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SHORT COMMUNICATION

Acetylsalicylic acid in prevention of preeclampsia

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ABSTRACT

Preeclampsia is a frequent and dangerous complication of pregnancy. It is a significant cause of death for the mother and baby. In the course of this disease, the blood flow in the placenta is impaired, what leads to foetus hypoxia. It is characterized by high blood pressure and frequently large amount of protein in urine. To describe whether acetylsalicylic acid is effective in prevention of preeclampsia. Standard up-to-date criteria were followed for review of the literature data. A search for English-language articles in PubMed database was performed. Papers published in 2017 were reviewed. In double-blind trial published in 2017 in The New England Journal of Medicine researchers divided women who were at high risk for preeclampsia into two groups. One group was receiving acetylsalicylic acid and other was receiving placebo. Preeclampsia was observed in 1.6% participants in the acetylsalicylic acid group, compared with 4.3% in the placebo group. From other study we found out that acetylsalicylic acid has a dose-response effect. Greater reduction in the risk of preeclampsia was reported with the acetylsalicylic acid dosage >75 mg/d. When acetylsalicylic acid was included in treatment at >16 weeks, there was less reduction of preeclampsia without relationship with acetylsalicylic acid dosage. Other meta-analysis shows that there was no statistically significant difference in occurrence of preeclampsia between women who started taking acetylsalicylic acid

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before and after 16th week of pregnancy. Acetylsalicylic acid is a good agent to prevent of preeclampsia. It should be prescribed to women in high risk groups regardless of the duration of pregnancy even though it may not reduce the risk of preeclampsia as much as before 16th week of gestation.

***Keywords*:** Preeclampsia, acetylsalicylic acid, pregnancy

1. BACKGROUND

Preeclampsia (PE) is very dangerous complication of the second half of pregnancy, labour and puerperium [1]. Maternal and fetal morbidity and mortality are very high [2, 3]. It may concern even 3% of women in Europe [2]. In the process of this disease, the blood flow in the placenta is reduced, what results in fetus hypoxia [3]. Preeclampsia is characterized by high blood pressure (≥140/90) with the loss of protein in urine (≥ 0.3g/day). Preeclampsia can be also diagnosed when there is no proteinuria but there is a pulmonary oedema, disorders of Central Nervous System, disturbances of the vision, incorrect kidney function, liver diseases or the number of platelets <100 000/μl [4]. Risk factors of preeclampsia are: prior preeclampsia, diabetes mellitus, hypertension, overweight, known antiphospholipid syndrome, prior fetal IUGR, mother's age over 40, kidney diseases, lupus erythematosus or multifetal pregnancy [4].

Acetylsalicylic acid is an anti-platelet agent which can reduce the frequency of migraines and is used in prevention therapy of stroke, cardiovascular disease or colorectal cancer [5-8].

The history of acetylsalicylic acid usage begins in 1978, when it was first used in a pregnant woman [9, 10]. In 1978, *Goodlin* et al. published a case report in The Lancet describing a 31-year-old woman with thrombocytopenia at the 15th week of pregnancy. She was burdened with two premature births in the interview, ended with the birth of dead newborns. Each of these cases was caused by "recurrent toxaemia". At the time when *Goodlin* et al. began to rescue the woman, her platelets were in the number of 59 000/ml. First time they used heparin - for 4 weeks without any success. Then, an attempt in which they used acetylsalicylic acid was successful. Within 10 weeks, the number of platelets increased twice after the dose 600 mg 3 times daily. During the whole period of taking acetylsalicylic acid, hypertension was not developed. In 32nd week, acetylsalicylic acid was discontinued due to the risk of closing the Botalel ductus arteriosus. The patient immediately deteriorated and developed severe hypertension. Therefore, acetylsalicylic acid was brought back into treatment and after that condition of the patient improved. She gave birth to a child at 34th week of pregnancy. It was alive child with limited growth, though. The patient's history was a groundbreaking event for the use of acetylsalicylic acid in obstetrics [9, 10]. It has resulted in a huge amount of researches over the next decades to determine whether acetylsalicylic acid can prevent preeclampsia [10].

The previous studies show that low-dose acetylsalicylic acid can reduce the risk of preeclampsia when started ≤ 16th week of gestation [11-13]. Papers show that acetylsalicylic acid is more effective in prevention of preeclampsia when the treatment is started before 16th week of gestation than after it [14]. Some researchers reported that there is no significant decrease in the prevalence of preeclampsia when the treatment is started after the 16th week

of pregnancy [15]. On the other hand, another study shows that there is no difference in effectiveness when initiated before or after 16th week [16]. A meta-analysis from 2011 shows that acetylsalicylic acid is effective in prevention of preeclampsia only in high risk groups and does not reduce the risk in the group with the low risk of preeclampsia [17]. Many studies claim that acetylsalicylic acid is safe for both, mother and fetus [12, 18].

There are reports of the possibility of replacing acetylsalicylic acid with other drugs in the treatment of preeclampsia, but these are new studies that require further verification. Various drugs are proposed, for example, eclectic mixesildenafil, esomeprazole, metformin and pravastatin [19-22]. Soluble Fms-like protein tyrosine kinase-1 (sFlt-1) is also being investigated. It is a protein which level is significantly elevated in preeclampsia states. It is an antiangiogenic protein that is believed to indicate the symptoms of preeclampsia. *Ravi Thadhani* et al. attempted to treat patients with therapeutic apheresis, which had the potential to be effective, using a plasma-specific dextran sulphate column to remove circulating sFlt-1 in 11 pregnant women aged between 20-38 years with very early preeclampsia (they were in 23rd- 32nd weeks of pregnancy). However, these are the results that require further re-verification. Therapeutic apheresis reduced sFlt-1 circulation in those women with very early preeclampsia, reduced proteinuria and appeared to prolong pregnancy without serious adverse consequences for the mother or fetus [23].

Perhaps one day it will be possible to replace acetylsalicylic acid with another specific treatment, but researches today are still underway on the doses that are the most effective in the treatment of preeclampsia with acetylsalicylic acid, with simultaneous researches on the use of other drugs for this purpose. To sum up, the problem of preeclampsia treatment is one of the most frequently studied.

2. PURPOSE

The purpose of this work is to present the results of three studies published in 2017 concerning acetylsalicylic acid in preeclampsia.

3. RESULTS

In double-blind trial published in 2017 in The New England Journal of Medicine researchers offered screening for preeclampsia to women at 11th to 14th week of gestation who had a routine prenatal visit at 13 maternity hospitals in the United Kingdom, Spain, Italy, Belgium, Greece, and Israel [24]. The screening was performed by the screening algorithm that included factors like maternal height and weight, arterial pressure, uterine-artery pulsatility index, and pregnancy-associated plasma protein A levels. Gestational age was calculated from the measurement of the crown–rump length of the fetus. Women older than 18 years with singleton pregnancies and high risk (>1%) of preterm preeclampsia were eligible for the trial. 1,776 of them agreed to participate in the trial and were enrolled and divided into two groups. One group was receiving acetylsalicylic acid at a dose of 150 mg per day until 36th week of gestation and other was receiving placebo. Women were told to take one tablet at bedtime which was based on observation from other trial where acetylsalicylic acid ingested at that time reduced the incidence of preeclampsia more than during the day

[25]. The primary outcome measure was delivery with preeclampsia before 37th week of gestation. Adherence was good and there were no significant differences between the acetylsalicylic acid group and the placebo group. Preeclampsia was observed in in 13 of 798 participants in the acetylsalicylic acid group (1.6%), compared with 35 of 822 in the placebo group (4.3%) (adjusted odds ratio in the acetylsalicylic acid group, 0.38; 95% confidence interval, 0.20 to 0.74; P = 0.004).

Another research was a meta-analysis which included 45 studies that enrolled 20,909 participants [26]. Scientists performed review of the literature data through a search of Embase, MEDLINE, the Cochrane Central Register of Controlled Trials and the Web of Science databases. Papers published between January 1985 and December 2015 were reviewed. Studies with low risk of PE (<7% prevalence in control group) were excluded. Studies were divided by gestational age (<16th weeks vs. >16th week). In both groups the dose of acetylsalicylic acid oscillated between 50-150 mg daily. Relative risks (RR) were calculated for each study and gathered for global analysis. Data for patients randomized before 16th week of gestation were available from 21 studies (5130 participants). Acetylsalicylic acid was significantly reducing risk of PE, with a significant dose-response relationship (Table 1).

Table 1. Relative risk of preeclampsia, ≤16th week of gestation [26]

Dose of acetylsalicylic acid	Relative risk (95% confidence interval) random effect	P value
50 mg	0.33 (0.04-3.04)	.33
60 mg	0.93 (0.75-1.15)	.49
75 mg	0.42 (0.25-0.70)	.001
80 mg	0.52 (0.26-1.01)	.06
100 mg	0.48 (0.31-0.74)	.0009
150 mg	0.07 (0.00-1.25)	.07
Total	0.57 (0.43-0.75)	<.001

Researchers additionally compared 2 dosages that were used most often in studies (60 mg vs 100 mg). Acetylsalicylic acid in dose 100 mg/day was significantly more effective in reduction of PE, than 60mg acetylsalicylic acid daily (RR, 0.48; 95% confidence interval [CI], 0.31-0.74 vs. RR, 0.93; 95%CI, 0.75-1.15; P<.001).

Data for patients randomized >16th week of pregnancy were available from 27 studies (15,779 participants). When acetylsalicylic acid was included in treatment at >16th week, there was a significant reduction (Table 2) in the prevalence of PE without relationship with acetylsalicylic acid dosage, but less than when treatment was started at ≤16th week.

Egger test suggested asymmetry of the funnel plots (acetylsalicylic acid started ≤ 16th week: P value = .091; acetylsalicylic acid started >16th week: P value = .007).

Table 2. Relative risk of preeclampsia, >16th week of gestation [26]

Dose of acetylsalicylic acid	Relative risk (95% confidence interval) random effect	P value
50 mg	2.00 (0.44-9.08)	.37
60 mg	0.88 (0.68-1.12)	.30
75 mg	0.69 (0.42-1.15)	.16
80 mg	0.21 (0.06-0.70)	.01
100 mg	0.61 (0.26-1.44)	.26
150 mg	0.95 (0.67-1.35)	.77
Total	0.81 (0.66-0.99)	.04

Other meta-analysis performed by *Meher* et al. analyzed data from 23 trials that included 30,670 pregnant women [27]. The aim of the work was to answer the question whether the effects of treatment are different depending on whether treatment begins before or after 16th week of gestation. Data for patients randomized before 16th week of pregnancy were available from 17 trials (9241 women). The relative risk of preeclampsia in this group was 0.90 (95% CI 0.79-1.03). Data for patients randomized >16th week of gestation were available from 22 trials that enrolled 21,429 women. The relative risk was also 0.90 (95% CI 0.83-0.98). The research showed that there was no statistically significant difference in acetylsalicylic acid effectiveness between those groups.

Notwithstanding, it is worth to refer to the World Health Organization "Recommendations for Prevention and Treatment of Preeclampsia and Eclampsia" published in 2011. They recommended the use of acetylsalicylic acid in a dose of 75 mg up to 150 mg, however, not less than 75 mg in women with a high risk of pre-inclusion. High-risk women were those with preeclampsia in history, diabetes, chronic hypertension, kidney or autoimmune diseases and multiparous women. Early initiation of treatment was also recommended - before the 20th week of pregnancy [28]. The recommendations were based mainly on Cochrane review from 2007 in which 59 randomized controlled trials (RCTs) in women who had a risk of preeclampsia were conducted[29]. The above review found an important reduction in risk in women who received any antiplatelet medication compared to women who received placebo or did not receive treatment (relative risk [RR], 0.82 [95% CI, 0.78 to 0.89]) [29]. The risk reduction was more pronounced in women considered at high risk of preeclampsia development (RR, 0.75 [95% CI, 0.66 to 0.85]) and dependence on the dose of acetylsalicylic acid was also established. A greater reduction in the risk of

preeclampsia was evident at a low dose of acetylsalicylic acid ranging from 75 to 150 mg/day, but not in studies using a dose lower than 75 mg/day [29].

4. DISCUSSION & CONCLUSIONS

Acetylsalicylic acid is an effective drug in prevention of preeclampsia. It lowers the risk of preeclampsia before and after 16th week of gestation. The therapy with acetylsalicylic acid has a dose-response effect. Studies show that 60 mg of acetylsalicylic acid daily is much less efficient than 100 mg/day. There are also studies which say, that the dose lower than 75 mg of acetylsalicylic acid daily is not effective. It should be prescribed to women at high risk groups regardless of the duration of pregnancy. At the same time, research is being conducted on the use of other new drugs or treatments for preeclampsia but they require further testing and verification of their effectiveness.

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