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Research Article

A Consensus Approach for the use of ASA in the prevention of preeclampsia: Guidance from the Colombian Federation of Perinatology and Maternal-Fetal Medicine (FECOPEN)

Saulo Molina-Giraldo[1,2,3,7*], Issis judith Villa-Villa [4], Roberto Zapata [4], Mauricio Orozco [5], Nataly Velásquez-Muñoz [5,6], Diana Alfonso [2,7], Wilma Castilla-Puentes [8], Jose Luis Pérez [9], Oscar Ordoñez [10], Oscar Zuluaga [11], Jesús Andrés Benavides-Serralde [12], Carol Gisela Rueda-Ordoñez [13], Armicson Felipe Solano [2,14], Dario Santacruz [14], Juan Pablo Alzate-Granados [15].

[1]Section of Fetal Therapy and Fetal Surgery Unit, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology Hospital de San José, Department of Obstetrics and Gynecology Fundación Universitaria de Ciencias de la Salud - FUCS, Bogotá, Colombia., Bogotá, Colombia; [2]Fetal therapy and Surgery Network - FetoNetwork, Colombia, [3]Department of Gynecology and Obstetrics Faculty of Medicine, Universidad Nacional de Colombia, Bogotá, Colombia,[4]Unidad de Medicina y Terapia Fetal Organización Clínica General del Norte Clínica Misericordia Internacional, Barranquilla, Colombia; [5]Unidad de Medicina Materno Fetal Clínica SOMER, Rionegro, Colombia , [6]Clínica del Prado, Medellín, Colombia, [7]Section of Fetal Therapy and Fetal Surgery Unit, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology and Department of Obstetrics and Gynecology Clínica Colsubsidio 94, Bogotá, Colombia, [8]Servicio de Ginecologia y Obstetricia, Hospital Regional de Sogamoso, [9]Unidad de medicina materno fetal Clínica La Ermita, Cartagena, Colombia, [10]Departamento de Ginecologia y Obstetricia, Universidad del Cauca, Popayán, Colombia, [11]Servicio de Ginecobstetricia, Hospital San Juan de Dios, Armenia, Colombia, [12]Unidad de Medicina Materno Fetal Perinatal Care IPS. Servicio de Ginecología y Obstetricia, Clínica San Rafael. Departamento de Ginecología y Obstetricia, Fundación Universitaria Autónoma de las Américas, Pereira (Colombia). Unidad de Medicina Materno Fetal Perinatal Care IPS. Servicio de Ginecología y Obstetricia, Clínica San Rafael. Departamento de Ginecología y Obstetricia, Fundación Universitaria Autónoma de las Américas, Pereira, Colombia, [13]Medicina Materno Fetal de Colombia, Bucaramanga, Colombia, [14]Unidad de medicina materno fetal clínica Versalles, Departamento de Ginecología y obstetricia Universidad Libre de Cali, Colombia, [15]Pontificia Universidad Javeriana. Departamento de Epidemiologia clínica y bioestadística. Bogotá, Colombia.

ABSTRACT

Introduction: Preeclampsia is a multisystemic disease of pregnancy. Prevention of the disease has been a concern of health care models and more so of those that include pathology in which there is a compromise of the perinatal maternal outcome. It has been described that ASA (a cyclooxygenase inhibitor with anti-inflammatory and antiplatelet properties) could have an impact on the prevention of this disease. The purpose of this consensus is to summarize the evidence and provide current recommendations on the use of ASA in the prevention of preeclampsia

Methods: FECOPEN convened a national meeting of experts to create a non-formal consensus based on a review of the literature with the elaboration of a questionnaire with relevant questions to provide current recommendations on the use of ASA for the prevention of preeclampsia.

Results: A questionnaire of 30 questions was prepared. The consensus was reached on 28 of these questions. The daily use of ASA in the prevention of preeclampsia is considered safe and is associated with a low probability of serious maternal or fetal complications, or both, related to its use. Women at risk for preeclampsia are defined based on the presence of one or more high-risk factors (history of preeclampsia, multifetal gestation, renal disease). Current evidence does not support the prophylactic use of ASA in the absence of high-risk factors for preeclampsia. Additionally, its effectiveness is still debated in the prevention of early pregnancy loss, fetal growth restriction, fetal death, or preterm delivery.

Correspondence to: Saulo Molina Giraldo MD, MSc, PHD(e) Carrera 19C #90-30, 4th floor Maternal Fetal Medicine Unit, Therapy, Fetoscopic and Fetal Surgery Center. Clínica de la Mujer-Grupo Quironsalud. Bogotá Colombia, Phone number +573102128382, molina.saulo@urosario.edu.co , smolina@fucsalud.edu.co

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Conclusions: ASA at a dose of 150 mg every 24 hours is an effective and safe intervention in pregnant women at risk of preeclampsia. This intervention should be started before week 16 and discontinued at the end of week 36.

Keywords: Preeclampsia; Aspirin; prevention and control; pregnancy (MeSH)

INTRODUCTION

Preeclampsia is a multisystemic disease of pregnancy, characterized by the presence of gestational hypertension accompanied by 1 or more of the following conditions: Proteinuria (proteinuria/creatinuria ratio ≥ 30 mg/mol; ≥ 300 mg / 24 hours; or ≥ 2 + on dipstick), Maternal organ dysfunction, which includes: acute kidney injury (creatinine ≥ 90 µmol/L; 1 mg/dL); liver involvement (alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant pain or epigastric abdominal pain; neurologic complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headache, and persistent visual scotomas); or hematologic complications (thrombocytopenia-platelet count <150000/µL, disseminated intravascular coagulation, hemolysis), uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave analysis, or stillbirth). Prevention of disease has been a concern of health care models and more so of those that include pathology in which there is a compromise of the perinatal maternal outcome. It has been described that ASA could have an impact on the prevention of this entity [1,2].

On the other hand, ASA is a cyclooxygenase inhibitor with anti-inflammatory and antiplatelet properties. ASA has been used during pregnancy most frequently to prevent or delay the onset of preeclampsia. Other suggested indications for the administration of ASA in low doses have included prevention of fetal death, fetal growth restriction, preterm delivery, and early pregnancy loss. Recent systematic reviews of the use of low-dose ASA during pregnancy have improved our understanding of the role of it in each of these clinical situations [2]. Despite this, the use of low-dose ASA in obstetric clinical practice remains varied [3].

Risk factors for the use of ASA in pregnancy to prevent preeclampsia include multifetal gestation, chronic hypertension, type 1 or 2 diabetes mellitus, chronic kidney disease, an autoimmune disease with possible vascular complications (antiphospholipid syndrome, systemic lupus erythematosus).

The purpose of this document is to summarize the evidence and provide current recommendations on the use of ASA for the prevention of preeclampsia.

METHODS

Consensus document. A meeting of national experts affiliated with the Colombian Federation of Perinatology and Maternal Fetal Medicine - FECOPEN was held. The participants included 15 experts among whom were obstetricians and gynecologists, specialists in maternal-fetal medicine, researchers and professors, specialists in bioethics, in public health, in clinical epidemiology, and two participants with PhD.

We are oriented based on the Methodological Guide adoption-adaptation of clinical practice guidelines of the Ministry of Health published in 2017 [4,5].

The reproducibility of the measurements has been evaluated in previous studies where at least two independent observers evaluated the fetal parameters. While one of the observers performed two serial measurements to evaluate intraobserver reproducibility, the other obtained the same measurements to evaluate interobserver reproducibility, achieving a maximum inter- and intra-observer variability of 2 mm and limits of agreement of 95% according to the technique proposed by Balt and Altman [4,6,7].

Strategy for formulating questions

Three experts defined the fundamental aspects of preeclampsia prevention with the use of ASA. Based on this and with the accompaniment of the methodological advisor, the PICOS methodology (Patient, Intervention, Comparison, Outcome, Studies) was followed to elaborate an exhaustive list of questions related to each of the thematic axes. Once the questions had been defined, we proceeded to search for the available evidence for each one of them.

Evidence searches and screening

We carried out a systematic search for evidence-based clinical practice guidelines in computerized bibliographic databases of studies published in indexed journals (MEDLINE, EMBASE, Excerpta Medica, Índice Médico Español, Cochrane Library); review articles and meta-analyses; original articles (preliminary or complete publications) in primary publications; secondary publications: abstracts of articles published in other journals as original (EvidenceBased Medicine, ACP Journal Club, etc.); conference abstracts; doctoral theses (faculty publication registry); textbooks on the topic; personal contacts with experts, scientific societies, working groups, etc.; funding agencies (FIS, CICYT, foundations, etc.); clinical trial registries (Ministry of Health, Cochrane Collaboration, monographic registries, among others); pharmaceutical industry; manual searches based on the bibliographic citations of the original articles by preparing a questionnaire of 30 questions, which were designed taking into account the most relevant topics that included the use of ASA.

CPG developing bodies: NICE (https://www.nice.org.uk/), WHOLIS; CPG organizing bodies: CMA Infobase (https://joulecma.ca/cpg/homepage), Guidelines International Network (https://g-i-n.net/). We included articles in English or Spanish published in the last 10 years. Following the collection of information from databases, we selected the references. The titles and abstracts of each of the documents found were reviewed, adjusting to the questions identified by the authors, and those that best answered them were selected.

A first meeting was held in which 15 experts were included, three of whom acted as facilitators and moderators of the debate. Thirty questions were designed and sent to the 11 specialists mentioned above, who answered the questions based on the most appropriate scientific evidence available at the time of the answer and their own experience.

The consensus was defined when there was agreement among 80% or more of the participants, that is, 9 out of 11 consensus experts. If this was not achieved in the first instance, an argued

discussion was held justifying the responses until a consensus was reached. The results of the informal consensus and the conclusions of the selected articles were discussed in two sessions of the informal consensus of experts held virtually in February 2022. The preparation of the manuscript was done by two rapporteurs of the consensus [2,5,8].

Formulation of recommendations

Once consensus was reached, the final recommendations were established with their respective documentary support. A modified Delphi methodology was used to develop all these steps. The recommendations issued by the working group, that developed the consensus, considered the strength or confidence that, by following the recommendation, more benefit than harm would be achieved in the consensus population.

Ethical Considerations

This is a no-risk research according to the Colombian resolution 8430 of 1993 because it is a secondary study that does not change the treatment behavior of current patients.

The group consisted of physicians who have the clinical and methodological expertise and suitability to meet the objectives proposed in this consensus.

RESULTS

The questionnaire included a total of 30 questions, within the systematic review of the literature, 47 studies were included (Tables 1 and 2).

Indications for initiation of ASA

Recommendation: The use of ASA is recommended in patients at high risk of presenting the disease.

Strong recommendation in favor

High quality of evidence: There is evidence from the publication in NEJM in 2017: ASA vs Placebo in High Risk Pregnancies for Preterm Preeclampsia by a multicenter, double-blind study, where 150mg/day of ASA was administered in 1776 women with identification of high obstetric risk, in whom risk screening was performed between weeks 11-14 with Maternal History, Biophysical Methods: Systolic and Diastolic Blood Pressure, Uterine Artery Doppler (average IP) and Biochemical Methods: Placental Growth Factor and Placental Plasma Protein. This strategy allowed the identification of 76% of patients who had preterm preeclampsia with false positives of 10% and only 40% of patients with preeclampsia at term. ASA vs placebo was administered from 11 weeks-14 weeks to 36 weeks. The group receiving ASA had 1.6% cases of preterm preeclampsia (13 of 798) and the placebo group 4.3% (35 of 822), with an OR: 0.38 (95% CI: 0.20-0.74; P:0.004), corresponding to a risk reduction of 62% (8). In this clinical trial, good adherence to treatment was observed in 79.9%, fair adherence in 14.9% and poor adherence in 5.2%. Good adherence to treatment is required to obtain this reduction [2,5,8,9]. Other subsequently published prediction studies have demonstrated detection rates with the Fetal Medicine Foundation (FMF) algorithm of up to 91% to 93% of preterm preeclampsia before 32 weeks [3,5,10,11].

Table 1: The following are the recommendations or responses to each of the questions that were presented in consensus. The total number of responses

Questionnaire	Consensus approach
1) What ar the levels of prevention?What is primary prevention in health?Why is primary prevention in health important? What are the primary prevention measures?	There are three levels of prevention
	Primary: activities to prevent the onset of the disease
	Secondary: Early diagnosis
	Tertiary: complete recovery
2) Are there primary prevention measures in maternal-fetal medicine?	Prevention of birth defects
	Diet and physical activity measures
	Identification of risk factors
	Prevention of vertical transmission of infections
	Anemia screening
	Prevention of preeclampsia with ASA
	obstetric ultrasound
3) What is Acetyl Salicylic Acid?	Inhibitor of prostaglandin endoperoxidase H synthetase, also known as cyclooxygenase (COX)
4) Mai uses of ASA	anti-inflammatory
	Analgesic
	Antipyretic
	platelet antiaggregant
	cardiovascular protection

	Autoimmune diseases
3) What is the role of ASA in the prevention of Preeclampsia?	Tipping the balance between thromboxane A2 (TXA2) / Prostacyclin (PGI2), in favor of PGI2
4) What is the mechanism of action of ASA in the patient at high risk of preeclampsia?	The benefits of ASA in the prevention of PE and its vascular complications derive from both its anti-inflammatory action and its effect on restoring the balance between thromboxane and prostacyclin
5) What are the indications to start its use?	Prevention of preeclampsia is indicated in patients at high risk of presenting the disease
6) At what gestational age should it be started?	Before 16 weeks
7) What dose should be used and why?What is the best administration strategy in terms of cost effectiveness?	150 mg per day, however, if this dosage is not available, a dose of 100 mg per day can be used.
8) In what dosage does it achieve its best effect? What is the best time to take the medicine and why? (Split in the day, number of doses, Time)?	Once a day in a non-fractionated way and before going to bed.
9) Do you have drug interactions? What drug or clinical condition would contraindicate the use of ASA 150 mg is contraindicated for the prevention of preeclampsia?	Features interactions with:
	• Non-steroidal anti-inflammatory drugs
	• Diuretics
	• Selective Serotonin Reuptake Inhibitors
	• Oral anticoagulants
	• Thrombolytics and platelet antiaggregants • β-blockers
	• Insulin and sulfonylureas • Vancomycin
	• Alcohol
	• Antacids
	• Digoxin
	• Barbiturates
	• Zidovudine
	• Valproic acid
	• Phenytoin
	Clinical conditions:
	1. Hypersensitivity to acetylsalicylic acid or to any of its excipients

	medication, other salicylates, nonsteroidal anti-inflammatory drugs, or tartrazine (cross reaction).
	2. Acute, chronic or recurrent gastroduodenal ulcer; recurrent gastric discomfort.
	3. History of gastric bleeding or perforation after acid treatment
	aspirin or other nonsteroidal anti-inflammatory drugs.
	4. emorrhagic diathesis
	5. Patients with a history of asthma or asthma induced by the administration of salicylates or
	Drugs with a similar action, particularly non-steroidal anti-inflammatories.
	steroids.
	6. Patients with nasal polyps associated with asthma that are induced or exacerbated by
	acetylsalicylic acid.
	7. Diseases that occur with coagulation disorders, mainly hemophilia or
	hypoprothrombinemia.
	8. evere renal, hepatic or cardiac insufficiency.
10) Which patient is a candidate to start ASA 150 mg for the prevention of preeclampsia?	HIGH RISK FACTORS:
	Use of low-dose ASA with 1 or more of the following:
	History of preeclampsia, especially accompanied by adverse events.
	• Multiple gestation
	• Chronic hypertension
	• Type 1 or 2 diabetes
	• Renal disease
	• Autoimmune disease (Lupus, APS)
	MODERATE RISK FACTORS
	Consider use of low-dose ASA in patients with more than 1 of the following factors:
	• Nulliparity
	• Obesity (BMI >30)
	• Family history of preeclampsia (mother or sister)
	• Sociodemographic characteristics (Black race, low socioeconomic level)

	• Age: 35 years or older
	• Personal history factors (low birth weight or small-for-gestational-age fetus, previous adverse gestational outcomes, birth interval greater than 10 years).
	Multiparametric risk calculation >1/200
11) Does ASA have relative or absolute contraindications?	Absolute contraindications:
	• Allergy to ASA or known hypersensitivity to other salicylates due to high risk of anaphylaxis.
	• Known hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) due to cross-sensitivity.
	• Patients with nasal polyps due to the risk of bronchospasm
	• Patients diagnosed with asthma with a history of ASA-induced bronchospasm.
	Relative contraindications:
	• History of gastrointestinal bleeding
	• Active peptic ulcer
	• Other sources of gastrointestinal or genitourinary bleeding
	• Severe liver dysfunction
12) What maternal and fetal risks does its administration have?	Maternal Risks: There has been no evidence of an increased risk of hemorrhagic complications. No increased risk of abruption, postpartum hemorrhage, or blood loss from other sources has been demonstrated.
	Fetal Risks: There is no increased risk of abnormalities. It has not been shown to be associated with fetal structural abnormalities. It is not associated with premature closure of the ductus arteriosus. No association has been observed with the risk of cerebral hemorrhage in the newborn, nor the risk of abortion or death.
13) How long should it be used during pregnancy?	Start before week 16. However, in specific cases it can be started after week 16 up to week 20.

14) What is preeclampsia and how is it classified?	Multisystem disease of pregnancy, characterized by the presence of gestational hypertension accompanied by 1 or more of the following conditions:
	a) roteinuria
	b) Mater al organ dysfunction, including: acute kidney injury; hepatic compromise with or without right upper quadrant pain or epigastric abdominal pain; neurological complications; or hematologic complications.
	c) teroplacental dysfunction
	Preeclampsia is classified into:
	a) arly-onset preeclampsia (with delivery <34 + 0 weeks of gestation);
	b) reterm preeclampsia (with delivery <37 + 0 weeks of gestation);
	c) Late-onset preeclampsia (with delivery ≥34 + 0 weeks of gestation);
	Preeclampsia at term (with delivery ≥37 + 0 weeks of gestation)
15) Does ASA have a preventive effect on other endothelial or placental pathologies?	There is insufficient evidence of prevention of other endothelial pathologies in patients at low risk of preeclampsia
16) Does the use of ASA with other molecules enhance its effect? Speaking of PE prevention, does the use of ASA plus low molecular weight heparin (LMWH) improve PE prevention?	There is not enough evidence for or against to estimate or reject the concomitant use of these two molecules.
17) Should any special monitoring be performed on the fetuses of mothers in whom ASA was used for the prevention of preeclampsia?	There is no evidence for monitoring in addition to standard antenatal care. Additionally, there is no special monitoring method for the use of ASA.

18) What is the efficacy of the use of ASA for the prevention of preeclampsia compared to other interventions?	The ASPRE study reported a 62% decrease in the incidence of preterm preeclampsia in women at high risk for the disease who received ASA 150 mg daily between 11-14 weeks and 36 weeks of gestational age, but showed no significant effect. in the incidence of preeclampsia at term
19) What is the safety of the use of ASA for the prevention of preeclampsia compared to other interventions?	It has no teratogenic effects and does not increase the risk of abruption or fetal intracranial bleeding. Nor does it increase the risk of hemorrhage at the level of the medullary canal at the time of delivery if analgesia or anesthesia is required. • Moderate risk of Pre-eclampsia / Eclampsia • Obesity • Maternal age greater than 35 years
20) What are the main factors that influence the decision to start ASA for the prevention of preeclampsia?	• Teen
	• Family history of pre-eclampsia
	• Polycystic ovary syndrome
	• Positive uterineartery screening
	• Socio-demographic characteristics
21) Do you consider that preeclampsia is a public health problem (includes economic impact)?	Preeclampsia is one of the leading causes of maternal mortality in both developed and developing countries.
	Because of this and its consequences, such as maternal-fetal morbidity and mortality, it is considered a public health problem.
22) In what week is the start of ASA indicated and why?	ASA use is recommended before week 16.
23) In which week does the ASA suspend and why?	It is recommended to suspend the ASA at the end of week 36. (I s greatest benefit is in the prevention of preterm preeclampsia)
24) In what clinical scenarios do you consider the ASA should be discontinued?	a. In the event that you develop pre-eclampsia.
	b. t 36 weeks of gestation, or with the prospect of a preterm birth.
	c. 7 days before the birth is planned.
	d. In the presence of intolerable adverse events, or in the presence of a bleeding event

25) Do you consider that the use of ASA in Preeclampsia is a safe medication in terms of Teratogenicity Abortion/death Bleeding, Effects on the newborn, Others	a. Teratogenicity: safe.
	b. bortion/death: safe
	c. Bleeding: safe at a dose of 150 mg/day.
	d. Effects on the neonate: safe.
26) How do you rate ASA (in terms of efficacy, effectiveness, safety, adverse effects, acceptance) compared to other pharmacological possibilities?	It is considered a cost-effective and safe strategy.
27) Regarding the cut-off point to define high risk of preeclampsia, (OR or RR), what is the best cut-off point for our population?	It is decided to have a cut-off point of 1/200 due to the high prevalence of the Colombian scenario. Additionally, the creation of population calculators with multiparametric screening is recommended.
28) Regarding the predictive models of EP according to the literature, do you consider that: Do the predictive models adapt well to different populations? Is its implementation cost effective? Is its implementation stressful for patients?Would administration to the general population without any selection increase adverse effects?	Predictive models of preeclampsia should be implemented in our population. The method that combines maternal factors with biomarkers should be implemented to estimate the specific, individual risk of the patient. This method has been validated in other populations such as Asia with good results.
	These combined models have been evaluated in high-income countries and have shown substantial cost savings.

Table2: Regional subsidiaries of the Colombian Federation of Perinatology and Maternal-Fetal Medicine (FECOPEN).

Regional affiliates	PRESIDENT
Asociación de Medicina Materno fetal del atlántico (AMMFA)	Issis judith Villa Villa
Asociación Antioqueña de Medicina Materno fetal (AAMMFE)	Catalina Valencia
Asociación Bogotana de Perinatología (ABP)	Andres Mauricio Camacho
Asociación Boyacense de Ginecología y Obstetricia (ABGYO)	Wilma Castilla Puentes
Asociación de Perinatología de Bolívar (APB)	Jose Luis Pérez
Asociación Caucana de Perinatología (ACAUPER)	Oscar Ordoñez
Asociación Quindiana de perinatología (AQP)	Oscar Zuluaga
Asociación de Medicina Perinatal de Risaralda (AMPER)	Carlos Echeverry
Asociación Santandereana de Medicina Materno Fetal (ASMMAF)	Pablo Galvis
Asociación de Perinatología y Medicina Materno Fetal del Valle del cauca (PERIVAL)	Armicson Felipe Solano

Gestational age of onset

Recommendation: ASA for prevention of preeclampsia should be initiated before week 16. Thirty percent of patients would initiate ASA after week 16 until week 20 in selected cases [12-14].

Strong recommendation in favor

High quality of evidence: A meta-analysis showed that low-dose ASA, initiated at 16 weeks or earlier, was associated with a significant reduction in preeclampsia {Relative Risk (RR) 0.47, 95% Confidence Interval (CI) 0.34-0.65, prevalence 9.3% in the treated group compared with 21.3% in the control group} and intrauterine growth restriction (RR 0.44, CI 0.30-0.65, 7% in the treated group compared with 16.3% in the control group) [12,15,16].

The PREDO trial, Predicting and Preventing Preeclampsia, found that when ASA was started after 16 weeks there was no reduction in the risk of preeclampsia. The final report concludes that low-dose ASA (100 milligrams per day) is an effective and safe approach to prevent preeclampsia and its severe form when used before or after gestational week 16 in high-risk women [6,13,17].

Therapy before 16 weeks reduces the risk of early but not of late preeclampsia, which supports the hypothesis that administration of ASA before that gestational age may reduce placental disorders and decrease severe and early forms of preeclampsia. The gestational age at the start of treatment seems to have a direct relationship to the non-occurrence of preeclampsia, the higher the gestational age, the higher the probability of occurrence, and the strong relationship between drug efficacy and gestational age as determinants in the prophylactic use of ASA in preeclampsia [7,14,18,19].

ASA suspension week

Recommendation: With 100% agreement, it is recommended

that ASA must be discontinued at the end of week 36.

Strong recommendation in favor

High quality of evidence; It is discontinued at 36 weeks, because the reported benefit of preventive treatment with ASA is to reduce the risk of preterm preeclampsia, therefore, it would not make sense to use it in term pregnancy [20-23].

Dosage of use

Recommendation: With 90% agreement, it is recommended to use 150 mg of ASA per day once a day and before bedtime; however, if this dosage is not available, a dose of 100 mg per day can be used.

Strongly in favour

High quality of evidence: A meta-analysis published by Roberge et al. in 2017 identified a dose-response effect for the prevention of preeclampsia, severe preeclampsia, and fetal growth restriction, with higher doses associated with greater risk reduction, when administered before 16 weeks gestational age [16,24]. The ASPRE study used 150 mg per day, showing a large reduction (62%) in the incidence of preterm preeclampsia [21,25]. The International Federation of Gynecology and Obstetrics (FIGO) recommends the use of 150 mg ASA daily for the prevention of preeclampsia. [18].

In another meta-analysis with a total of 45 randomized controlled trials involving a total of 20,909 pregnant women randomized to doses between 50 mg and 150 mg ASA per day. When acetylsalicylic acid treatment was initiated at 16 weeks, there was a significant reduction and dose-response effect for the prevention of preeclampsia (RR, 0.57; 95% CI, 0.43-0.75; P <0.001; R 2 , 44% ; P=0.036), severe preeclampsia (RR, 0.47; 95% CI, 0.26-0.83; P=0.009; R 2 , 100%; P=0.008) and fetal growth restriction (RR, 0.56 ; 95% CI, 0.44-0.70; P <0.001; R 2, 100%; P=0.044), and higher doses of ASA are associated with a greater reduction in all 3 outcomes. The dose of 150 mg per day for PE prevention was further demonstrated in the ASPRE study published in 2017, where the primary endpoint preterm eclampsia (<37 weeks) occurred in 13 participants (1.6%) in the ASA group, compared with 35 (4.3%) in the placebo group (OR=0.38; 95% CI, 0.20-0.74; P=0.004) [19].

Preventive effect of ASA in other endothelial or placental pathologies

Recommendation: 70% of the participants considered that there is insufficient evidence for use as a method of prevention of other endothelial pathologies in low-risk patients. Thirty percent of the participants considered its use for the prevention of other endothelial pathologies, despite the lack of convincing evidence in its favor [26].

Weak in favor

Moderate quality of evidence: The evidence is not conclusive in this regard. The results are not considered conclusive regarding the possibility of IUGR prevention when the possibility of prevention of fetal growth restriction has been evaluated [3]. The ASPRE trial, for example, reports a statistically non-significant difference in small for preterm and term gestational age [27-29]. In the assessment of birth weight, this same study shows a trend towards a higher number of cases of newborns below the 10th percentile, but without a statistically significant difference [26]. However, other studies show the opposite. Bujold et al in a meta-analysis report that initiation of ASA administration at 16 weeks or earlier was associated with a significant reduction in the incidence of IUGR (RR 0.44, 95% CI, 0.30-0.65) [14,16,30]. More recently, Stanescu et al in an RCT of 150 patients found a significant decrease in the incidence of IUGR in the group given ASA versus placebo [27-30].

ASA and concomitant use of other molecules - low-molecular-weight heparin (LMWH)

Recommendation: With 90% agreement, there is no additional benefit with the concomitant use of ASA with LMWH, however, the current evidence is not consistent [26,31-35].

Weak recommendation in favor

Moderate quality of evidence: In a meta-analysis published in 2016, where 8 RCTs (Randomized Controlled Studies) were included where the pathology of the patients were recurrent miscarriage five studies (three included women with thrombophilia) and history of severe or early-onset PE in three studies (which included women with thrombophilia in one). LMWH was administered in seven studies and unfractionated heparin in one [2,3,32]. In women with a history of PE, treatment with LMWH and ASA, compared with ASA alone, was associated with a significant reduction in the development of PE (three trials (n=379); RR, 0.54 (95% CI, 0.31-0.92); P=0.03), These results were not reflected in women with recurrent miscarriage who received LMWH and ASA, compared with ASA alone [34,36-39].

Special monitoring with the use of ASA

Recommendation: With 50% agreement, it is concluded that there is no evidence for additional monitoring to standard prenatal control. In addition, there is no special monitoring method for the use of ASA [36,40].

Weak in favor

Moderate quality of evidence: In a 2019 Cochrane RSL the evidence showed that only a small number of participants showed postpartum hemorrhage (> of 500 ml of blood immediately after delivery), 190/11893 with 95% CI 0.46(0.17-1.25) as well as neither was placental abruption 260/15182 with 95% CI 1.01(0.26,3.94) which was not statistically significant, indicating that ASA is safe [32]. ASA doses lower than 75 mg appear to be safe [41-43].

Factors influencing the decision to initiate ASA for the prevention of preeclampsia

Recommendation: The following factors were considered with 100% agreement:

Moderate risk of Preeclampsia / Eclampsia

Obesity

Maternal age over 35 years

Teenager

Family history of preeclampsia

Polycystic ovary syndrome

Positive uterine artery screening

Socio-demographic characteristics

It is also suggested to screen with modified FIGO

Weak in favor

Moderate quality of evidence: The main factor that influences the decision to take ASA is the identification of pregnant women at high risk for preterm PE. Then we must consider whether there are any contraindications to taking it. The identification of risk depends on our screening strategy [44]. Thus, if we initiate ASA based on NICE guidelines we would do so based on risk factors, if we use the ACOG criteria we would consider patients with a history of two EPs or at least one EP with termination of pregnancy <34 weeks [2,3]. On the other hand, if we use the Fetal Medicine Foundation criteria we would base it on maternal characteristics, mean arterial pressure, average uterine artery pulsatility index and biochemical factors such as Pregnancy-Associated Plasma Protein (PAPPA) and Placental Growth Factor (PIGF) [34,45].

Most benefit for the use of ASA has been observed in the high-risk population: History of hypertensive disorder in previous pregnancy, Pre-existing chronic hypertension, Pre-existing type 1 or 2 diabetes , Chronic renal failure, Immunological diseases , Systemic Lupus Erythematosus (SLE), Anti-Phospholipid Antibody Syndrome (APAS) or patients with 2 moderate risk factors primigestation, age over 40 years, intergestational period greater than 10 years, BMI greater than or equal to 35 kg/m^2 at the first prenatal visit, family history of PE (mother or sisters), or multiple pregnancy [31,46].

Cut-off point to define high risk of preeclamsia

Recommendation: With 100% agreement, it was decided to have a cut-off point of 1/200 due to the high prevalence in the Colombian setting. Additionally, it is recommended the creation of population-based calculators with multiparametric screening [41,47].

Strongly in favor

Moderate quality of evidence: In pregnancies with HIGH risk of preterm preeclampsia identified by screening at 11-13 weeks of gestation, the outcome of VERY HIGH risk resulted (estimated risk >1 in 50), compared with estimated risk of 1 in 51 to 1 in 100, chronic hypertension compared with no chronic hypertension, and low placental growth factor concentrations.

A cut-off points for defining women at high risk of preeclampsia has been proposed as 1/100, which is equivalent to approximately 10% of the population of pregnant women. Although the magnitude of the effect of ASA in reducing the risk of early onset preeclampsia was particularly greater in women who had a preeclampsia risk of 1/50 or greater. It appears that it is necessary to practice neonatal screening of a large number of patients to avoid a case of preeclampsia. In ASPRE, 25,797 patients were included and 630 developed preeclampsia. ASA was associated with a reduction of 21 cases of preterm preeclampsia. Therefore, to prevent one case of preterm preeclampsia, 1228 patients should be screened and almost 10% of the population should be treated with ASA [26,47].

Discussion

Aspirin inhibits the production of thromboxane A2 by platelets and, therefore, increases the prostacyclin/TXA2 ratio and reduces platelet aggregation. It also decreases the production of the tissue factor thrombin [3,48]. The indications for aspirin in primary prevention are a matter of debate, but recent publications suggest a strategy based on screening for preeclampsia in the first trimester (with clinical parameters, biomarkers and uterine Doppler measurements) and the administration of aspirin to high-risk patients. The usefulness of this strategy is still under evaluation and more data are needed before its implementation in real practice. Aspirin should be administered once daily in the evening in low doses ranging from 80 to 150 mg. There is good evidence showing that the efficacy of aspirin increases with increasing dose. However, aspirin crosses the placental barrier and inhibits fetal platelet aggregation. Although low-dose aspirin has a good maternal-fetal safety profile, the number of patients exposed to doses higher than 100 mg is low and the safety of a prevention strategy based on 150 mg aspirin per day should be confirmed.

Daily use of low-dose ASA during pregnancy is considered safe and is associated with a low likelihood of serious maternal or fetal complications, or both, related to use. Low-dose ASA prophylaxis is recommended in women at high risk for preeclampsia and should be initiated before 16 weeks' gestation and continued daily until 36 weeks. Low-dose ASA prophylaxis should be considered for women with more than one of several moderate risk factors for preeclampsia. Women at risk for preeclampsia are defined based on the presence of one or more high-risk factors (history of preeclampsia, multifetal gestation, renal disease. In the absence of high-risk factors for preeclampsia, current evidence does not support the prophylactic use of low-dose ASA for the prevention of early pregnancy loss, fetal growth restriction, fetal death, or preterm delivery [49-51].

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Supplementary data are available at www.fecopen.org

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