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The comparison assessment of effectiveness of low-dose aspirin in women with gestational endotheliopathy for prevention of preeclampsia depending on beginning of treatment

Abstract: We are estimated the effect of low-dose aspirin (75 mg/day) depending on beginning (gestational age 11–14 vs. 16–20 weeks) in women with gestational endotheliopathy, on the incidence of preeclampsia and other perinatal complications. Our investigation showed statistically significant effect of low-dose aspirin initiated in 11–14 weeks in preventing the incidence of preeclampsia and IUGR in women with gestational endotheliopathy.

Keywords: gestational endotheliopathy, low-dose aspirin, preeclampsia, IUGR.

Preeclampsia (PE), which affects about 2–8% of pregnancies, is a multisystem complication that occurs after 20 weeks of pregnancy [6]. PE is estimated to affect 8370000 women worldwide every year and is a major cause of maternal, fetal and neonatal morbidity and mortality. Early-onset preeclampsia means that the delivery of the baby is needed before 34 weeks of pregnancy because the disorder is having an adverse effect on the mother´s or the baby´s condition. Although less common than the late form of the disorder, early-onset preeclampsia contributes most to the mortality and morbidity statistics. There is evolving evidence that both the degree of impaired placentation and the incidence of adverse fetal and maternal short- and long-term consequences of preeclampsia are inversely related to the gestational age at onset of the disease [2].

Early in normal placental development, extravillous cytotrophoblasts of fetal origin invade the uterine spiral arteries of the decidua and myometrium. These invasive cytotrophoblasts replace the endothelial layer of the maternal spiral arteries, transforming them from small, high-resistance vessels to high-caliber capacitance vessels capable of providing adequate placental perfusion to sustain the growing fetus. In preeclampsia, this transformation is incomplete. Cytotrophoblast invasion of the spiral arteries is limited to the superficial decidua, and the myometrial segments remain narrow. Fisher et al. showed that in normal placental development the cytotrophoblasts assume an endothelial phenotype in a process called pseudovasculogenesis, or vascular mimicry, by down-regulating the expression of adhesion molecules characteristic of their epithelial cell origin and adopting an endothelial cell surface adhesion phenotype. The underlying cause of preeclampsia is thought to be abnormal placenta-

tion, characterized by defective invasion of trophoblast cells and remodeling of the uterine vasculature (cytotrophoblasts do not undergo this switching of cell-surface molecules and thus are unable to adequately invade the myometrial spiral arteries), resulting in reduced uteroplacental perfusion, which leads to activation of mechanisms promoting maternal vasoconstriction. Intravascular volume is shunted, across the ``leaky'' capillaries, to extravascular spaces. PE can characterized as a clinical manifested gestational endotheliopathy, with microalbuminuria, and increased levels of proinflamatory cytokines, vascular cell adhesion molecule and a disturbance of the tPA/PAI-1 [5,6]. Preeclampsia is associated with an impairment of endothelium-dependent relaxation in maternal resistance arteries. The endothelium is believed to be a primary target of mediators generated by the placenta [9].

Primary prevention of preeclampsia is controversial and subject of active research, particularly with regard to the use of anti-inflammatory agents and micronutrients including calcium, vitamin D and antioxidant vitamins C and E supplements. The only definitive treatment for preeclampsia is termination of pregnancy/delivery of the fetus and placenta, though some women with preeclampsia also present a transient aggravation of the disease in the postpartum period. Management of women with preeclampsia aims at minimizing further pregnancy-related complications, avoiding unnecessary prematurity and maximizing maternal and infant survival [4].

Bujold et al. [7] reported that when low-dose aspirin is started after 16 weeks of gestation there is no significant decrease in the risk of the disease, whereas with treatment starting at or before 16 weeks there is a halving in the risk. This finding suggests that early administration of aspirin may reduce the risk of preeclampsia, possibly by improving placentation.

The aim of this paper was to determine the effect of the lowdose aspirin started at 12 weeks of gestation on the risk of preterm and term preeclampsia in a population of women at gestational endotheliopathy.

Methods

We enrolled 44 pregnant women between 11 and 14 weeks of gestation (clinical group № 1) and 26 pregnant women between 16 and 20 weeks of gestation (clinical group № 2) with gestational endotheliopathy who were receiving prenatal care at the maternity hospital № 1 in Vinnytsya between 2010 till 2012. We included patients with gestational endotheliopathy, which were diagnosed when microalbuminuria more than 3,4 mg/mmol (screening test), and endothelium-dependent vasodilation less than 10% (approving test) [1]. We excluded patients with multiple gestation, diabetes mellitus, pre-existing hypertension and renal disease, autoimmune disease.

Each participant received 1 pill (75 mg) of aspirin per day. Participants were scheduled for clinical follow-up every three to four weeks. Each visit from this point included the following: arterial pressure measurement, using the auscultatory method

with mercury sphygmomanometers, to measure of microalbuminuria, and to measure of endothelium-dependent vasodilation.

Acceptable reference standards for preeclampsia were persistently as hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or both) and proteinuria (>300 mg/24 hours) presenting after 20 weeks of gestation in women known to be previously normotensive. We also assessed several neonatal end points, including preterm birth (born before 37 weeks of gestation), birth weight, small for gestational age (according to institutional charts), and APGAR scores.

Ethical permission for the study was obtained from the Vinnitsya National Medical University Trust Ethical Committee, and all subjects had given informed written consent for participation.

Continuous variables between study groups were compared using the independent sample t-test and categorical variables by chi-square test. Relative risks and odds ratio were calculated to compare the risk of each outcome between aspirin (starting from 11–14 weeks) and aspirin (starting from 16–20 weeks) groups [8].

Results and their discussion

70 women were observed, with good balance between the treatment groups for the main characteristics. Of the women enrolled, we didn't found any differences between maternal age (24,2 ± 2,5 versus 24,6 ± 2,6), 51,4% were primigravidae. Post-delivery follow up forms were obtained for 94 63% of the observed women (42 allocated aspirin from 11–14 weeks and 24 allocated aspirin from 16–20 weeks), and these women had 66 infants. Reported compliance with study treatment was good, with no difference between the clinical groups allocated aspirin. Of the 70 women initially recruited into the aspirin trial, 4 women were left out of the study. Women were lost to follow up or discontinued for various nonmedical reasons, two of these were in the first clinical group and two in the second group.

We conducted an intention-to-treat analysis, in which we included all observed women. The relative risk (RR) in the groups allocated aspirin were as follows for: preeclampsia 0,29 (95% CI 0,1–0,85), placental insufficiency 0,57 (95% CI 0,23–1,33), intrauterine growth restriction 0,36 (95% CI 0,13–0,97), preterm delivery 0,14 (95% CI 0,02–1,21). The odds ratio (OR) in the groups allocated aspirin were as follows for: preeclampsia 0,21 (95% CI 0,05–0,80), placental insufficiency 0,47 (95% CI 0,15–1,48), intrauterine growth restriction 0,27 (95% CI 0,08–0,95), preterm delivery 0,12 (95% CI 0,01–1,16). The overall rate of preterm birth was also reduced in women used aspirin in the first trimester, although this was not because of a reduction in spontaneous preterm births (preterm premature rupture of membranes or preterm labor). We found no difference in mean assessment by APGAR score. No maternal deaths occurred. We did not find concerning side effects during treatment by aspirin. However, caution is needed in women with peptic ulcer disease, as administration of aspirin may worsen their symptoms.

In recent meta-analyses aspirin and other antiplatelet agents have shown a moderate but consistent reduction in the risk of preeclampsia. In the Paris collaboration meta-analysis of 32 217 mothers, which included randomized studies regardless of their inclusion criteria, the relative risk of preeclampsia was 0,9 in women receiving antiplatelet agents compared with control women. Whereas this reduction was not sufficient to warrant treatment for all pregnant women, the authors recommended low-dose aspirin started in early pregnancy to women with high-risk of preeclampsia [4]. However, specific criteria for a high-risk group could not be identified based on the reviewed literature. Results of our investigation, together with the results of the meta-analyses by Bujold et al. are in agreement with previous suggestions that aspirin in prevention of preeclampsia should be started in early gestation, before the second active phase of trophoblast invasion, which takes place from 14 weeks of gestation. During that phase the trophoblast invasion is completed [7].

Although in our study aspirin was started between 11 and 14 weeks of gestation (the first group), an even earlier start of treatment might carry more benefits. This was suggested by a recent study, in which women received aspirin or placebo from the time of in vitro fertilization until 12 weeks of gestation. The incidence of hypertensive complications was lower in the aspirin group (3,6% vs. 26,9%, P = 0,02). However, this was not confirmed in another study in which aspirin was also started before pregnancy and the incidence of hypertensive pregnancy complications did not differ significantly between the low-dose aspirin (n = 52) and placebo (n = 52) groups (15,4% vs. 18,2%, P = 0,7) [3].

Placental dysfunction is a result of the shallow invasion of trophoblast into the placental bed spiral arteries, which leads to reduced placental perfusion and ischemia. This activates platelets and causes an imbalance of the prostacyclin-thromboxane ratio in favor of vasoconstrictive and aggregatory thromboxane. Prostacyclin is produced by endothelial cells and is vasodilatory and antiaggregatory. The dosage of 0,5–2,0 mg/kg of aspirin significantly inhibits the production of thromboxane but leaves prostacyclin production unaffected [2]. It is however of note that this process is most likely to be active in early-onset, severe preeclampsia. The investigation, performed by us and others, support the hypothesis that aspirin started early is effective in preventing preeclampsia. However, further studies are needed, especially to assess the effectiveness of aspirin on early-onset preeclampsia [3].

In conclusion, many women who develop severe preeclampsia are nulliparous with no other known clinical risk factor. To include them in a prevention trial, an early predictive marker such as markers gestational endotheliopathy (microalbuminuria and endothelium-dependent vasodilation) would be necessary. We determined that daily low-dose aspirin (75 mg/day) initiated from 11–12 weeks of gestation was associated with a significant decrease in the incidence of preeclampsia and IUGR in women, who has gestational endotheliopathy and identified to be at risk for preeclampsia.

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