68]. However, biochemical aspirin non-responsiveness, based on PFA-100, with low-dose aspirin (81 mg daily) is overcome in pregnant women with higher doses of aspirin (162 mg daily) [68]. A similar study which used Verifynow, a point-of-care assay in patients with coronary artery disease, demonstrated better inhibitory activity with higher doses of aspirin. Daily aspirin doses of < 100 mg were associated with increased prevalence of biochemical aspirin resistance compared with 150 mg and 300 mg daily (30.2% vs. 16.7% vs. 0%, $P = 0.0062$) [69]. Early studies of prophylactic aspirin in high-risk women utilised an aspirin dose range of 50–150 mg. The first study to suggest a prophylactic role of aspirin in preeclampsia utilised 150 mg of aspirin concurrent with dipyridamole [25]. However, Benigni et al. [70] demonstrated a prophylactic role with the use of only 60 mg daily. The common factor in both these studies was the early (before the end of the first trimester) use of aspirin. The current clinical guidelines recommend the use of low-dose aspirin with a dose range from 81–150 mg [14, 15, 59]. Although most centres use aspirin 100 mg daily, there has been a recent shift to 150 mg daily based on more recent clinical studies [11, 16]. There, however, is a need for stronger evidence to support the use of 150 mg aspirin over 100 mg aspirin in the prevention of preeclampsia in addition to more data on its safety profile.

Poor adherence has been identified as the most common reason for clinical and laboratory aspirin resistance [71, 72]. Non-adherence with prescribed medications among pregnant women is reported to vary from 20% to 80% [73–75]. Non-adherence to aspirin in pregnant women was found to vary from 20% to 45% [76, 77]. Recent data suggest that high-risk women will have to be at least 90% adherent with their prescribed aspirin to demonstrate a benefit from it; however, most studies have utilised self-reporting questionnaires to assess adherence, which have not been validated with biochemical assessment [76, 77]. The utility of biochemical measure of

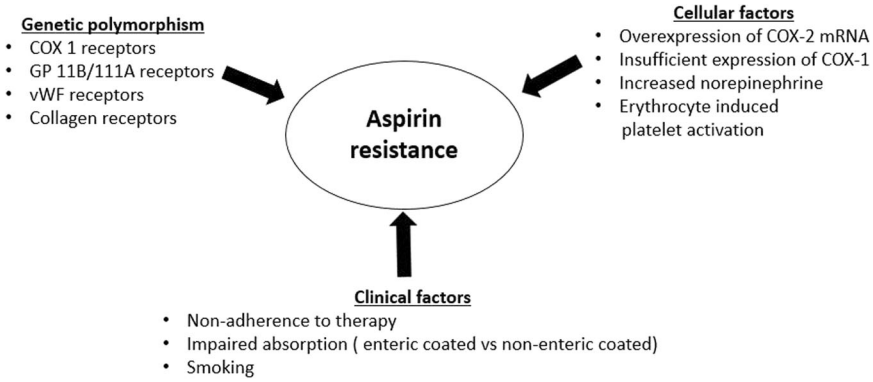

Fig. 3 Factors that influences aspirin resistance. Legends for Fig. 3 GP glycoprotein, vWF Von Willebrand factor

aspirin adherence was recently examined by Navaratnam et al. [72] with the use of PFA100 and serum salicylate. They demonstrated that in women with a variable response or lack of response in PFA 100 levels, aspirin non-adherence or variable adherence was more likely than aspirin resistance (41% vs. 0%) [72].

Other factors that may contribute toward aspirin resistance include differences in aspirin preparation: enteric coated vs. non-enteric coated, the effect of smoking, and the presence of gene polymorphism or cellular dysregulation (Fig. 3). The consensus on the recommended preparation of aspirin to be used in pregnancy remains unclear. Enteric-coated aspirin slows and reduces systemic absorption by ~20% in healthy non-pregnant volunteers [78]. Others have demonstrated that it does not alter absorption [79, 80]. These factors, however, have not been examined in the pregnant population and its influence on the clinical efficacy of aspirin in the high-risk pregnancy population remains unknown.

Conclusion

The use of aspirin in preventing preeclampsia has evolved over the last 40 years. Although the evidence supporting the use of aspirin in the obstetric setting has re-emerged, many unanswered questions remain in optimizing the use of aspirin in preventing preeclampsia. The key questions that warrant clarification to assist clinicians are the mechanism of action, optimal dose of aspirin, and the chronotherapy of aspirin. Clinicians should also pay more attention to patients' adherence as recent evidence suggests an underestimation of aspirin non-adherence among high-risk pregnant women.

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Compliance with ethical standards

Details of ethics approval Not applicable.

Conflict of interest The authors declare that they have no conflict of interest.

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