

# Effects of Acetylsalicylic Acid in Preterm Preeclampsia Prevention

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*Acetylsalicylic acid, classified under the non-steroidal anti-inflammatory drugs (NSAIDS) has well known anti-inflammatory, anti-pyretic properties, anti-platelet aggregation effect and analgesic properties. Preeclampsia (PE) is a pathology of pregnancy characterized by the onset of hypertension and often accompanied by the lost of significant amount of protein in the urine. In pregnant women with risk of preeclampsia, low doses of aspirin have been shown to have a beneficial effect on the incidence of this disorder. Using a retrospective design, we screened for preeclampsia all pregnancies followed in a time interval of 2 years. We have observed that in preeclampsia high risk patients based on the screening done between 11 to 13 weeks and 6 days, the administration of low doses of acetylsalicylic acid reduced the burden of disease. Identifying the pregnancy having high risk for preeclampsia in the first trimester helps us in decision making for initiating prophylactic treatment with Aspirin.*

**Keywords:** acetylsalicylic acid, anti-platelet agents, arterial hypertension, pregnancy, preeclampsia prevention

Acetylsalicylic acid well known as Aspirin was first discovered by Charles Gerhardt in 1853, and later on in 1882 its mechanism of action was discovered by Jon Vane, for which he was even awarded Nobel Prize in Physiology [1, 2]. The chemical formula of this over the counter drug is  $C_9H_8O_4$  or  $CH_3COOC_6H_4COOH$  or  $HC_9H_7O_4$ , having a molecular weight of 180.158 g/mol, and bioavailability of 80-100%.

It is classified under the NSAIDS (non-steroidal anti-inflammatory drug) group of medications due to its anti-inflammatory properties and it is also known to have anti platelet aggregation effect for which it has been widely used in stroke, myocardial infarction and post stenting procedures etc. It is administered orally and is metabolized in the liver. It has a tendency to form gastric ulcers and hence it is recommended to use enteric-coated tablets, to lower its harmful effects on the gastric mucosa.

Preeclampsia (PE) remains to be a major threat in pregnancy even today. By definition it is a multisystem disorder of pregnancy where the presence of hypertension and proteinuria at or after 20 weeks of gestation leads to its diagnosis. Diagnosis of hypertension is established if the pregnant woman has 140 mmHg or more systolic blood pressure and a diastolic blood pressure equal to or more than 90 mmHg on two separate measurements at a duration gap of 4 to 6 h [3]. Preeclampsia is fatal as can lead to seizures (eclampsia), hepatic and renal failure, as well as to clotting problems. Preeclampsia can be diagnosed based on screening guidelines "The First Trimester Screening Program" risk calculator provided by the Fetal Medicine Foundation, which are done in the first trimester of pregnancy (specifically between 11 weeks to 13 weeks and 6 days of pregnancy). The screening results divides the pregnant women into two groups, having high risk or low risk based on several criteria's consisting of clinical and para-clinical parameters (blood investigations, biomarkers as well as ultrasound evaluations) as well as demographic data and case history. Based on multiple study results Aspirin (Acetylsalicylic acid), is found to have beneficial effects if administered to high risk cases based on above screening criteria.

It is clear that the therapeutic conduct must be ethical, personalized, guided in function of some relevant characteristics [4-8]. Also the aspects concerning the potential adverse events, quality of life and vulnerabilities, must be carefully approached [9-11].

To prevent pregnancy-related vascular disorders such as intrauterine growth retardation (IUGR), preeclampsia, and maternal disorders like antiphospholipid syndrome [12], low dose aspirin is widely used nowadays. The proof of its efficacy is not yet known precisely, still it continues to being prescribed on a larger scale and in increasing proportions of patients having high risk for PE in order to prevent it [13].

## Mechanism of action

Acetylsalicylic acid (fig. 1) inhibits the conversion of arachidonic acid into prostaglandins, lipid-soluble molecules derived from arachidonic acid [14], by suppressing the action of cyclooxygenase, fact that has been backed up by many studies [15] (fig. 2).

Another metabolic pathway involves diacylglycerol, which releases prostaglandins [16]. During pregnancy aspirin not only helps in preventing platelet aggregation and ensures a physiological state of the circulatory system, but also mediates cell stress response, homeostasis and inflammation. Based on this and the discovery of correlated increased values of thromboxane with decreased values of prostacyclin in over 90% preeclampsia patients [17], there were an indication for treating preeclampsia women with low-dose aspirin [18]. While inhibiting the production

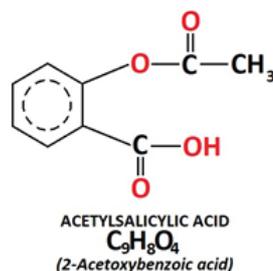


Fig. 1. Chemical formula of Acetylsalicylic acid (Aspirin)

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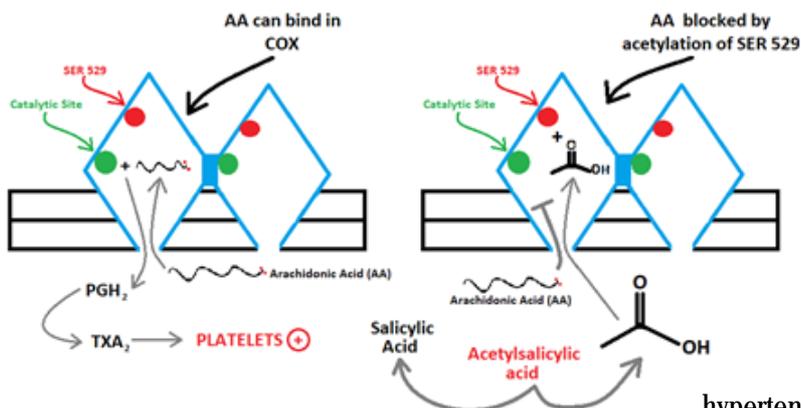


Fig. 2. Mechanism of action of acetylsalicylic acid

of thromboxane, aspirin does not have a major effect on prostacyclin metabolism [19], if administered in low doses (60 to 81 mg/24h). The role of Thromboxane is to increase vasoconstriction while stimulating platelet aggregation. Also thromboxane, a placental secreted hormone [20], has a role in uterine contraction and at the same time decreases uterine and placental blood flow. As expected, those effects of thromboxane are attenuated by low-dose aspirin intake, altering the ratio of thromboxane to prostacyclin in favor of the latter [21]. Prostacyclin mediates vasodilatation, inhibiting aggregation of platelets, lowering uterine contractility, but increasing blood flow to the placenta and uterus, having an opposing action to thromboxane [22]. The very encouraging results of the initial clinical studies documented in the medical literature shows that low-dose aspirin has a significant role in decreasing the incidence of preeclampsia in women, inhibiting the effects of angiotensin II. Angiotensin II has an essential role in increasing systemic arterial blood pressure. A more direct approach, such as with infused prostacyclin has been proven inefficient, because its effects are too potent, and are considered to be incompatible with fetal stability.

### Experimental part

The aim of the study was to screen the patients for risk of developing preeclampsia and to demonstrate the effects of Aspirin in preventing preeclampsia in high risk patients based on the screening test criteria.

A cohort of 7968 cases admitted in our Gynecology and Obstetrics County Emergency Hospital, Timisoara, Romania during the time period of 15<sup>th</sup> January 2015 to 14<sup>th</sup> January 2017, were screened for preeclampsia, among which 4000 were found to be absolutely normal from hypertension point of view. Remaining were further evaluated for the risk of developing preeclampsia. A selective number of cases were prescribed Aspirin as a prophylactic measure to avoid developing preeclampsia. The results obtained are presented below. The risk screening calculations for preeclampsia were performed using the Fetal Medicine Foundation Software ([www.fetalmedicine.com](http://www.fetalmedicine.com)). A written formal consent was obtained for the inclusion in study from all the cases under the guidance of Regional Ethical Committee and in accordance to some published models [23-28], and proper permissions were obtained from the hospital board for conducting this experimental study. The results were analyzed with the help of SPSS software.

### Inclusion criteria

All the pregnant women with no known chronic illness and who had naturally conceived were included.

### Exclusion criteria

All artificial conception methods pregnancy cases were excluded from the study lot. Known cases of chronic

hypertension were excluded from the screening as well as from the cohort to study the effects of aspirin. Women who suffered from miscarriage or had undergone elective termination of pregnancy were not included.

### Results and discussions

A total of 7698 of cases that were admitted in our hospital were evaluated. The statistical analysis showed the following results: the maternal age at the time of pregnancy was found to be below 30 years in 3099 (40.2%) of cases, while rest 4599 (59.8%) had the age above 30 years. Around 3080 (40%) patients had the body mass index (BMI) below 25, while 4618 (60%) were found to have a BMI score above 25. Active smoking was found to be present in 5147 (66.86%) pregnant women, among which few had stopped smoking intermittently, while the rest 2551 (33.13%) women were constant non-smokers.

A total of 304 (3.9%) pregnant women had a positive PE background, as their mothers had suffered from preeclampsia. A total of 5008 (65%) cases had no family history of preeclampsia. While, one third of the whole group unable able to state whether their mothers suffered from PE or not. The study showed that 5179 (67.2%) patients were nulliparous, while 814 (10.5%) from the total number of patients were multiparous presenting PE, and the remaining 1705 (22.3%) pregnant women were multiparous without presenting any signs of preeclampsia. Chronic hypertension was present in 522 (6.7%) patients; while the remaining 7176 (93.3%) did not suffer from chronic hypertension. We had to exclude 544 (7.06%) patients, which did not fit the inclusion criteria as they had suffered from the following conditions: 116 (1.5%) had a miscarriage, 88 (1.14%) choose to terminate the pregnancy, while 72 (0.93%) cases withdrew their consent from being included in the study and 268 (3.48%) patients had no follow-up. After excluding these patients the remaining patients 7154 (92.93%) were further divided based on the risk for preterm preeclampsia  $\leq 1$  in 100 ( $n=6404$ , 83.19%) and risk for preterm preeclampsia  $\geq 1$  in 100 ( $n = 751$ , 9.75%) from the total lot of 7698 patients, as per the Fetal Medicine Foundation risk calculation score program.

From the group of pregnant women categorized in the low risk group for preterm preeclampsia were further subdivided into three groups based on the appearance of preeclampsia; term, preterm preeclampsia or those who did not develop preeclampsia at all. The results were as follows: preterm PE was found to be present in 12 women (0.15%), while 71 had term preeclampsia (0.92%) and 6321 (82.11%) were documented to have no PE.

From the high risk group 751 (9.75%), only 217 (2.81%) received prophylactic treatment with Aspirin for PE, at the dose of 150 mg/day. These were further classified based on term PE, preterm and no PE having the following distribution: 9 (0.11%) patients were found to have preterm PE, 14 (0.18%) patients had term PE whereas 194 cases



Fig. 3. Flow diagram

(2.52 %) were having no sign and symptoms of PE later on (fig. 3).

Hence, it can be stated that among the 2.81% patients who received aspirin majority (2.52%) of cases were prevented completely of developing preeclampsia, which proves that Aspirin has beneficial effects.

Aspirin has been documented in many researches worldwide to be a safe choice when it comes to preventing the development of preeclampsia. Two observational studies on aspirin use during pregnancy had null findings for the potentially harmful outcomes considered (miscarriage and cryptorchidism). Similar results were seen in our experimental study. Many authors have stated that initiating prophylactic treatment with aspirin in high risk groups based on screening leads to a significant decrease in development of preeclampsia, and the same was confirmed in this study. Preeclampsia can be fatal if not treated and can lead to eclampsia giving rise to convulsions in pregnant women, but as demonstrated in such cases prevention is better than cure. Hence, prophylactic treatment given to high risk individuals can lower the incidence of this severe state, as seen and confirmed in our study [23].

When choosing the therapeutic conduct, the risk factors must be known and evaluated and the whole approach must be ethical with the lowest number of adverse events encountered [29-34].

The approach must take into account all present comorbidities, associated pathologies, medical and heredo-collateral antecedents [35-39].

## Conclusions

The study demonstrates that administering Aspirin at a dose of 150 mg to pregnant women, bearing high risk of developing preeclampsia, based on the screening done between 11 to 13 weeks and 6 days, reduces the incidence of preeclampsia significantly. Identifying the pregnancy having high risk for preeclampsia in the first trimester helps us in decision making for initiating prophylactic treatment with Aspirin and hence reduces the incidence of preeclampsia notably.

The beneficial effects of Aspirin in prevention of preeclampsia can be demonstrated by this study, despite of the fact that the mechanism of action of Acetylsalicylic

acid is not fully elucidated. Taking into consideration the minimal side-effects caused by this chemical drug, as well as its low price and easy availability in majority of the countries makes it the drug of choice for preventing preeclampsia. At the same time, it should be made clear that aspirin should not be used in non-selected patients based on the first trimester screening program of pregnancy. It should be given only to risk bearing patients who might develop preeclampsia in future. Aspirin in low doses selectively inhibits the lipid peroxide and thromboxane without affecting the prostacyclin.

With the fast evolving new medical technologies, may be in near future, it will be possible to understand the way preeclampsia is produced as well as the mechanism of action of acetylsalicylic acid in preventing it.

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