

Low Dose Aspirin as a Reliable Preventive Tool of Preeclampsia

Abanoub Gabra^{1*} and Mariam Gabra²

¹Department of Obstetrics and Gynecology, Assuit University, Egypt

²Registered Nurse Program, Hillsborough Community College, Tampa, Florida, USA

*Corresponding author: Abanoub Gabra, Department of Obstetrics and Gynecology, Assuit University, Egypt, E-mail: abanoub.gabra@med.au.edu.eg

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Abstract

Preeclampsia is a disease of significant morbidity and mortality at pregnancy. Therefore, researchers focus on prevention and early detection of this disease in order to maintain adequate health care to both mother and fetus. One of the promising preventive tools is Low Dose Aspirin (LDA). Although both pathogenesis of preeclampsia and role of LDA in it are not completely understood, there is strong evidence with good quality that LDA is considered a good preventive tool for preeclampsia. The beneficial effects of LDA include prevention of early-onset disease, associated maternal complications, and fetal complications. That is why many societies include American College of Obstetricians and Gynecologists (ACOG), United States Preventive Services Task Force (USPSTF), World Health Organization (WHO), American Heart Association, American Stroke Association, and others agreed on recommending its use for high-risk patients. On 2013, ACOG recommended LDA for preventing Preeclampsia and its complications besides delaying the onset of the disease for those patients with a past medical history of the early-onset disease and preventing preterm labor before 34 weeks due to preeclampsia. Later on, the USPSTF confirmed LDA use in this regard but they recommended its use for more expanded indications than that considered by ACOG. USPSTF highly recommended LDA for patients with a history of preeclampsia, especially if complicated, history of Diabetes Mellitus (DM), chronic hypertension, multiple gestation, renal disease or autoimmune disease. Moreover, with moderate evidence-based practice, they recommended LDA for patients who have more than one of the following risk factors: nulliparity, obesity (BMI>30), age>35 years, family history of preeclampsia in mother or sister, social factors like low socioeconomic level or previous adverse outcome of pregnancy.

Pregnancy; WHO: World Health Organization; DM: Diabetes Mellitus; IUGR: Intrauterine Growth Restriction; LMWH: Low Molecular Weight Heparin; VEGF: Vascular Endothelial Growth Factor; PLGF: Placental Growth Factor; SGA: Small for Gestational Age

Introduction

Hypertensive Disorders of Pregnancy (HDP) can affect many pregnant women all over the world putting significant health burden on the health care system in those countries. For instance in the USA, around 240,000 pregnant have HDP, it is equal to 6-10% of all pregnancies [1] with recurrence rate up to 25% in subsequent pregnancies [2]. Being one of the most common medical complications during pregnancy, HDP are responsible for 10% of maternal mortality and they are among the top 6 causes of maternal mortality [3]. The incidence of preeclampsia is markedly increased over the past three decades [4]. Besides, neonatal mortality has been doubled in preeclampsia versus normal pregnancy [4]. Neonatal morbidity of HDP is due to intrauterine fetal death, intrauterine growth restriction and premature labor [5]. In developing countries, higher incidence of morbidity and mortality is expected due to limited resources of health care in terms of lack of screening and effective therapy. Higher incidence of HDP was found in African Americans, obese, patients with renal disease, chronic hypertensive patients, patients with autoimmune diseases, multiple pregnancy, diabetics and in pregnant women >35 years old or less than twenty [6,7].

According to ACOG, preeclampsia is defined as high systolic BP equal or more than 140 mmHg or high diastolic BP equal or more than 90 mmHg in presence of proteinuria although the amount of proteinuria is no longer considered a marker of severity [8,9]. Preeclampsia is considered severe if one of the following occurs: BP above 160/110 mmHg, thrombocytopenia, impaired renal and liver functions, cerebral edema, pulmonary edema and visual disturbances [4]. The course of the disease is unpredictable as preeclampsia with or without severe features may progress to eclamptic fits or hemolysis-elevated liver enzymes-low platelet syndrome and disseminated intravascular coagulopathy which has high mortality rates [10]. The main priority of management is to prevent these highly morbid

Keywords: Low dose aspirin; Prevention; Preeclampsia

Abbreviations:

LDA: Low Dose Aspirin; ACOG: American College of Obstetricians and Gynecologists; USPSTF: United States Preventive Services Task Force; HDP: Hypertensive Disorders of

complications and associated mortality risk that may affect both the mother and her fetus [11]. Many maternal complications may occur like liver failure, renal failure, HELLP syndrome, disseminated intravascular coagulation, placental abruption and cerebrovascular stroke especially with severe hypertension and fits [12]. Moreover, the fetus may suffer growth restriction and oligohydramnios due to inadequate placental perfusion besides preterm labor and associated neonatal risks [10]. With adequate evidence-based practice, Aspirin is found to prevent or delay the early onset of disease in high-risk patients [7]. Also, it was found to decrease the incidence of Intrauterine Growth Restriction (IUGR), preterm labor, stillbirth and early pregnancy loss [13].

HDP is a multi-systemic disease in nature, the most severe forms like preeclampsia and eclampsia can affect liver and kidney functions and other systems [14]. Also, studies showed an increased future risk of a cardiovascular and cerebrovascular event and its mortality in those patients through their abnormal systematic metabolic and vascular changes [15]. Because of all those complications, researchers believed that focusing on prevention would improve overall maternal health care worldwide especially during pregnancy [15,16], and screening may allow clinicians to identify patients at risk and offer prompt management.

Recently researchers study many therapies as preventive tools of preeclampsia-like calcium supplements, Low Molecular Weight Heparin (LMWH), progesterone and antioxidant but those therapies still have inconsistent evidence [17]. On 2013, ACOG recommends LDA to prevent preeclampsia and its complications besides delaying the onset of the disease for those patients with a past medical history of the early-onset disease, preterm labor before 34 weeks due to preeclampsia or more than one prior pregnancy with preeclampsia [9]. Later on, USPSTF confirms LDA use but they recommend its use for more indications [5]. USPSTF highly recommends LDA for patients with a history of preeclampsia especially if complicated, DM, chronic hypertension, multiple gestations, renal disease or autoimmune disease [5]. Moreover, with moderate evidence-based practice they recommend LDA for patients who have more than one of the following risk factors: nulliparity, obesity (BMI>30), age>35 years, family history of preeclampsia in mother or sister, social factors like low socioeconomic level or previous adverse outcome of pregnancy [5]. After the release of USTSTF recommendations, a retrospective cohort study was designed to study the incidence of recurrence before and after these guidelines to evaluate the effectiveness of these guidelines. Interestingly, Researchers found that the recurrence rate was decreased by 30% after applying those guidelines. They also recommend further studies on the impacts of patient compliance and racial variation on the effectiveness of Aspirin as a primary preventive tool [13]. Therefore, an ethnic variation of the protective effect of Aspirin is also studied, for example, East Asians were found to equal to non-east Asians in terms of decreased incidence of preeclampsia in high-risk patients and subsequently decreased the risk of IUGR and preterm labor [18]. We still need more studies on African American which are known to have a higher incidence of the disease [4].

Pathogenesis of Preeclampsia

Etiopathogenesis of preeclampsia remains not completely understood despite extensive researches focused on it along years [19,20]. Placental ischemia remains the most accepted theory that was postulated to explain the pathogenesis of preeclampsia because the delivery of fetoplacental unit remains the main curative line of treatment [10,20]. In addition to that, placental ischemia also explains other complications e.g., IUGR and oligohydramnios. Also, it explains a higher incidence of disease in patients with chronic hypertension, DM and autoimmune diseases. In a normal pregnancy, invasion of uterine arteries to cytotrophoblast causes their transformation from epithelial to endothelial cells with low resistance pressure allowing enough blood supply to the fetus through a process called "pseudo-vasculogenesis" [10]. Cytotrophoblast cells initiate migration of extravillous trophoblast to decidua of the uterus and invade partially myometrium inducing remodeling of spiral arteries [19].

The 2-stage theory has been hypothesized recently to understand this pathology [6,20]. The first stage is abnormal events during embryogenesis of trophoblast which contributes to fetoplacental oxidative distress and abnormal release of anti-angiogenic factors in maternal circulation and subsequent multisystemic endothelial dysfunctions [20,21]. Abnormal remodeling of spiral arteries and early immunologically mediated events are considered major causes of those events [10]. Moreover, trophoblast fails to adequately invade uterine wall and spiral arteries and subsequently, vascular resistance in this area could not be decreased to allow adequate placental transfusion to the fetus [22]. Also, failure of obliteration of tunica media of myometrial vessels contributes to the inability of the placenta to accommodate enough blood supply due to lack of thinning of those vessels [20]. This leads to excessive secretion of sFlt-1 (soluble-fms like tyrosine kinase-1) and soluble endoglin [23]. sFlt-1 binds in the blood to both the Vascular Endothelial Growth Factor (VEGF) and the Placental Growth Factor (PLGF). Both sFlt-1 and low VEGF/PLGF play a major role in the development of systematic hypertension [6,23]. Later on, the maternal syndrome may occur in terms of vascular endothelial dysfunction, intravascular hypercoagulability and vasospasm leading to multiple systematic dysfunctions [6]. Abnormal vascular changes in the placenta are confirmed by histopathological examination of postpartum specimens of placentae which showed vascular infarcts and sclerosis of arterioles [20]. Immunological maternal reaction towards fetal and paternal derived antigens may also contribute, which is considered a certain type of immunological intolerance [24]. Immunological theory is supported by a high serum level of cell-free fetal DNA. This theory has been also postulated to understand the pathogenesis of hyperemesis gravidarum [25,26]. Recently, genetic factors were found to contribute to preeclampsia, Angiotensinogen gene T235 and Leiden factor deficiency were found to be associated with disease [27]. Also, higher incidence of preeclampsia was found in trisomy 13 pregnancy than pregnancy with normal karyotyping [28,29]. Interestingly, the gene for sFlt-1 which is known for contributing to preeclampsia, is also encoded in chromosome 13q [30].

Pharmacological and Biochemical Role of Aspirin in Preeclampsia

Aspirin is theorized to be protective against preeclampsia due to its well-known anti-inflammatory, anti-angiogenesis, and antiplatelet properties. The active ingredient of Aspirin "acetylsalicylic acid" inhibits both cyclooxygenase 1 and 2 (COX 1 and 2) [31]. COX-1 regulates the synthesis of Thromboxane-A₂ (TXA-2) and Prostacyclin (PG I-2). TXA-2 causes vasoconstriction and induction of platelet aggregation which PGI-2 causes vasodilatation and inhibition of platelet aggregation [31]. COX-1 is constantly expressed but COX-2 gene expression is inducible by inflammation [7]. Although Aspirin has dose-related effects on both COX-1 and COX-2, LDA inhibits only TXA-2 allowing PGI-2 synthesis and subsequently, it allows the beneficial effects on blood vessels and platelets. On the other hand, higher doses inhibit synthesis of all prostaglandins [7,32].

During normal pregnancy, TXA-2/PGI-2 balance favors PGI-2 to regulate maternal hemodynamics and enhance fetoplacental perfusion [33]. TXA-2/PGI-2 imbalance favoring TXA-2 was theorized to explain the pathogenesis of preeclampsia [31]. Due to placental ischemia, activation of COX enzymes occurs leading to release of oxidative substance, cytokines, and TXA-2 into circulation [31]. A gush of these substances causes widespread endothelial dysfunction [24,34]. Aspirin also attenuates the nitrous oxide pathway which minimizes oxidative distress in preeclamptic patients [33]. Those pieces of evidence make researchers start thinking of the possible preventive role of Aspirin in preeclampsia [19,21]. Indeed, LDA is still effective in cases that may not be explained by the theory of placental ischemia, which means that the role of LDA is still not completely understood [2].

Safety of Aspirin in Pregnancy

Many clinical randomized trials confirmed the safety of LDA use during pregnancy even at first trimester when embryogenesis occurs [7]. Report of USPSTF also confirms the safety of LDA and absence of risk of placental abruption in 11 trials including 23,332 women (RR=1.17 and CI=0.93-1.48). Moreover, there is no increased risk of postpartum hemorrhage in nine trials which included 22,760 women (RR=1.02, CI=0.96-1.09) besides no increase in mean blood loss in 5 trials including 2,478 women [4]. In a cohort study, Aspirin was associated with increased 5-year risk of gastrointestinal bleeding and cerebrovascular hemorrhage [35]. In another clinical trial, Aspirin was associated with an increased risk of blood transfusion [36].

Cochrane review of the use of antiplatelets in the prevention of preeclampsia reports in absence of risk of congenital anomalies for LDA was compared to controlled matched patients [37]. Also, this review showed no increase in the risk of neonatal intracranial hemorrhage (10 trials including 26,184 infants) or any other type of neonatal hemorrhage in eight trials including 27,032 infants [37]. Also, systematic reviewing of 10 clinical randomized trials by USPSTF confirms that there is no increased

risk of neonatal intracranial hemorrhage, they review 10 trials including 22,158 women RR=0.84, CI=0.61-1.16 [5].

Data and Trials Support Aspirin Role

Many trials support Aspirin effectiveness in the prevention of preeclampsia in high-risk patients besides the prevention of further complications like IUGR and preterm labor [4,38,39]. Despite the limitations of these studies, they give us good evidence of Aspirin effectiveness in those cases more than placebo [40].

A study focused on ethnicity, discussed effectiveness on Aspirin in East Asian versus non-East Asian high-risk mothers regarding prevention of preeclampsia, they found that Aspirin is beneficial with more obvious effect in preventing IUGR in East Asian than non-East Asian [18]. Regarding multiple pregnancies, it was found that Aspirin effectiveness in the prevention of preeclampsia is of low evidence and is limited to mild preeclampsia [41]. Also, they found Aspirin not associated with any significant change in the incidence of Small for Gestational Age (SGA), so they recommended further studies and trials before recommending LDA generally in multiple pregnancies [41].

Trials are designed to determine the best time to start LDA in high-risk pregnancy, it was found that LDA effect is constant regardless of time of administering it so clinicians should offer LDA to those patients regardless of gestational age at that visit whether before or after 16 weeks [42]. USPSTF recommends LDA use after 12 weeks in this regard [5]. ACOG committee prefers limiting the indications of LDA to pregnant women with a history of early-onset preeclampsia or preterm labor before 34 weeks as a complication of preeclampsia or to women with more than one prior pregnancy complicated by preeclampsia [7]. They also recommend its use between 12 and 28 weeks optimally before 16 weeks of gestation [7,17,39]. Secondary analysis of Maternal-Fetal Medicine Unit High-risk Aspirin study also confirmed the beneficial effect of starting Aspirin <17 weeks as it was associated with decreased incidence of late-onset preeclampsia [43]. Studies also found that association between early initiation and lower incidence of preeclampsia is dose dependent which means that a higher dose of Aspirin may be associated with more beneficial effects [17]. Most of the recent studies focused on 81 mg Aspirin which is the most commonly used dose in the United States [7], compliance of patients to its intake plays a major role in its effectiveness especially in the prevention of early-onset preeclampsia [44]. Moreover, it is also found that early screening for preeclampsia by antenatal care, in addition to LDA intake, is more beneficial [45]. Screening is mainly based on the analysis of maternal characteristics, medical and obstetric history because all blood screening tests are experimental until now [40].

Other Pharmacological Therapies

Many observational studies and randomized clinical trials suggest the role of LMWH in the prevention of preeclampsia [46-48]. A systematic review of randomized clinical trials of the use of LDA plus LMWH versus LDA only shows a possible benefit

of co-administration of LMWH in terms of lower incidence of preeclampsia [33]. It was also found that this effect is more with Deltaparin than Enoxaparin [47]. This effect is emphasized as a potential role of LMWH to reverse endothelial and vascular damage caused by preeclampsia [49]. There is no significant difference in the incidence of IUGR or SGA [50]. Use of LMWH was found to be beneficial for antiphospholipid syndrome but the use as a preventive tool in preeclampsia or other placenta related pregnancy disorders is in need of further studies to establish that beneficial effect [47,48,51,52]. Calcium is now recommended to prevent preeclampsia especially for high-risk women with low calcium diet [53,54] Although, studies found no significant difference if calcium is added to LDA as preventive tools against preeclampsia [55].

Guidelines and Societies Support Aspirin Role

Besides ACOG and the USPSTF guidelines, other societies provide guidelines supporting the role of LDA and stating their expert opinions about dose, timing, and indications of intake. WHO strongly recommends LDA use in the prevention of preeclampsia in high-risk patients with moderate quality of evidence. Regarding the onset of therapy, they consider its onset before 20 weeks as low quality of evidence. They recommend 75 mg dose, but clinician can recommend the nearest available dose. They also recommend that the selection criteria of targeted high-risk patients should be determined according to local epidemiological studies of the disease. Although they admit the beneficial effect of LDA, they believe that the administration of LDA could not be individualized to determine which subgroup of high-risk patients get the most beneficial effect of LDA [56]. Moreover, the American Heart Association and American Stroke Association recommend LDA for women with essential or secondary or previous pregnancy-related hypertension starting in 12 weeks of gestation till delivery [57]. Also, the American Academy of Family Physicians recommends it from 12 weeks till 36 weeks of gestation which may decrease the incidence of preeclampsia by 20% [58].

In the United Kingdom, The National Institute for Health and Care Excellence (NICE) recommends it for high-risk pregnant women (chronic hypertension, DM, chronic renal disease and autoimmune disorder like systemic lupus. They also recommend it for patients with 2 or more of these moderate risk factors, first pregnancy, multifetal pregnancy, high body mass index, positive family history of preeclampsia, maternal age above 40 years and the long interval between pregnancies >10 years. They consider the role of LDA as modest but based on reliable evidence and good safety profile [59]. Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) recommends the dose of 50-150 mg of Aspirin as one of the preventive tools that help in reduction of preeclampsia rate, preterm delivery and perinatal death in addition to low dose Calcium [60]. The International Society of Study of Hypertension in Pregnancy (ISSHP) recommended that placental growth factor and uterine Doppler may help in determining patients who may get the benefit of 150 mg Aspirin. They also recommend dose 75-162 mg for high-risk patients using the same criteria and they add assisted

reproductive technique as a risk factor indicating the need for LDA [61]. Canadian Hypertensive Disorders of Pregnancy Working Group admit that evidence of LDA role is strong and of high quality. They recommend dose (75-162 mg) at bedtime after diagnosis of pregnancy and before 16 weeks until delivery [62].

Summary

Although both pathogeneses of preeclampsia and role of LDA in it are not completely understood, there is strong well-qualified evidence of LDA role as a preventive tool for preeclampsia. The beneficial effects of LDA include prevention of early-onset disease, associated maternal complications, and fetal complications. Because of all those complications, researchers believed that focusing on prevention would improve overall maternal health care worldwide especially during pregnancy, and screening may allow clinicians to identify patients at risk and offer prompt management as needed. Many societies include ACOG, USPSTF, WHO, American Heart Association, American Stroke Association, and other societies agreed on its use for high-risk patients providing guidelines for LDA administration.

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