ROLE OF ASPIRIN IN PREVENTION OF PRE-ECLAMPSIA

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ABSTRACT
Pre-eclampsia, the obstetric disorder characterized by hypertension and proteinuria prevails all over the world and presents as a pressing peril for fetal and maternal lives. Though inflammation, increased levels of TXA₂, ischemic placenta, dysfunction of endothelium are discerned, the exact pathophysiology yet remains a mystery. The absolute treatment is still to be discovered, however its prevention by low dose aspirin presents as a relieving factor for Pre-eclampsia. In this review, with the pathophysiology, diagnosis, risk factors, prevention and various trials done, low dose aspirin stands as the recommended choice. The various outcomes of research include controlled blood pressure, decreased proteinuria, pregnancy complications, miscarriages and growth restrictions in foetus.

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INTRODUCTION

In less developed countries, Pre-eclampsia dwells as one of the substantial obstetrical hypertensive problems. Pre-eclampsia is a pregnancy complication characterized by increased blood pressure and large amounts of proteins in urine. It continues to be a prime contributor to the maternal as well as the neonatal morbidity and mortality. As little is known about the etiology, the precise treatment of Pre-eclampsia is passably impractical. To avoid the after effects, preventive measures are beneficial. While the exact cause of Pre-eclampsia remains a mystery, various risk factors can be attributed for its development. The common risk factors associated with Pre-eclampsia are family history, nulliparity, pregnancy during teenage, late pregnancy diseases like obesity, Diabetes mellitus type-I, disorders of vascular and connective tissue, multiple pregnancies, nephropathy, urinary tract infections, anti-phospholipid antibody syndrome, smoking, stress etc.

As there is no single reliable biomarker for the early detection of Pre-eclampsia, a combination of markers assist in its identification. Pre-eclampsia can be diagnosed by Uterine Doppler Assessment, use of several biochemical and ultrasonographic markers like Pregnancy associated Plasma protein-A, Placental protein-13, Disintegrin and Metalloprotease 12, Inhibin-A, Activin-A, etc. Studies have reported that, the cases of miscarriage due to no treatment of Pre-eclampsia are as high as 90%. Compared to the untreated pregnancies, the use of anti-platelet agents as preventive measure has shown a remarkable denouement besides being relatively safe in pregnancy. Among the various antiplatelet drugs available, aspirin has been studied as the prototype. The purpose of this review is to deliver an insight into the development of Pre-eclampsia and to ascertain the role of low-dose aspirin in its prevention.

ETIOPATHOGENESIS

Hypertension (BP ≥140/90 mm Hg) and proteinuria (≥ 5g/24hrs) are the two most typical features of Pre-eclampsia. Other symptoms less commonly witnessed include seizures, acute renal failure and various pulmonary complications. The onset of disease is usually after the first trimester and the exact cause reason is unbeknownst. Predisposing factors like age, family history and number of children previously born contribute to primary pathophysiology of Pre-eclampsia whereas endothelial injury ensuing from various micro vascular diseases or in certain conditions of women with large placenta is responsible for secondary pathophysiology. The pathogenesis of Pre-eclampsia is a composition of diverse factors. Placenta, a fleeting organ is the primary site for the origin and development of Pre-eclampsia. Various abnormalities in the placenta may arise due to hypoxic conditions.

The failure of physiological conversion of the spiral arteries resulting from incursion of fetal trophoblasts in arteries causing abated oxygen supply to the fetus may be regarded as the initial step in the Pre-eclampsia development. The decreased oxygen supply triggers low levels of vascular endothelial growth factors terminating in endothelial dysfunction. This invasion also inhibits the remodeling of endothelium leading to hypoxia and ischemia of placenta. Inflammation is also seen due to increased levels of pro-inflammatory mediators found in the circulating blood and presents as a contributing factor for Pre-eclampsia. Due to decreased diffusion of oxygen in placenta, platelets activate and initiate the clotting system. An imbalance between the levels of prostacyclin and thromboxane A_2 unfolds. Increased thromboxane A_2 promotes rapid aggregation of platelets and hence their levels further augment in Pre-eclampsia. All the above changes may eventually end up in Preeclampsia, preterm birth or miscarriage.

PREVENTION

Though Pre-eclampsia is characterized by increased blood pressure, antihypertensive drugs are customarily avoided due to their adverse effects on the fetus. They may benefit the mother but the impact on perinatal outcomes is unclear. The administration of ACE inhibitors and β blockers in pregnancy has been proved to induce severe adverse effects on fetal life. The ultimate cure of Pre-eclampsia is delivery. Calcium pump inhibitors, magnesium sulfate, vitamin C and E supplements and low-dose aspirin have been used to prevent pre-eclampsia in the past. Among them, the use of magnesium sulfate has fallen out of favour, as the serum levels have to be strictly monitored. The results of using low-dose aspirin have outgrown other preventative options, making it the drug of choice. There are no adverse effects of aspirin on newborn’s platelet functions and it is relatively safe. Pre-clinical trials on mice further support the use of aspirin in Pre-eclampsia. The effects of aspirin largely depend on the dose, time of administration and the initiation of therapy. Low-dose aspirin administered after 16 weeks of gestation has shown positive outcomes. The risk of mortality and morbidity is greatly reduced if aspirin is used in combination with other drugs like low molecular weight heparin, elemental calcium etc. Aspirin had better effect on Pre-eclampsia when compared to alternative drugs. More commonly, heparin is added to aspirin as it binds to antiphospholipid antibodies and reduces fetal loss.

ACTION OF ASPIRIN

Imbalance of Prostaglandins and Thromboxane A_2 is the biochemical abnormality seen in Pre-eclampsia. Thromboxane A_2, Prostaglandins and Prostacyclins are formed from a common precursor called Arachidonic acid through cyclooxygenase pathway. This pathway requires the enzyme cyclooxygenase for the oxidation of Arachidonic acid to prostaglandins PGH_2. The so formed PGH_2 further gives rise to Prostaglandins (PGE_2 and PGD_2), Prostacyclin (PGI_2) and Thromboxane A_2 by enzymatic action. Aspirin causes an irreversible inactivation of cyclooxygenase enzyme and hence decreases Prostaglandin H_2 levels. As the levels of Prostaglandin H_2 decline, Thromboxane A_2 levels also begin to diminish. In conclusion, the ill effects of Thromboxane in Pre-eclampsia viz., vasoconstriction, platelet aggregation, uterine contractility and reduced uteroplacental flow of blood are antagonized by aspirin.
EVIDENCE IN SUPPORT OF ROLE OF LOW DOSE ASPIRIN IN PRE-ECLAMPSIA

Researches spanning decades have highlighted favorable effects of low dose aspirin in preventing Pre-eclampsia. Though the inclusion criteria of the studies differed, the outcome was very similar (Table 1). Meta-analysis of various randomized controlled trials (RCTs) to evaluate low-dose aspirin for preventing preeclampsia and its complications has shown that low dose aspirin can reduce the incidence of preeclampsia, severe preeclampsia, preterm birth, and intrauterine growth restriction (IUGR). Low-dose aspirin is more effective in reducing incidence of preeclampsia or IUGR if used before 16 gestational weeks than if used later without posing a major safety risk to mothers or fetuses.

Table 1: Clinical Trials of low dose aspirin in Pre-eclampsia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Onset of treatment</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. E.V.Souza 2014</td>
<td>Onset treatment 20-27 weeks of gestation</td>
<td>BP 140/90 on 2 occasions over 6hr apart before week 20</td>
<td>Aspirin 100mg or 2gm calcium</td>
<td>reduced the rate of preeclampsia by 28.6% and the rate of fetal growth restriction by 80.8%</td>
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<tr>
<td>2. CLASP 1994</td>
<td>12-32 weeks of gestation</td>
<td>DBP 90, 90-109, 110</td>
<td>60mg Aspirin or placebo</td>
<td>6.7% of aspirin-allocated women developed proteinuric pre-eclampsia after randomization. 7.6% of those allocated placebo</td>
</tr>
<tr>
<td>3. Mervi Haapsamo 2010</td>
<td>First day of gonadotropin stimulation</td>
<td>Age ≤ 40 years, ≤ 4 previous ovarian stimulation, no contraindication for aspirin</td>
<td>100mg oral aspirin or placebo</td>
<td>The incidence of hypertensive pregnancy complications in aspirin- 15.4%; placebo- 18.2%</td>
</tr>
<tr>
<td>4. J.I.P.Devries [35]</td>
<td>LMWH 6 weeks of gestation, aspirin before 12 weeks</td>
<td>Pregnancy ≤ 12 weeks, age ≥ 18yrs</td>
<td>LMWH 5000IU with 80mg aspirin or only 80mg aspirin</td>
<td>LMWH-with-aspirin reduced the recurrence of Pre-eclampsia before 34 weeks gestation. There were no early recurrences in the LMWH-with-aspirin arm and six in the aspirin-only arm</td>
</tr>
<tr>
<td>5. Bujold 2010</td>
<td>16-20 weeks gestation</td>
<td>Nulliparity, single gestation, first prenatal care visit before 20 weeks of gestation, BP ≤ 130/80mmHg, no proteinuria by dipstick</td>
<td>50-150mg aspirin alone or with 300mg dipyridamole</td>
<td>The reduction of preeclampsia was significantly seen in the women who began the intervention at 16 weeks of gestation or less whereas it was not observed among women who initiated the intervention at more than 16 weeks gestation.</td>
</tr>
<tr>
<td>6. Ali Akbar 2002</td>
<td>First half pregnancy</td>
<td>Nulliparity, single gestation, first prenatal</td>
<td>Group 1- 75mg aspirin</td>
<td>Preeclampsia occurrence: 4.6% in the aspirin group, 4%</td>
</tr>
</tbody>
</table>
CONCLUSION

As the treatment of Pre-eclampsia remains a challenge, prevention serves as a better option to avoid the ill effects and the use of low dose aspirin to prevent pre-eclampsia in high risk patients appears to outweigh the use of other drugs. Initiation of aspirin therapy before 16 weeks of gestation has been associated with greater positive outcomes. As the high levels of thromboxane in uteroplacental blood are indicated in Pre-eclampsia aspirin prevents further formation of thromboxane by blocking the pathway of its formation.

Although many studies have confirmed the role of aspirin in preventing pre-eclampsia, in few cases aspirin could not successfully display its preventive effects indicating that its action depends on few other factors. As the incidence of Pre-eclampsia is at increase, several long-term clinical trials are needed to be conducted in order to completely understand the role of aspirin in Pre-eclampsia prevention.
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