

## Review Article

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# Aspirin to Prevent Preeclampsia

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### Abstract:

**Background:** Pre-eclampsia is a major cause of mortality and morbidity during pregnancy and childbirth. There are recommendations on use of medications to prevent preeclampsia, including low dose aspirin.

**Objective:** The objective of this review is to discuss role of aspirin in reducing the incidence and maternal mortality and morbidity due to preeclampsia including its dose and duration of use.

**Methods:** Review of available literature in internet and from libraries.

**Results:** Four large randomized trials have demonstrated a reduction in the incidence of preeclampsia in patients treated with low-dose aspirin prophylaxis compared with placebo/no treatment (15 versus 19 percent, 18 versus 20 percent, 6.7 versus 7.6 percent, and 1.6 versus 4.3 percent); however, the results were statistically significant in only the last trial. When data from these and other trials were pooled, meta-analyses supported the significance of the trend observed in individual trials. When begun early in the second trimester, use of low-dose aspirin (75-150 mg) reduced the incidence of preeclampsia by at least 10 percent, with the greatest absolute benefit in women at moderate to high risk of developing the disease. Serious sequelae of early onset preeclampsia, such as preterm birth and fetal growth restriction, were also reduced.

**Conclusion:** Low-dose aspirin reduces the frequency of preeclampsia, as well as related adverse pregnancy outcomes (preterm birth, growth restriction), by about 10 to 20 percent when given to women at moderate to high risk of the disease. It has an excellent maternal/fetal safety profile in pregnancy. WHO recommends Low-dose acetylsalicylic acid (aspirin, 75 mg) for the prevention of preeclampsia in women at high risk of developing the condition; should be initiated before 20 weeks of pregnancy. It should be taken preferably from 13<sup>th</sup> week of pregnancy, daily, regularly and may be discontinued 5 to 10 days before delivery.

**Key words:** Aspirin, pre eclampsia, aspirin in prevention of pre-eclampsia, antiplatelet agents, prevention of pre-eclampsia

### Introduction:

Preeclampsia is one of the most serious health problems affecting pregnant women. It is a complication in 2% to 8% of pregnancies worldwide and contributes to both maternal and infant morbidity and mortality.<sup>1</sup> Eclampsia, a complication of preeclampsia causes about 20 percent of maternal death in Bangladesh.<sup>2</sup> Preeclampsia also accounts

for 15% of preterm births.<sup>1</sup> Preeclampsia is defined by the onset of hypertension (blood pressure >140/90 mm Hg) and proteinuria (>0.3 g of protein in the urine within a 24-hour period) during the second half of pregnancy (>20 weeks). In the absence of proteinuria, preeclampsia is classified as hypertension with any of the following: thrombocytopenia, impaired liver function, renal

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insufficiency, pulmonary edema, or cerebral or visual disturbances.<sup>3</sup> Standard prenatal care, including close follow-up of high-risk women after midgestation, increases the chance that preeclampsia will be detected early in the course of disease. Early diagnosis followed by appropriate management, including delivery, may prevent some of the serious sequelae of the disease, such as eclamptic seizures and multiorgan failure.

Since there is no curative treatment other than delivery, an intervention that could prevent preeclampsia would have a significant impact on maternal and infant health worldwide. Many different strategies to prevent preeclampsia have been investigated in randomized trials. It is not surprising that most simple approaches have been unsuccessful, given the complexities in pathogenesis and the likelihood that multiple etiologies cause the syndrome. In women at high risk of developing preeclampsia, low-dose aspirin prophylaxis has preventive effects, but the magnitude of benefit in this group is variable and depends on a number of factors.

After the physiological effects of prostacyclin (epoprostenol) and thromboxane on platelets and vessel walls were elucidated,<sup>4</sup> it was suggested that many of the pathophysiological features of preeclampsia might be explained by disordered eicosanoid metabolism. The effects of aspirin in low concentrations, including reductions in platelet aggregation and constriction of arterial smooth muscle, made it an attractive choice for potentially ameliorating the pathophysiological effects of preeclampsia.

On the basis of the 2014 systematic review,<sup>1</sup> World Health Organization (WHO)<sup>5</sup> and NICE<sup>6</sup> and the US Preventive Services Task Force (USPSTF)<sup>7</sup> currently recommend daily low-dose aspirin therapy beginning at 12 weeks of gestation in patients who are considered to be at "high risk for preeclampsia" according to medical and obstetrical criteria. The American College of Obstetricians and Gynecologists has endorsed these guidelines.<sup>3</sup>

The objective of this review is to discuss role of aspirin in reducing the incidence and maternal mortality and morbidity due to preeclampsia.

#### **Methods:**

Literature review using Medline, WHO RHL, UPTODATE and GOOGLE in the internet and from libraries.

#### **Results:**

##### *Clinical significance of pre-eclampsia*

Pre-eclampsia is a multi-factorial condition. Although its aetiology remains unclear, there have been significant advances in the understanding of the pathophysiology of the disorder. The primary lesion is thought to be deficient trophoblastic invasion of the maternal spiral arteries in the second trimester, leading to underperfusion of the uteroplacental circulation and placental ischaemia.<sup>8</sup> The resulting placental damage is thought to lead to release of factors into the maternal circulation, which are responsible for the maternal syndrome. Activation of platelets and the clotting system may occur early in the course of the disease, before clinical symptoms develop<sup>9,10</sup>. Deficient intravascular production of prostacyclin, a vasodilator, with excessive production of thromboxane, a platelet derived vasoconstrictor and stimulant of platelet aggregation,<sup>11,12</sup> have also been demonstrated to occur in preeclampsia. These observations have led to the hypothesis that antiplatelet agents, low dose aspirin (<300 mg/day) in particular, might prevent or delay the development of pre-eclampsia or reduce its severity and the risk of adverse events. It is further hypothesised that the effect of antiplatelets may be different if treatment is started before placental implantation is complete.<sup>13</sup> If this hypothesis were correct, the greatest benefit should be seen in women who started treatment before 16 weeks gestation, with the effect attenuating with later onset of treatment. Similarly, it remains unclear as to the most appropriate dose of antiplatelet therapy for the prevention of pre-eclampsia in order to maximise benefits whilst minimising harms.<sup>14</sup> It has been suggested that low doses of aspirin may selectively inhibit the cyclo-oxygenase pathway in platelet production but not in vessel wall endothelium thereby diminishing the synthesis of thromboxane but not of prostacycline. A higher dose may inhibit both thromboxane and prostacycline thereby neutralising the effect of the intervention.<sup>12</sup> However, there is also limited evidence from randomised trials that a higher dose of aspirin may effect a greater reduction in the risk of pre-eclampsia.<sup>15</sup>

##### *Aspirin and its mechanism of action*

Aspirin is one of the oldest medications still in widespread modern use. The first records of aspirin-

related compounds, 'salix', derived from willow tree bark, were documented on papyrus scrolls used by Egyptian physicians in 1534 BC.<sup>16</sup> Around 460 BC, Hippocrates recommended herbal tea made from the leaves of the white willow (*Salix alba*) to alleviate pain and fever. The translation of this knowledge into modern practice began in Oxford in 1758 when Reverend Edward Stone consumed, and later successfully trialled willow tree bark for relief of headaches, myalgia and fever.<sup>17</sup> Much later, in 1829, French pharmacist Pierre Joseph Leroux obtained crystals of salicin after boiling the powdered bark of white willow. In 1842, Raffaele Piria performed the first synthesis of salicylic acid from salicin, a little before Hermann Kolbe prepared salicylic acid from sodium phenate and carbon dioxide. In 1953, Charles Gerhardt was the first to isolate acetylsalicylic acid, and, in 1971, Vale, Samuelson and Bergstrom discovered its mechanism of action, work for which they won the 1982 Nobel Prize<sup>18,19</sup> and clinical research investigating the antiplatelet effects of aspirin began. Later research showed that aspirin works by inhibiting cyclooxygenase, the enzyme responsible for converting arachidonic acid into prostaglandins.<sup>20,21</sup>

Although aspirin was initially used as an analgesic and antipyretic, its antiplatelet effects mean it has become one of the most frequently prescribed medications worldwide, taken by more than 50 million people for prevention of cardiovascular disease alone, with approximately 40 000 tons administered annually. Aspirin's broad clinical effectiveness, cost-effectiveness and safety profile have led to its inclusion in the WHO Essential Medicines list for basic healthcare systems.<sup>22</sup> Aspirin's most frequently reported adverse effect is gastric irritation. Enteric formulations do not appear to reduce this effect but they have been associated with diminished platelet effects and may reduce bioavailability.<sup>23</sup> A systematic review published in 2014 supports the safety of aspirin in pregnancy, particularly for women at high-risk of pre-eclampsia, finding no increase in maternal or neonatal bleeding complications.<sup>24</sup> Aspirin is administered orally and is readily absorbed in the upper gastrointestinal tract with most platelet effects occurring in the portal system.<sup>25</sup>

The principal pharmacological target of acetylsalicylic acid is the platelet enzyme cyclooxygenase (COX), responsible for producing prostaglandins which mediate pain and induce platelet activation. In non-

pregnant individuals, low-dose aspirin (0.45 mg/kg, 60–150 mg) administered once daily has been demonstrated to reduce serum thromboxane B2 (TxB2, the stable serum metabolite of thromboxane A2) by a minimum of 95% within 5 days of commencing treatment.<sup>26-28</sup> It is important to note that thromboxane A2 is also produced in smaller quantities via COX-independent pathways, and from non-platelet sources such as monocytes and macrophages. These pathways have considerable inter-connections.<sup>27</sup> Following acetylsalicylic acid exposure, COX-dependent generation of thromboxane A2 (TxA2) and TxA2-induced platelet aggregation remain inhibited for the lifespan of the platelet. In the healthy non-pregnant state the average platelet lifespan is 8–9 days. It was suggested that many of the pathophysiological features of preeclampsia might be explained by disordered eicosanoid metabolism. The effects of aspirin in low concentrations, including reductions in platelet aggregation and constriction of arterial smooth muscle, made it an attractive choice for potentially ameliorating the pathophysiological effects of preeclampsia.

#### *How safe is aspirin use in pregnancy*

The safety of low-dose aspirin use in the second and third trimesters is well established,<sup>29-32</sup> but questions linger regarding use in the first trimester (eg, possible increase in minor vaginal bleeding or gastroschisis).<sup>33,34</sup>

#### *Randomised trials of antiplatelet agents*

In 1993, the National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units reported the effects of low-dose aspirin on the occurrence of preeclampsia in normotensive nulliparous women.<sup>35</sup> Patients were randomized at 13 to 26 weeks to either 60 mg of aspirin per day (n=1485) or placebo (n=1500). The authors noted a modest reduction in the occurrence of preeclampsia in the aspirin group (4.6%) compared with placebo (6.3%) (relative risk [RR] of 0.7; 95% CI: 0.6 to 1.0). Greater relative reductions were observed among patients with initially elevated systolic pressures. However, they observed no significant differences in birth weight, the incidence of fetal growth restriction (FGR) or either maternal or neonatal bleeding episodes, and the occurrence of placental abruption was slightly higher in aspirin recipients (1.3% vs 0.4%).

The largest trial to date of aspirin to prevent preeclampsia in pregnant women, the Collaborative Low-Dose Aspirin Study in Pregnancy (CLASP),<sup>2</sup> which involved more than 9300 women at high risk for preeclampsia or intrauterine growth restriction, showed that the incidence of preeclampsia with aspirin at a dose of 60 mg daily was not significantly lower than the incidence with placebo. However, treatment with aspirin resulted in a significantly lower risk of preterm delivery, and a significant trend toward a progressively lower rate of preeclampsia with progressively earlier preterm delivery was reported.<sup>36</sup> Subsequently, Subtil and colleagues conducted a large multicenter, randomized, double-blinded placebo-controlled trial of aspirin (100 mg) vs placebo beginning at 14 to 20 weeks among more than over 3000 nulliparous women.<sup>37</sup> They found no differences in the incidence of preeclampsia between treated and control patients (1.7% vs 1.6%; RR 1.08; 95% CI: 0.64-1.83). Moreover, no differences were found in the occurrence of hypertension, HELLP (hemolysis, elevated liver enzyme levels, and low platelet levels) syndrome, placental abruption, perinatal deaths, or FGR, and, of concern, mothers receiving aspirin had a significantly higher rate of hemorrhage.

By 2007, more than 32,000 pregnant women at varying risk for preeclampsia had been enrolled in 31 randomized control trials (RCTs) testing the efficacy of various doses of aspirin or other antiplatelet agents (eg, dipyridamole) initiated at differing gestational ages for the prevention of preeclampsia. A meta-analysis of these studies found that antiplatelet agents conferred a modest reduction in preeclampsia (RR 0.90; 95% CI: 0.84-0.97), and preterm births (PTB) before 34 weeks (RR 0.90; 95% CI: 0.83-0.98), but had no effect on stillbirth, FGR, or maternal or fetal bleeding.<sup>38</sup> Estimated numbers of patients needed to treat in order to prevent various adverse pregnancy outcomes, however, indicate a small clinical benefit, especially for the most serious events — that is, 333 to prevent a perinatal death, 167 to prevent small-for-gestational-age status in the baby, and 143 to prevent a delivery before 34 weeks of gestation.

Many, although not all, subsequent trials showed lower risks of preeclampsia with aspirin than with placebo.

In 2014, after pooling all available studies, many of which were small and of lower quality, the US Preventive Services Task Force (USPSTF) concluded

that aspirin was associated with absolute risk reductions in preeclampsia of 2% to 5% (RR 0.76; 95% CI: 0.62 to 0.95), as well as 1% to 5% reductions in FGR (RR 0.80; 95% CI: 0.65 to 0.99), and 2% to 4% reductions in PTB (RR 0.86; 95% CI: 0.76 to 0.98).<sup>1</sup> The USPSTF ultimately recommended low-dose aspirin as a preventive medication after 12 weeks gestation in women who had 1 or more high-risk factor(s) and consideration of such treatment in patients with “several” moderate-risk factors (see Table I and Table II).<sup>7</sup> No specific dosage was recommended but use of 81 mg tablets was considered “reasonable” and a wide gestational age range (12 to 28 weeks) was provided for initiating therapy.

Rolnik et al. present the results of another large, multicenter, randomized, placebo-controlled, double-blind trial of low-dose aspirin (150 mg per day) to prevent preeclampsia in high-risk women.<sup>39</sup> Unique to this trial was the use of a multimodal screening tool that included maternal height and weight, mean arterial pressure, Doppler ultrasonographic measurements of the uterine-artery pulsatility index, biochemical measurements of pregnancy-associated plasma protein A and placental growth factor, and medical and obstetrical history. Women with singleton pregnancies whose risk of preterm preeclampsia was estimated to be greater than 1% were enrolled at 11 to 14 weeks of gestation and were randomly assigned to receive aspirin or placebo daily until 36 weeks of gestation. The primary outcome was delivery with preeclampsia before 37 weeks of gestation; the authors focused on preterm preeclampsia on the basis of previous evidence that suggested a greater efficacy of aspirin with regard to this outcome than with delivery with preeclampsia at term ( $\geq 37$  weeks of gestation).

Roberge and associates sought to address both dosing and timing questions by performing an exhaustive systematic review and meta-analysis of RCTs comparing aspirin to either placebo or no treatment.<sup>40</sup> The authors identified 45 relevant trials involving 20,909 pregnant women randomized to 50 to 150 mg of aspirin daily. They stratified analyses according to whether aspirin was initiated at  $\leq 16$  or  $>16$  weeks gestation. Of note, when aspirin was initiated at  $\leq 16$  weeks there was both a significant reduction in preeclampsia and a clear dose-response effect (ie, higher aspirin doses had greater efficacy).

The latter effect is an important indicator of biological plausibility. When started at 16 weeks, aspirin markedly reduced the occurrence of preeclampsia (RR 0.57; 95% CI: 0.43-0.75), severe preeclampsia (RR of 0.47; 95% CI: 0.26-0.83) and Fetal Growth Restriction (FGR) (RR of 0.56; 95% CI: 0.44-0.70). In contrast, when aspirin was initiated at > 16 weeks, beneficial effects, while still observed, were of a lower magnitude for preeclampsia (RR 0.81; 95% CI: 0.66-0.99) and no effects were observed for severe preeclampsia or FGR. In addition, no dose response was observed when treatment was started > 16 weeks. The authors speculated that earlier treatment enhanced placentation while the higher dose exerted a greater antiplatelet turnover effect.

The study by Roberge and associates appeared to explain many of the contradictory results observed in the literature and might have led to a complete re-thinking of preventative strategies for preeclampsia, had it not been for the simultaneous publication of another meta-analysis in the same journal on the same date with conflicting findings. The latter study,

by Meher et al, examined individual participant data on 32,217 women and 32,819 babies recruited in 31 RCTs comparing low-dose aspirin or other antiplatelet agents versus either placebo or no treatment.<sup>41</sup> These authors stratified results to initiation of therapy at < 16 weeks versus  $\geq$ 16 weeks. In contrast to Roberge et al, these authors found a lesser overall benefit from aspirin and no significant difference in treatment effects among women randomized at <16 versus  $\geq$ 16 weeks for preeclampsia (RR 0.90; 95% CI: 0.79-1.03 vs 0.90; 95% CI: 0.83-0.98, respectively). They concluded that, "The effect of low-dose aspirin and other antiplatelet agents on preeclampsia and its complications is consistent, regardless of whether treatment is started before or after 16 weeks gestation."

The incidence of pre-eclampsia is also explained by several risk factors (described in Table 3), that include maternal age under 20 years old or over 40 years old, history of pre-eclampsia, previous hypertension, autoimmune diseases, and obesity A woman is at moderate risk for pre-eclampsia if she has no more than one risk factor (Table 2); a woman

**Table-I**

*Low-dose aspirin for prevention of morbidity and mortality from preeclampsia*  
(Clinical summary of U.S. preventive services task force recommendation) [7]

Population	Asymptomatic pregnant women who are at high risk for preeclampsia
Recommendation	Prescribe low-dose (81 mg/d) aspirin after 12 weeks of gestation.
Risk Assessment	<p>Pregnant women are at high risk for preeclampsia if they have 1 or more of the following risk Factors:</p> <ul style="list-style-type: none"> <li>• History of preeclampsia, especially when accompanied by an adverse outcome</li> <li>• Multifetal gestation</li> <li>• Chronic hypertension</li> <li>• Type 1 or 2 diabetes</li> <li>• Renal disease</li> <li>• Autoimmune disease (i.e., systemic lupus erythematosus, the antiphospholipid syndrome)</li> </ul>
Preventive Medication	Low-dose aspirin (60 to 150 mg/d) initiated between 12 and 28 weeks of gestation reduces the occurrence of preeclampsia, preterm birth, and IUGR in women at increased risk for preeclampsia. The harms of low-dose aspirin in pregnancy are considered to be no greater than small.
Balance of Benefits and harms	There is a substantial net benefit of daily low-dose aspirin to reduce the risk for preeclampsia, preterm birth, and IUGR in women at high risk for preeclampsia.

**Table-II**  
*Clinical Risk Assessment for Preeclampsia\*7*

Risk Level	Risk Factors	Recommendation
High†	History of preeclampsia, especially when accompanied by an adverse outcome Multifetal gestation Chronic hypertension Type 1 or 2 diabetes Renal disease Autoimmune disease (i.e., systemic lupus erythematosus, antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has >1 of these high-risk factors
Moderate‡	Nulliparity Obesity (body mass index 30 kg/m <sup>2</sup> ) Family history of preeclampsia (mother or sister) Sociodemographic characteristics (low socioeconomic status) Age >35 y Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, 10-y pregnancy interval)	Consider low-dose aspirin if the patient has several of these moderate-risk factors§
Low	Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

\* Includes only risk factors that can be obtained from the patient medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.† Single risk factors that are consistently associated with the greatest risk for preeclampsia. The preeclampsia incidence rate would be approximately 8% in a pregnant woman with 1 of these risk factors (1, 5).‡ A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk for preeclampsia. These risk factors are independently associated with moderate risk for preeclampsia, some more consistently than others (1).§ Moderate-risk factors vary in their association with increased risk for preeclampsia.

**Table-III**  
*Summary of risk factors for pre-eclampsia.<sup>42</sup>*

Risk Factors for Pre-Eclampsia	Mean Relative Risk(95% Confidence Interval)	References
Antiphospholipid syndrome	9.72 (4.34–21.75)	[16]
Relative risk of preeclampsia	7.19 (5.85–8.83)	
Previous pre-eclampsia	7.19 (5.85–8.83)	
Diabetes mellitus (type I or II)	3.56 (2.54–4.99)	
Multiple pregnancy	2.93 (2.04–4.21)	
First pregnancy	2.91 (1.28–6.61)	
Familiar history of pre-eclampsia	2.90 (1.70–4.93)	
BMI e" 35 Kg/m <sup>2</sup>	2.47 (1.66–3.67)	
Maternal age <20 or >40 years old	1.96 (1.34–2.87)	
Chronic hypertension	1.38 (1.01–1.87)	
Chronic autoimmune disease	6.9 (1.1–42.3)	[19]
Venous thromboembolism (VTE)	2.2 (1.3–3.7)	[20]
Intergestational interval e"10 years	2.93 (2.04–4.21) Similar to multiple pregnancy	[21]
Chronic kidney disease	1.70 (1.30–2.23) *	[22]

\* Values for odd ratio.

is at high risk for pre-eclampsia if she has two or more risk factors for the disease.<sup>42</sup> According to this classification, the clinician can consider the

prescription of low-dose aspirin to the patient. WHO recommendations on maternal health (November 2017) is shown in Table 4.<sup>5</sup>

**Table IV**  
*WHO Recommendation for Prevention of Pre-eclampsia and Eclampsia*<sup>5</sup>

In populations with low dietary calcium intake, daily calcium supplementation (1.5–2.0 g oral elemental calcium) is recommended for pregnant women to reduce the risk of preeclampsia. (Context-specific recommendation).

Low-dose acetylsalicylic acid (aspirin, 75 mg) is recommended for the prevention of preeclampsia in women at high risk of developing the condition. (Strong recommendation, moderate quality evidence).

Low-dose acetylsalicylic acid (aspirin, 75 mg) for the prevention of pre-eclampsia and its related complications should be initiated before 20 weeks of pregnancy. (Weak recommendation, low quality evidence).

*Guidelines from selected organizations*

The following summaries represent the recommendations of some major groups:

- The American College of Chest Physicians guidelines for management of venous thromboembolism, thrombophilia, and pregnancy recommend low-dose aspirin for women considered to be at risk for preeclampsia.<sup>43</sup> They noted the relative effect of antiplatelet therapy appears to be similar in women at low and high risk for preeclampsia, but women at low risk have a substantially lower absolute benefit.
  - The American Heart Association and American Stroke Association recommend low-dose aspirin for women with chronic primary or secondary hypertension or previous pregnancy-related hypertension for prevention of preeclampsia-related stroke.<sup>44</sup>
  - The USPSTF recommends the use of low-dose aspirin 81 mg/day in women at high risk of developing preeclampsia to reduce the risk for preeclampsia, preterm birth, and fetal growth restriction.<sup>7</sup> They acknowledged that there are no validated methods (biomarkers, clinical diagnostic tests, medical history) for identifying women at high risk for preeclampsia, but offered a pragmatic approach to identify a patient population with an absolute risk for preeclampsia of at least 8 percent: Women with  $\geq 1$  high-risk factors should receive low-dose aspirin. For women with multiple moderate risk factors, the benefit of aspirin therapy is less clear, so clinicians should use clinical judgment and talk with their patients about the benefits and harms of low-dose aspirin use. Aspirin should be initiated between 12 and 28 weeks of gestation.
  - In July 2016, the American College of Obstetricians and Gynecologists (ACOG) endorsed the USPSTF recommendation for use of low-dose aspirin 81 mg/day in women at high risk of developing preeclampsia and based high-risk status on the same high-risk factors designated by the USPSTF.<sup>3</sup>
  - The NICE guideline on management of hypertensive disorders during pregnancy advises use of low-dose aspirin 75 mg/day for women with at least one high risk factor for preeclampsia (chronic hypertension or kidney disease, diabetes, autoimmune disease, hypertension in previous pregnancy) or at least two moderate risk factors for preeclampsia (age  $\geq 40$  years, first pregnancy, multiple gestation,  $>10$  years between pregnancies, body mass index  $\geq 35$  kg/m<sup>2</sup> at presentation, family history of preeclampsia).<sup>6</sup>
  - The World Health Organization recommends the use of low-dose aspirin 75 mg/day for high-risk women (history of preeclampsia, diabetes, chronic hypertension, renal or autoimmune disease, or multifetal pregnancies)<sup>5</sup>
  - The Society of Obstetricians and Gynaecologists of Canada recommends low-dose aspirin 75 to 162 mg/day for women at high risk of preeclampsia<sup>45</sup>. They define increased risk as those with previous preeclampsia, relevant preexisting medical conditions (eg, hypertension, renal disease, diabetes, antiphospholipid syndrome), multiple gestation, or two or more lower risk factors.
- Despite good evidence that antiplatelet agents (principally low dose aspirin) reduce the incidence

**Box 1. Recommendation for use of low dose aspirin for prevention of preeclampsia**

**Dose and administration:** Begin daily low-dose acetylsalicylic acid (aspirin 75 mg) in the 12th or 13th week of gestation<sup>3,6,48-49</sup> If aspirin is not initiated at the end of the first trimester, initiation after 16 weeks (but before symptoms develop) may also be effective.<sup>41</sup>

**The optimum low dose:** A daily dose of 75 mg (some evidence say 100-150 mg) aspirin<sup>39,40</sup>

**Candidates:** Based on the available data it is suggested that low-dose aspirin prophylaxis is for women at high risk for preeclampsia. There is no consensus on the criteria that confer high risk. The US Preventive Services Task Force (USPSTF) risk criteria are reasonable.<sup>7</sup>

**Compliance:** Good compliance with therapy is important; compliance <90 percent may not be effective.<sup>50</sup> Some authors believe that aspirin may be more effective if taken at bedtime;<sup>51,52</sup> however, bedtime administration is not standard practice and may increase gastric irritation.

**When to stop:** Aspirin is discontinued 5 to 10 days before expected delivery to diminish the risk of bleeding during delivery;<sup>53-55</sup> however, no adverse maternal or fetal effects related to use of low-dose aspirin at delivery have been proven.

**Safety:** The safety of low-dose aspirin use in the second and third trimesters is well established<sup>29-32</sup>, but questions linger regarding use in the first trimester (eg, possible increase in minor vaginal bleeding or gastroschisis).<sup>33,34</sup>

of preeclampsia and its consequences, such as preterm birth and perinatal mortality, uncertainty remains regarding whether some women (in terms of risk) benefit more than others, when in pregnancy treatment should ideally start, and whether treatment effectiveness is dependent on antiplatelet dose.

In high-risk pregnant women, low-dose aspirin (LDA) also confers a 10% risk reduction for pre-eclampsia and a 20% risk reduction for fetal growth restriction.<sup>24,38</sup> However, it has been postulated that a significant proportion of individuals exhibit suboptimal response to aspirin, defined biochemically as diminished suppression of platelet activation or clinically as development of thrombotic events while on treatment.<sup>46</sup> This has been referred to interchangeably, as 'aspirin non-responsiveness', 'aspirin resistance' and 'aspirin treatment failure'. Controversies remain regarding the definition, optimal means of identification, and management strategy in affected individuals.<sup>47</sup> Determination of compliance with aspirin is likely to be of central importance to discriminate non-compliance from true suboptimal response and begin to explore causal mechanisms including pharmacokinetic, pharmacodynamic and genetic factors. Recently, the concept of 'aspirin resistance' has been extended to high-risk obstetric populations where sustained platelet activation despite LDA has been linked to subsequent pre-eclampsia and/or fetal growth restriction.

At the end of this extensive literature review, the recommendation for use of low dose aspirin for prevention of preeclampsia is shown in Box 1.

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