

Received: 8 June 2019

Accepted: 11 August 2019

DOI: 10.1111/bcpt.13308

## MINIREVIEW



# Aspirin for the prevention and treatment of pre-eclampsia: A matter of COX-1 and/or COX-2 inhibition?

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## Funding information

KMMC was supported by a National Health and Medical Research Council (NHMRC) of Australia CJ Martin Early Career Fellowship (GNT1112125). AHJD and RIN were supported by a grant from the foundation Lijf en Leven.

## Abstract

Since the 1970s, we have known that aspirin can reduce the risk of pre-eclampsia. However, the underlying mechanisms explaining this risk reduction are poorly understood. Both cyclooxygenase (COX)-1- and COX-2-dependent effects might be involved. As a consequence of this knowledge hiatus, the optimal dose and timing of initiation of aspirin therapy are not clear. Here, we review how (COX-1 versus COX-2 inhibition) and when (prevention versus treatment) aspirin therapy may interfere with the mechanisms implicated in the pathogenesis of pre-eclampsia. The available evidence suggests that both COX-1- and COX-2-dependent effects play important roles in the early stage of aberrant placental development and in the next phase leading to the clinical syndrome of pre-eclampsia. Collectively, these data suggest that high-dose (dual COX inhibition) aspirin may be superior to standard low-dose (selective COX-1 inhibition) aspirin for the prevention and also treatment of pre-eclampsia. Therefore, we conclude that more functional and biochemical tests are needed to unravel the contribution of prostanoids in the mechanisms implicated in the pathogenesis of pre-eclampsia and the potential of dual COX and/or selective COX-2 inhibition for the prevention and treatment of pre-eclampsia. This information is vital if we are to deduce the suitability, optimal timing and dose of aspirin and/or a specific COX-2 inhibitor (most likely using modified forms that do not cross the placenta) that can then be tested in a randomized, controlled trial instead of the current practice of empirical dosing regimens.

## KEYWORDS

aspirin, hypertension, pre-eclampsia, Prostaglandin-Endoperoxide Synthases

## 1 | INTRODUCTION

Pre-eclampsia affects 2%-8% of all pregnancies and is associated with maternal, foetal and neonatal morbidity and mortality.<sup>1</sup> For more than 30 years, we have known that cyclooxygenase (COX) inhibition with aspirin can prevent the

onset of pre-eclampsia. Presently, more than 45 randomized, controlled trials (RCTs) involving 30 000 patients have investigated the efficacy of selective COX-1 inhibition with low-dose aspirin for the prevention of pre-eclampsia.<sup>2</sup> While this preventative strategy is now generally accepted in clinical practice, the risk reduction is modest and the optimal dose

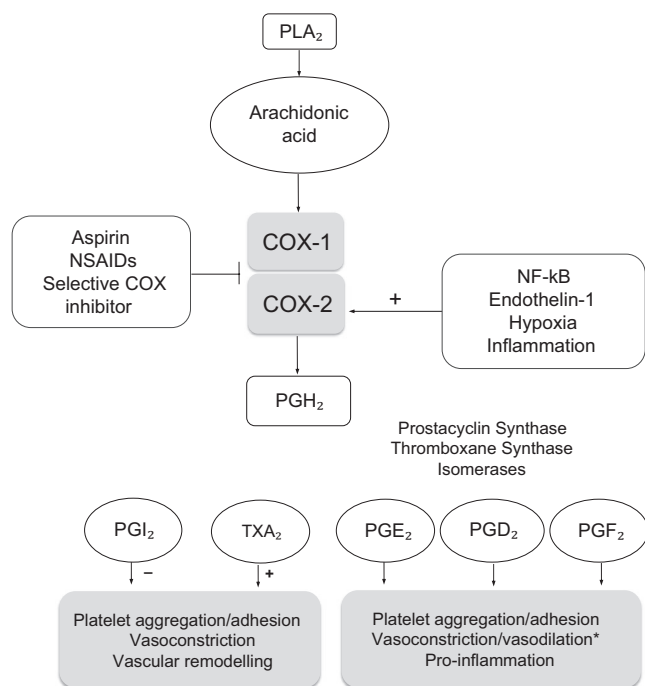
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and timing of initiation of aspirin therapy are ongoing areas of debate. These controversies may, at least in part, be due to differences in the contribution of COX-1 and COX-2 to the pathophysiology of pre-eclampsia which remains poorly understood. Here, we review how (COX-1 versus COX-2 inhibition) and when (prevention versus treatment) aspirin may interfere with the mechanisms implicated in the pathogenesis of pre-eclampsia. The available evidence suggests that high-dose (dual COX inhibition) aspirin may be superior to standard low-dose (selective COX-1 inhibition) aspirin for the prevention and also treatment of pre-eclampsia.

## 2 | THE PROSTANOID BIOSYNTHESIS PATHWAY

COX is essential for prostanoid biosynthesis (Figure 1). In this pathway, arachidonic acid is sequentially metabolized by COX into the short-lived intermediates prostaglandin (PG)  $G_2$  and  $PGH_2$ . Once formed,  $PGH_2$  is rapidly converted into thromboxane ( $TXA_2$ ), prostacyclin ( $PGI_2$ ) and other PGs ( $PGE_2$ ,  $PGD_2$  and  $PGF_{2\alpha}$ ) via  $TXA_2$  synthase,  $PGI_2$  synthase and specific isomerases, respectively.  $TXA_2$  is produced primarily by platelets and induces vasoconstriction, vascular remodelling, platelet aggregation and adhesion.  $PGI_2$ , which is released from vascular endothelial cells, induces vasodilation



**FIGURE 1** Aspirin and the prostanoid biosynthesis pathway. Abbreviations: COX, cyclooxygenase; NF-κB, nuclear factor-κB; NSAIDs, non-steroidal anti-inflammatory drugs;  $PGD_2$ , prostaglandin  $D_2$ ;  $PGE_2$ , prostaglandin  $E_2$ ;  $PGF_{2\alpha}$ , prostaglandin  $F_{2\alpha}$ ;  $PGH_2$ , prostaglandin  $H_2$ ;  $PGI_2$ , prostacyclin;  $PLA_2$ , phospholipase  $A_2$ ;  $TXA_2$ , thromboxane. \*Depending on the receptor stimulated

and inhibits vascular remodelling, platelet aggregation and adhesion, thereby counterbalancing the effects of  $TXA_2$ . PGs modulate vascular tone, inflammation and platelet aggregation.  $PGD_2$  inhibits platelet aggregation and induces vasodilation and (via thromboxane receptor (TP) activation) vasoconstriction. Both  $PGE_2$  and  $PGF_{2\alpha}$  contribute to the regulation of blood pressure via their effects on vascular tone and renal function. Additionally,  $PGF_{2\alpha}$  and 8-iso- $PGF_{2\alpha}$ , a major isoprostane generated through the non-enzymatic peroxidation of arachidonic acid, are markers of oxidative stress.<sup>3</sup>

There are two COX isoforms: COX-1 and COX-2. Constitutive COX-1 is ubiquitously expressed and generates the majority of prostanoids during physiological situations.<sup>4</sup> Conversely, expression of constitutive COX-2 is low and mainly restricted to the brain, thymus, gut, kidney and placenta.<sup>4</sup> Inflammatory mediators (eg, nuclear factor-κB (NF-κB),<sup>5</sup> hyperosmolality,<sup>6</sup> endothelin (ET)-1<sup>7</sup> and hypoxia<sup>8</sup>) are key drivers for an up-regulation in inducible COX-2. The affinity of aspirin is 10-100 times higher for COX-1 than COX-2. When administered at low doses (75-100 mg/d), aspirin will only bind to COX-1 in platelets. Because of the irreversible action of aspirin (ie, acetylation), its inhibitory effects on COX-1 and  $TXA_2$  production last for the life-time of the platelet, which is approximately 1 week for mature platelets. Consequently, low-dose aspirin rapidly tips the  $PGI_2/TXA_2$  balance in favour of  $PGI_2$ , but has no impact on  $PGI_2$  production. High-dose aspirin (>325 mg/d) inhibits both COX-1- and COX-2-dependent prostanoid generation.<sup>3</sup>

## 3 | PATHOPHYSIOLOGY OF PRE-ECLAMPSIA

Pre-eclampsia is defined as de novo hypertension after 20 weeks' gestation with new-onset proteinuria and/or maternal renal insufficiency, increased liver enzymes, neurological complications, haematological complications and/or utero-placental dysfunction.<sup>9</sup> Early-onset pre-eclampsia tends to develop before 34 weeks' gestation, whereas late-onset pre-eclampsia occurs at or after 34 weeks' gestation. The placenta is thought to play a key role in the pathophysiology of both early- and late-onset pre-eclampsia since delivery of the placenta resolves the clinical manifestation of pre-eclampsia. The prevailing theory is that failure of the placental vasculature to adequately develop, due to impaired trophoblast invasion and spiral artery remodelling, leads to reduced uteroplacental perfusion and episodes of hypoxia/reperfusion.<sup>1</sup> This placental dysfunction results in the generation and release of reactive oxygen species (ROS), cytokines, lipid peroxidases, ET-1 and soluble Fms-like tyrosine kinase-1 (sFlt-1), a naturally occurring antagonist of vascular endothelial growth factor (VEGF), which all contribute to the clinical manifestation of pre-eclampsia. It is well-established that the production of prostanoids is

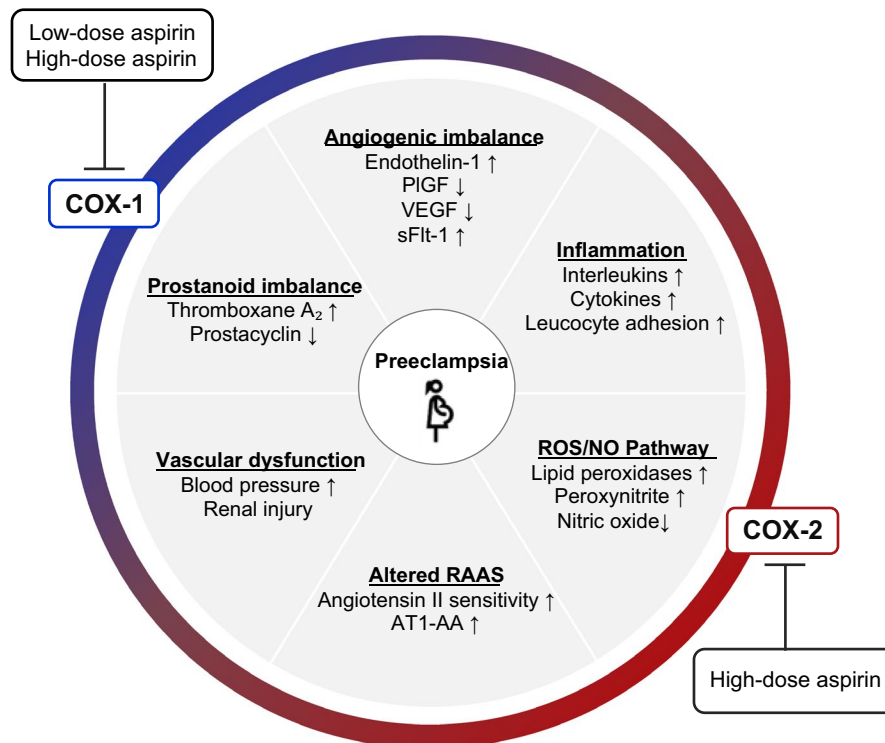
altered during pre-eclampsia such that the  $\text{PGI}_2/\text{TXA}_2$  ratio is reduced<sup>3,10,11</sup> and  $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$  levels are increased.<sup>12-14</sup> Accumulating evidence suggests that both COX-1- and COX-2-dependent prostanoids contribute to the activation, either upstream or downstream, of the pathways implicated in the pathogenesis of pre-eclampsia. Consequently, both low- and high-dose aspirin may be efficacious for the prevention and also treatment of pre-eclampsia (Figure 2).

#### 4 | ASPIRIN FOR THE PREVENTION OF PRE-ECLAMPSIA

The first case report describing the use of aspirin for the treatment of recurrent toxemia of pregnancy used high-dose aspirin (600 mg) three times daily.<sup>15</sup> Thereafter, an observational study reported a lower prevalence of pre-eclampsia in women who used aspirin during pregnancy, presumably as an analgesic meaning higher doses.<sup>16</sup> However, all RCTs investigating prophylactic use of aspirin in women at high risk of pre-eclampsia have used low-dose aspirin

(50-160 mg/d). Meta-analyses of these RCTs demonstrate a lower prevalence of pre-eclampsia when aspirin therapy is initiated  $\leq 16$  weeks' gestation particularly for early-onset pre-eclampsia.<sup>2,17,18</sup> Accordingly, clinical guidelines recommend that aspirin therapy is initiated  $\leq 16$  weeks' gestation in women at high risk for pre-eclampsia.<sup>9,19</sup> Observational and prospective cohort studies suggest that 60-80 mg/d of aspirin may be suboptimal and that doses of 100-160 mg/d may be more efficacious for the prevention of pre-eclampsia.<sup>20-22</sup> Consistent with these studies, a recent meta-analysis of RCTs demonstrated that the relationship between aspirin (50-150 mg/d) and the prevention of pre-eclampsia is dose-dependent when started  $\leq 16$  weeks' gestation,<sup>2</sup> suggesting that higher doses of aspirin are superior for the prevention of pre-eclampsia.

The main rationale for using low-dose aspirin for the prevention of pre-eclampsia is to restore the  $\text{PGI}_2/\text{TXA}_2$  ratio. In contrast to uncomplicated pregnancies where the normal increase in platelet  $\text{TXA}_2$  (due to pregnancy being a hypercoagulable state) is offset by an increase in  $\text{PGI}_2$ ,<sup>23,24</sup> circulating, urinary and placental levels of  $\text{PGI}_2$  drop sharply during pre-eclampsia.<sup>10,11</sup>



**FIGURE 2** Proposed mechanisms by which COX-1 and COX-2 contribute to the pathogenesis of pre-eclampsia and the ability of low and high dose to prevent these effects. The generation of thromboxane  $\text{A}_2$  is mediated via COX-1 (blue). Both low- and high-dose aspirin inhibit COX-1, thereby improving the thromboxane  $\text{A}_2$ /prostacyclin balance in favour of prostacyclin during pre-eclampsia. COX-2 (red) is implicated in the enhanced sensitivity to angiotensin II, activation of the immune system and increased oxidative stress during pre-eclampsia. Consequently, COX-2 inhibition with high-dose aspirin may attenuate these effects. Both COX isoforms (purple) are implicated in the vascular dysfunction and angiogenic imbalance that occurs during pre-eclampsia. Therefore, high-dose aspirin may be the best option to restore the angiogenic balance and improve vascular function during pre-eclampsia.  $\text{AT}_1$ -AA, angiotensin II type I receptor autoantibodies; COX, cyclooxygenase; NO, nitric oxide; PIGF, placental growth factor; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; sFlt-1, soluble Fms-like tyrosine kinase; VEGF, vascular endothelial growth factor

Consequently, the PGI<sub>2</sub>/TXA<sub>2</sub> ratio is skewed towards TXA<sub>2</sub> during pre-eclampsia.<sup>3</sup> This shift towards vasoconstriction is potentiated by altered PGF<sub>2α</sub> and PGE<sub>2</sub> production.<sup>12-14</sup> Since the reduction in PGI<sub>2</sub> precedes the clinical onset of pre-eclampsia<sup>11</sup> and the severity of pre-eclampsia is positively correlated with TXA<sub>2</sub>,<sup>25</sup> alterations in vasodilator/vasoconstrictor prostanoid balance seem to play a major role in the pathogenesis of pre-eclampsia. Within the placenta, both COX-1 and COX-2 are expressed in the villi.<sup>26-28</sup> TXA<sub>2</sub> is primarily produced by trophoblast cells near the maternal circulation, whereas PGI<sub>2</sub> is produced by endothelial cells near the foetal circulation.<sup>26,29</sup> During pre-eclampsia, *in vitro* studies have demonstrated an increase in trophoblast TXA<sub>2</sub> production,<sup>29,30</sup> which may contribute to the rise in TXA<sub>2</sub> in the maternal circulation. Moreover, COX-2 expression and activity are also increased in trophoblast cells from pre-eclamptic placentas, an effect that was associated with increased TXA<sub>2</sub> and PGE<sub>2</sub> production.<sup>31</sup> Placental up-regulation of key drivers of inducible COX-2 including hypoxia and inflammatory mediators likely contributes to the shift towards vasoconstrictor prostanoids during pre-eclampsia.<sup>8,32,33</sup> Additionally, prostanoids might also alter their effect on vascular contractility during pre-eclampsia. For example, vascular relaxation to PGI<sub>2</sub> is associated with smooth muscle cell hyperpolarization, such that PGI<sub>2</sub> acts as an endothelium-derived hyperpolarizing factor (EDHF).<sup>34</sup> However, during pathological situations such as hypertension, obesity and diabetes, PGI<sub>2</sub> can elicit vasoconstriction via stimulation of smooth muscle cell TPs, thereby acting as an endothelium-derived contracting factor (EDCF).<sup>34-37</sup> All prostanoids are able to bind to TPs, albeit with varying affinities, and PGI<sub>2</sub> is the most important prostanoid involved in this constrictor response. However, it should be noted that this phenomenon is typically seen with very high agonist concentrations and in an *ex vivo* setting.<sup>35,36</sup> TXA<sub>2</sub>, PGE<sub>2</sub> and PGF<sub>2α</sub> may also contribute to endothelium-dependent contractions.<sup>34</sup> In recent years, multiple pathways have been identified in the pathogenesis of pre-eclampsia which may act in concert with prostanoids to promote the development of pre-eclampsia. Since majority of these mechanisms are implicated in the genesis of pre-eclampsia in early pregnancy, this may explain why the efficacy of aspirin for the prevention of pre-eclampsia is greater when initiated ≤16 weeks' gestation. Moreover, consistent with a dose-dependent relationship existing between aspirin and pre-eclampsia, accumulating evidence suggests a greater contribution of COX-2 than COX-1 in the mechanisms implicated in the pathogenesis of pre-eclampsia.

## 4.1 | Initiating aspirin therapy in early pregnancy (≤16 weeks' gestation)

### 4.1.1 | VEGF inactivation

VEGF, which is integral to placental vasculogenesis and angiogenesis, increases progressively during uncomplicated

pregnancies.<sup>38</sup> During pre-eclampsia, VEGF is reduced in association with increased (placental) production of sFlt-1. This increase in sFlt-1 is evident weeks before the clinical onset of pre-eclampsia, suggesting a key role for VEGF inactivation in the pathogenesis of pre-eclampsia. Likewise, artificial increases in sFlt-1 induce hypertension, renal injury and proteinuria in pregnant rodents.<sup>39,40</sup> Of interest, cancer patients and animals treated with VEGF inhibitors (VEGFi), which function in much the same way as sFlt-1, exhibit a pre-eclampsia-like syndrome characterized by hypertension and kidney damage.<sup>41</sup> In mice, VEGFi induces an up-regulation of COX-2 and PGE<sub>2</sub>, at least in tumour tissue.<sup>42</sup> In line with this, sFlt-1-induced hypertension in mice is abolished by high-dose aspirin or picotamide, a TXA<sub>2</sub> synthase and TP antagonist,<sup>43</sup> suggesting that prostanoids may contribute to the hypertension and renal injury during VEGF inactivation. Similarly, in BPH/5 mice which spontaneously develop the hallmarks of pre-eclampsia, decidual COX-2 inhibition diminishes pregnancy-induced hypertension and improves foetal outcome.<sup>44</sup> Interestingly, Li et al<sup>45</sup> recently demonstrated that aspirin and the specific COX-1 inhibitor, sc-560, can inhibit the expression and release of sFlt-1 in primary cytotrophoblasts cultured from pre-eclamptic placentas. Consistent with these findings, Murtoniemi et al<sup>46</sup> reported an association between low-dose aspirin started <14 weeks' gestation and higher longitudinal increase in serum placental growth factor (PlGF) concentration in women at high risk of pre-eclampsia. As PlGF is homologous to VEGF and similarly acts as a natural ligand of sFlt-1, the up-regulation of PlGF during low-dose aspirin therapy may be indirectly through sFlt-1 inhibition. Unfortunately, other trials reporting that aspirin prevents pre-eclampsia have not investigated the effect of aspirin on angiogenic markers such as VEGF or sFlt-1. Nevertheless, since VEGF contributes to placental vasculogenesis which is completed in the first trimester, an inhibitory effect of aspirin on sFlt-1 may underlie the long-held belief that commencing aspirin therapy <13 weeks' gestation facilitates placentation.<sup>47</sup>

### 4.1.2 | Dysregulation of the nitric oxide (NO) pathway

NO deficiency, due to (a) decreases in NO-dependent vasodilators (eg oestrogen and VEGF) or increases in sFlt-1 and inflammatory mediators, or (b) reduced bioavailability of NO secondary to increased oxidative stress, contributes to the pathogenesis of pre-eclampsia and maternal endothelial dysfunction.<sup>48,49</sup> NO can stimulate or suppress the COX pathway depending on basal NO release, the cell type in which prostanoid biosynthesis occurs and the intensity of the stimulus for prostanoid generation.<sup>50</sup> Decreased NO bioavailability may lead to a compensatory increase in endothelial PGI<sub>2</sub> to induce vasodilation and endothelium-dependent hyperpolarization,<sup>3</sup>

while ROS generation potentiates EDCF-mediated responses by reducing NO and increasing vasoconstrictor prostanoid generation.<sup>34</sup> The coupling product of NO and superoxide is peroxynitrite which directly increases the catalytic activity of COX-2 and the production of PGE<sub>2</sub> and PGD<sub>2</sub>.<sup>51</sup> Peroxynitrite also decreases PGI<sub>2</sub> synthase, thereby leading to a reduction in PGI<sub>2</sub>, but has no effect on TXA<sub>2</sub> synthase.<sup>3</sup> Consequently, oxidative stress may contribute to the shift in the PGI<sub>2</sub>/TXA<sub>2</sub> ratio during pre-eclampsia. Additionally, since oxidative stress increases the non-enzymatic generation of isoprostanes which are endogenous ligands for TP,<sup>3</sup> isoprostanes may contribute to the deleterious effects attributed to TXA<sub>2</sub> during pre-eclampsia. COX activation can alter NO synthesis.<sup>50</sup> In vitro studies suggest that both PGI<sub>2</sub> and PGE<sub>2</sub> induce vascular NO release from the endothelium by cyclic AMP (cAMP)-mediated effects.<sup>50</sup> Conversely, aspirin has been suggested to be able to rescue ROS-induced down-regulation of eNOS which may in turn alter NO production, but this has never been studied in human beings.<sup>52</sup> Furthermore, oxidative stress generates lipid peroxidases which increase COX and TXA<sub>2</sub>. In women at risk of pre-eclampsia, low-dose aspirin (81 mg/d) initiated between 9 and 34 weeks' gestation decreased lipid peroxidases and TXA<sub>2</sub> without altering PGI<sub>2</sub> (measured after 3-4 days and 3-4 weeks of treatment).<sup>53</sup> Moreover, in pre-eclamptic placental tissue incubated with varying doses of aspirin, the inhibitory effect of aspirin on lipid peroxidases was demonstrated to be dose-dependent.<sup>54</sup>

#### 4.1.3 | Immunity and inflammation

The immune system is normally suppressed during pregnancy to prevent the rejection of the foetus. During pre-eclampsia, both the innate and adaptive immune systems are activated<sup>55</sup> with elevations in circulating pro-inflammatory cytokines including tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>56</sup> Interestingly, both TNF- $\alpha$  and IL-1 $\beta$  induce PGE<sub>2</sub> biosynthesis within the decidua.<sup>57</sup> Activation of the NF- $\kappa$ B pathway during pre-eclampsia, initiated by toll-like receptors, induces the release of inflammatory cytokines and causes an up-regulation of COX-2.<sup>58</sup> Aspirin can bind to the cellular kinase IKK- $\beta$ , thereby preventing NF- $\kappa$ B-mediated regulation of gene expression, independent of the COX-prostanoid pathway.<sup>59</sup> Thus, aspirin administration could impede NF- $\kappa$ B-induced downstream activation of COX-2- and TNF- $\alpha$ -mediated endothelial dysfunction in vivo, significantly lowering hypertension and proteinuria.<sup>52,58</sup> Inflammatory cells, particularly macrophages which make significant amounts of NO and superoxide, may also contain high levels of COX as peroxynitrite is an important modulator of COX activity.<sup>51</sup> In addition, aspirin can induce lipoxin production which reduces leucocyte adhesion in human umbilical vein endothelial cells exposed to pre-eclamptic plasma.<sup>60</sup> Hence, through different mechanisms, both COX-1 and COX-2 inhibition might

be able to dampen the aberrant inflammatory state during pre-eclampsia.

## 4.2 | Additional effects of aspirin therapy in later pregnancy (>16 weeks' gestation)

### 4.2.1 | Activation of the endothelin (ET) system

Circulating ET-1 is increased ~1.5-2-fold during pre-eclamptic pregnancies,<sup>61</sup> and multiple regression analysis demonstrates that ET-1 is an independent determinant of hypertension and proteinuria during pre-eclampsia.<sup>62</sup> Furthermore, circulating ET-1 is elevated in cancer patients and animals treated with VEGFi,<sup>63</sup> suggesting that activation of the ET system is secondary to the angiogenic imbalance occurring in early pregnancy. Importantly, hypertension and renal damage are prevented by ET receptor blockade in animal models of pre-eclampsia and VEGFi-induced hypertension, demonstrating a key role for activation of the ET system in pre-eclampsia.<sup>64</sup> In mice treated with sFlt-1, pressor responsiveness to ET-1 is enhanced in isolated carotid artery segments and this effect is abrogated by indomethacin, a non-specific COX inhibitor.<sup>43</sup> In vitro COX-2 expression is increased by ET-1 in endothelial cells<sup>65</sup> and mesangial cells.<sup>66</sup> In vivo COX-2 expression is down-regulated by dual ET<sub>A/B</sub> receptor blockade or selective ET<sub>A</sub> receptor blockade in cirrhosis-related angiogenesis in rats.<sup>67</sup> Hypoxia is also a key driver of overexpression of ET-1,<sup>68</sup> with increases in both ET-1 and 8-iso-PGF<sub>2 $\alpha$</sub>  observed in both the maternal and foetal circulations in the ex vivo dually perfused placental perfusion model in response to hypoxia.<sup>69</sup> Moreover, decreased vasodilatory endothelial ET<sub>B</sub> receptor expression may contribute to the decline in PGI<sub>2</sub> during pre-eclampsia.<sup>70</sup> Collectively, these data suggest that the deleterious effects of activation of ET-1 system during pre-eclampsia are in part mediated via prostanoids and that high-dose aspirin or a selective COX-2 inhibitor may be more efficacious than low-dose aspirin for the prevention of these effects. Whether COX inhibitors reduce ET-1 levels has not been investigated.

### 4.2.2 | Enhanced sensitivity to angiotensin II

The characteristic refractoriness to angiotensin II observed during uncomplicated pregnancies is lost during pre-eclampsia, with an enhanced pressor response to angiotensin II evident as early as 23 weeks' gestation.<sup>71,72</sup> In normotensive pregnant women ( $\geq$ 28 weeks' gestation), administration of indomethacin or high-dose aspirin (600 mg) reduces the concentration of angiotensin II needed to evoke a 20 mm Hg rise in blood pressure,<sup>73</sup> suggesting that prostanoids mediate the reduced sensitivity to angiotensin II. Similar findings are also reported in pregnant ewes, with both PGI<sub>2</sub> and

PGE<sub>2</sub> implicated in the refractoriness to angiotensin II.<sup>74,75</sup> Whether the shift in the vasodilator/vasoconstrictor prostanoid balance or PGI<sub>2</sub> acting as an EDCF via stimulation of TP during pre-eclampsia contributes to the enhanced sensitivity to angiotensin II is unknown. However, in isolated aortic rings from (non-pregnant) spontaneously hypertensive rats, the enhanced sensitivity to angiotensin II was associated with the release of vasoconstrictor prostanoids.<sup>76</sup> This effect was inhibited by a preferential COX-2 inhibitor,<sup>76</sup> suggesting that COX-2-dependent prostanoids enhance the sensitivity to angiotensin II during pathological situations such as hypertension. In pre-eclampsia, agonistic antibodies against the angiotensin type 1 receptor (AT<sub>1</sub>-AA)<sup>70,77</sup> may potentiate this effect. Studies utilizing human primary trophoblasts and vascular smooth muscle cells and the reduced uterine perfusion model of pre-eclampsia have demonstrated that AT<sub>1</sub>-AA stimulate the generation of ROS, inflammatory mediators (NF-κB), ET-1 and sFlt-1,<sup>77,78</sup> which in turn increase COX-2-dependent prostanoid generation. Consequently, COX-2 inhibition may normalize the sensitivity to angiotensin II during pre-eclamptic pregnancies.

## 5 | ASPIRIN FOR THE TREATMENT OF THE CLINICAL MANIFESTATION OF PRE-ECLAMPSIA

The clinical manifestation of pre-eclampsia is hypertension, widespread endothelial damage and end-organ damage. In addition to aspirin intervening in the pathogenesis of pre-eclampsia, it might have an independent effect on these clinical manifestations. Low-dose aspirin may lower blood pressure, although a recent RCT did not confirm this.<sup>79,80</sup> On the other hand, higher doses of non-steroidal anti-inflammatory drugs (NSAIDs) can cause hypertension, probably due to salt retention. A similar contradiction is the case for renal effects, where NSAIDs, that is inhibitors of COX-1 and/or COX-2, increase the risk of acute renal insufficiency. The underlying mechanism is decreased PGE<sub>2</sub> and PGI<sub>2</sub> leading to an inability to maintain renal blood flow. The risk is greatest in cases of a low circulating volume, for instance due to diuretics, or when using renin-angiotensin-aldosterone system inhibitors (RAASi) which prevent compensatory vasoconstriction of the efferent arteriole; the combination of a diuretic, RAASi and NSAID is known as ‘triple whammy’.<sup>81</sup> However, COX-2 inhibition seems beneficial in nephropathy in normotensive or hypertensive individuals and might be a drug target for proteinuria.<sup>82,83</sup> During pregnancy, the increased plasma volume will most likely prevent the unfavourable haemodynamic effects of NSAIDs, although once pre-eclampsia develops one should be careful due to potentially relative hypovolaemia.<sup>70</sup> A last potential way of action is the best-known effect of

aspirin and the mechanism underlying the use of aspirin for the secondary prevention of cardiovascular disease (and earlier as primary prevention of cardiovascular disease though the risk of bleeding may outweigh the benefit<sup>84,85</sup>): irreversible inhibition of platelet COX-1 leading to less platelet activation and consequently thrombus formation. However, a recent study did not show a relationship between the effect on platelet function and placental outcome although this study may have been underpowered.<sup>22</sup> However, this antithrombotic effect may influence the risk/benefit balance since high-dose aspirin could increase the risk of bleeding, especially gastrointestinally. This would also be an argument in favour of selective COX-2 inhibition.<sup>86</sup> Alternatively, a proton pump inhibitor (PPI) could be advised since PPI use after 28 weeks’ gestation was associated with a reduced risk of early-onset pre-eclampsia,<sup>87</sup> although the first RCT was negative.<sup>88</sup>

## 6 | FOETAL AND NEONATAL CONSIDERATIONS OF ANTENATAL COX INHIBITION

In mice, genetic COX-1 deficiency is associated with delayed parturition and reduced offspring survival,<sup>3</sup> whereas COX-2-deficient mice are infertile, develop nephropathy and die earlier than their wild-type counterparts.<sup>3</sup> Accordingly, animal studies suggest that NSAIDs induce teratogenicity and other adverse foetal effects.<sup>89</sup> However, human data concerning adverse foetal and neonatal effects of NSAIDs are less conclusive.<sup>89</sup> In the first two trimesters, NSAIDs seem to have limited risk. In the last trimester, lower prostaglandin levels increase the risk of premature closure of the ductus arteriosus (DA), oligohydramnios as well as foetal renal failure.<sup>89</sup> Low-dose aspirin is known to be safe throughout human pregnancy with no association between its use and pregnancy (placental abruption, miscarriage) or foetal (congenital anomalies, neonatal intraventricular haemorrhage and premature closure of the DA) complications.<sup>18,90-92</sup> Negative long-term effects on the offspring following antenatal aspirin therapy are unlikely, although a recent epidemiological study from China suggests that maternal aspirin use during pregnancy is associated with childhood asthma by 7 years of age.<sup>93</sup> However, a positive effect of maternal aspirin use during pregnancy on childhood blood pressure has also been reported.<sup>94</sup> Whether high-dose aspirin or a specific COX-2 inhibitor is safe to use during pregnancy requires further investigation. We know that COX inhibitors including aspirin and indomethacin are able to cross the human placental barrier.<sup>89</sup> COX inhibitors including indomethacin are used in clinical practice for tocolysis, since they provide a better combination of delayed delivery (for at least 48 hours and up to 7-10 days) and

maternal tolerance<sup>89</sup> than conventional tocolytics. However, the use of indomethacin as a tocolytic agent is limited by adverse foetal and neonatal effects as described above.<sup>89</sup> In contrast, a recent cohort study in women with short cervix reported that starting indomethacin treatment earlier in pregnancy (initiated <25 weeks' gestation and continued until delivery or 32 weeks' gestation, whichever came first) did not increase foetal (oligohydramnios and DA constriction) or neonatal (pulmonary haemorrhage, patent DA requiring medical intervention, necrotizing enterocolitis, spontaneous intestinal perforation, intraventricular grade III-IV or other intracranial haemorrhage and mortality) complications.<sup>95</sup> This suggests that COX-2 inhibition may be safer during early pregnancy rather than later which is in line with known safety data for NSAIDs. To the best of our knowledge, no study has investigated human placental transfer of selective COX-2 inhibitors (although it is expected that they are able to cross the placental barrier) and little is known about the foetal and neonatal effects of selective COX-2 inhibitors.

## 7 | PERSPECTIVES AND CLINICAL IMPLICATIONS

Accumulating evidence demonstrates a greater role for COX-2 than COX-1 in the pathogenesis of pre-eclampsia, suggesting that high-dose aspirin or a selective COX-2 inhibitor (potentially on top of low-dose aspirin to obtain maximum benefits of both without the deleterious gastrointestinal effects associated with excessive COX-1 inhibition) may be more efficacious than low-dose aspirin. More functional and biochemical tests are needed in preclinical and clinical studies to unravel the contribution of prostanoids in the mechanisms implicated in the pathogenesis of pre-eclampsia and the potential of dual COX and/or selective COX-2 inhibition for the prevention and treatment of pre-eclampsia. Positive findings in these studies will provide a strong rationale for the development of modified forms of aspirin and/or selective COX-2 inhibitors that do not cross the placental barrier. These studies will give more information about the suitability, optimal timing and dose of aspirin and/or a specific COX-2 inhibitor that could then be tested in an RCT instead of the current practice of empirical dosing regimens. This is vital if we are to prolong pregnancy without compromising maternal or foetal health. Understanding how aspirin prevents pre-eclampsia may improve lifelong cardiovascular health for both mother and child.

### ACKNOWLEDGEMENTS

The authors would like to thank Mr Wichor Bramer (Erasmus MC Medical Library, Rotterdam, The Netherlands) for his help searching the literature.

### CONFLICT OF INTEREST

The authors declare that they have nothing to disclose.

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**How to cite this article:** Mirabito Colafella KM, Neuman RI, Visser W, Danser AHJ, Versmissen J. Aspirin for the prevention and treatment of pre-eclampsia: A matter of COX-1 and/or COX-2 inhibition? *Basic Clin Pharmacol Toxicol*. 2019;00:1–10. <https://doi.org/10.1111/bcpt.13308>