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ASPIRIN AND CALCIUM AS A PREVENTIVE THERAPY OF EARLY AND LATE PREECLAMPSIA

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Annotation. *Preeclampsia and fetal growth restriction are major causes of perinatal death and handicap in survivors. Indications for aspirin during pregnancy are a matter of debate. The optimum dosage, from 75mg/day to 150mg/day, needs to be determined. The aim of the research was to estimate the impact of low-dose aspirin and calcium on prevention of preeclampsia. During the research there was conducted a prospective analysis of the effectiveness of aspirin and calcium in pregnant women with preeclampsia from VMCM hospital №1, in a period from 2016 till 2018. 88 women participated, they were divided into two investigated groups: I - 36 women with early preeclampsia (EP), and II group - 52 women with late preeclampsia (LP). In EP group 28 women were taking aspirin in dose of 75 mg, in LP - 36. Also, in EP group 12 women were taking low doses of calcium (<1g/day), and 26 in LP group (tab. 1). Main diagnostically significant indexes were determined, which later underwent comparative analysis for all groups. Statistical processing of the obtained results was performed by odds ratio, its standard error and 95% confidence interval were calculated according to Altman, 1991. We didn't define significant preventive differences in preeclampsia phenotype compared subgroups. Aspirin in dose of 75 mg/day and Calcium <1g/day is ineffective, also taking to account irregular intake - for 4-5-6 times per week. Preventive therapy requires definite period of beginning - 12 weeks of gestation and systemic everyday intake of drugs. In future, we need to explore a perfect dose of aspirin and calcium supplementation to prevent preeclampsia and hypertensive disorders in pregnancy.*
Keywords: *preventive therapy, preeclampsia, aspirin, calcium.*

Introduction

Preeclampsia is one of the most serious health problems that affect pregnant person. Preeclampsia and fetal growth restriction are major causes of perinatal death and handicap in survivors [10]. Indications for aspirin during pregnancy are a matter of debate and there is a recent trend to an extended prescription and an overuse of aspirin in pregnancy. Aspirin is efficient in secondary prevention of preeclampsia essentially in patients with a personal history of preeclampsia. The optimum dosage, from 75mg/day to 150mg/day, needs to be determined. Fetal safety data at 150mg/day are still limited. The efficacy of aspirin seems to be subject to a chronobiological effect. It is recommended to prescribe an evening or bedtime intake [3]. Since the first evidence of the obstetric efficacy of aspirin in 1985, numerous studies have tried to determine the effect of low-dose aspirin on the incidence of preeclampsia, with very controversial results. However, guidelines regarding the usage of aspirin to prevent preeclampsia differ considerably from one country to another [2]. Low-dose aspirin is more effective in reducing incidence of preeclampsia or intrauterine growth restriction if used before 16 gestational weeks than if used later [8, 13]. It favors placentation by its proangiogenic, antithrombotic, and anti-inflammatory effects. Further studies are needed to improve the identification of patients likely to benefit from prophylactic aspirin [8].

Reducing serum calcium can lead to increased blood pressure in preeclamptic women. Changes in calcium metabolism during pregnancy could be one of the potential causes of preeclampsia [1, 7].

The aim of the research was to estimate the impact of low-dose aspirin and calcium on prevention of preeclampsia.

Materials and methods

During the research there was conducted a prospective analysis of the effectiveness of aspirin and calcium in pregnant women with preeclampsia from Vinnitsya Municipal Clinical Maternity hospital №1, in a period from 2016 till 2018. Women were selected according to criteria of International Society of Hypertension, during pregnancy, which determines PE when sBP $\geq$140 mmHg and dBP $\geq$90 mmHg at two multiple measuring with interval more than 4 hours, or sBP $\geq$160 mmHg and dBP $\geq$110mmHg, at a single measuring; proteinuria or hypertension of any degree with one or more of next symptoms [5, 9]: severe head pain, paropsis, edema of disk of visual nerve, pain in epigastric area, nausea, vomiting, pain during liver palpation, increase of tendon reflexes, general edema, oliguria (<0,5ml/kg/hour), thrombocytes below 100x109/l, increase of liver enzymes (ALT and AST >70 IU/l), fetal growth restriction. 88 women participated, they were divided into two investigated groups: I - 36 women with early preeclampsia (EP), and II group - 52 women with late preeclampsia (LP). In EP group 28 women were taking aspirin in dose of 75 mg, in LP - 36. Also, in EP group 12 women were taking low doses of calcium (<1g/day), and 26 in LP group (Tab. 1). Main diagnostically significant indexes were determined, which later underwent comparative analysis for all groups. Statistical processing

Table 1. Number of pregnant women with preeclampsia, who underwent preventive therapy during pregnancy.

Name of drug	Early preeclampsia (n=36)	Late preeclampsia (n=52)
Aspirin (75 mg/day)	28 (78%)	34 (65%)
Calcium (<1g/day)	12 (33%)	26 (50%)

of the obtained results was performed by odds ratio, its standard error and 95% confidence interval were calculated according to Altman (1991).

This work was carried out within the R & D "Optimization of early diagnostics and preventive treatment of perinatal complications caused by gestational endotheliopathy" № state registration 0121U109141.

Results. Discussion

Average period of the beginning of preventive therapy in subgroup with EP was 16±3,1 weeks of gestation, in LP subgroup - 16±1,4 weeks (Tab. 2).

According to table 3, even undergoing preventive therapy the percent of women with moderate and severe preeclampsia was 78,5% and 21,5% in A1 subgroup. These results are connected to untimely (89,3% started therapy after 12 week of gestation) and irregular intake of Aspirin. Even in one case of moderate PE we have marked disorder of utero-placental circulation and highly resistant blood flow in uterus arteries, which is mostly tied to delayed preventive therapy starting week 20, 5 times per week. Average period of preventive intake of Calcium in this subgroup was 17±2,4 weeks of gestation, in dose 600-800 mg/day. In subgroup A_2 the percent of moderate PE was 88,3, but this also shows ineffectiveness of this dose of Aspirin for prophylaxis of PE. Average period of preventive intake of Calcium in this subgroup was 16±1,7 weeks of gestation, in dose 600-800 mg/day.

As we see in table 4, obstetrical consequences of PE, such as morning sickness, edema, reverse blood blow and others, differ in subgroups, but to our opinion this is connected to different phenotypes of preeclampsia, not to preventive effect of drugs in this groups.

Severe neonatal consequences, such as distress and intrauterine fetal growth restriction, are traditionally worse in subgroup with early preeclampsia, even with aspirin intake. In LP subgroup we have marked high percent of big fetus and decreased blood flow in MUA, which indicates ineffectiveness of preventive dose starting from week 14 of gestation (Tab. 5).

We compared our results to a multicenter, double-blind, placebo-controlled trial, that randomly assigned 1776 women with singleton pregnancies who were at high risk for preterm preeclampsia to receive aspirin, at a dose of 150 mg per day, or placebo from 11 to 14 weeks of gestation until 36 weeks of gestation. Treatment in this trial with low-dose aspirin in women at high risk for preterm preeclampsia resulted in a lower incidence of this diagnosis than placebo, but there were no significant between-group differences in the incidence of neonatal adverse outcomes or other adverse events [11].

Also, USPSTF concludes with moderate certainty that there is a substantial net benefit of daily low-dose aspirin use to reduce the risk for preeclampsia, preterm birth, small for gestational age/intrauterine growth restriction, and perinatal mortality in pregnant persons at high risk for preeclampsia. The USPSTF recommends the use of low-dose aspirin (81 mg/d) as preventive medication for preeclampsia after 12 weeks of gestation in persons who are at high risk for preeclampsia [4].

In meta-analysis of 1,609 articles, 23 randomized trials,

Table 2. The beginning of aspirin intake in subgroups.

Period (weeks of pregnancy)	EP (n_{a1}=28)	LP (n_{a2}=34)
10-12 weeks	3 (10,7%)	-
12-14 weeks	1 (2,8%)	-
14-16 weeks	6 (21,4%)	9 (26,5%)
16-18 weeks	8 (28,6%)	15 (44,1%)
18-20 weeks	3 (10,7%)	10 (29,4%)
>20 weeks	7 (25%)	-

Table 3. Severity of PE in subgroups with preventive therapy.

	EP (n_{a1}=28)		LP (n_{a2}=34)	
Severity of PE	Moderate	Severe	Moderate	Severe
	22 (78,5%)	6 (21,5%)	30 (88,3%)	4 (11,7%)

Table 4. Obstetrical complications of PE in subgroups with preventive therapy.

Name of pathology	EP (n_{a1}=28)	LP (n_{a2}=34)
Primipara	21 (75%)	23 (67,6%)
Morning sickness	3 (10,7%)	1 (2,9%)
Edema	8 (28,6%)	5 (14,7%)
Polyhydramnion	2 (7,1%)	1 (2,9%)
Olygohydramnion	9 (32,1%)	-
↓FPC	6 (21,4%)	2(5,8%)
↓UPC	-	1 (2,9%)
Reverse blood flow	1 (2,8%)	-
Highly resistive blood flow	1 (2,8%)	-
C-section	15 (53,6%)	13 (38,2%)
Blood loss >0,5%	11 (39,2%)	14 (41,2%)

Table 5. Neonatal complications of PE in subgroups with preventive therapy.

Name of condition	Підгрупа РП (n_{a1}=28)	Підгрупа ПП (n_{a2}=34)
Big fetus	3 (10,7%)	3(8,8%)
↓blood flow in MUA	3 (10,7%)	2 (5,9%)
Distress	3 (10,7%)	1 (3,4%)
UFGR	1 (2,8%)	-
Low weight fetus	4 (14,3%)	1 (3,4%)
Low marks according to Apgar	5 (17,9%)	3 (8,8%)
Neonatal jaundice	1 (2,8%)	-

which included 32,370 women, fulfilled the inclusion criteria. In preterm preeclampsia, women assigned at random to 150 mg experienced a significant 62% reduction in risk of preterm preeclampsia (RR=0.38; 95% CI: 0.20-0.72; p=0.011). Aspirin doses <150 mg produced no significant reductions. The number needed to treat with 150 mg of aspirin was 39 (95% CI: 23-100). There was a maximum 30% reduction in risk of all gestational age preeclampsia at all aspirin doses [14].

When speaking about calcium supplements we've made an overlook of articles which included 27 studies, with 28 492 pregnant women were included. The results showed calcium supplement was associated with lower incidence of preeclampsia (RR 0.51, 95% CI: 0.40 to 0.64) and gestational hypertension (RR 0.70, 95% CI: 0.60 to 0.82). Sub-analyses revealed high-dose (1.2-2 g/day), moderate-dose (0.6-1.2 g/day), and low-dose (<0.6 g/day) of calcium supplement could reduce the risk of preeclampsia. For gestational hypertension, only high dose and moderate dose groups were associated with reducing the risk of gestational hypertension [7, 12]. Another placebo-controlled trial conducted between July 12, 2011, and Sept 8, 2016, in South Africa, Zimbabwe, and Argentina of calcium supplementation that commenced before pregnancy until 20 weeks' gestation, compared with placebo, also did not show a significant reduction in recurrent pre-eclampsia [6].

Conclusions and perspectives for further developments

1. We didn't define significant preventive differences in preeclampsia phenotype compared subgroups.

2. Aspirin in dose of 75 mg/day and Calcium <1g/day is ineffective, also taking to account irregular intake - for 4-5-6 times per week.

3. Preventive therapy requires definite period of beginning - 12 weeks of gestation and systemic everyday intake of drugs.

In future, we need to explore a perfect dose of aspirin and calcium supplementation to prevent preeclampsia and hypertensive disorders in pregnancy.

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АСПІРИН ТА КАЛЬЦІЙ ЯК ПРЕВЕНТИВНА ТЕРАПІЯ У ЖІНОК З РАННЬОЮ ТА ПІЗНЬОЮ ПРЕЕКЛАМПСІЄЮ

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Анотація. *Прееклампсія та затримка внутрішньоутробного розвитку є основними причинами перинатальної смерті та інвалідності у тих, хто вижив. Покази до прийому аспірину під час вагітності основна із причин дебатів на сьогодні. Має*

бути визначена оптимальна доза, що варіюється від 75 до 150 мг/добу. Метою дослідження було оцінити вплив низьких доз аспірину та кальцію на профілактику прееклампсії. Під час дослідження було проведено проспективний аналіз ефективності профілактичного прийому аспірину та кальцію серед 88 вагітних з прееклампсією, на базі КНП ВМК ПБ №1, в період з 2016 по 2018 роки. Жінок було розділено на дві досліджувані групи: I - 36 жінок з ранньою прееклампсією (РП), II група - 52 жінки з пізньою прееклампсією (ПП); з яких у першій підгрупі 28 жінок та 34 - у другій, отримували аспірин в дозі 75 мг починаючи з 12-14 тижня вагітності. Також у групі РП - 12 та у групі ПП - 26 жінок отримували кальцій в низьких дозах (<1 г/добу). Було визначено основні діагностично значущі показники та проведено порівняльний аналіз у кожній групі. Під час статистичної обробки даних вираховували вірогідність шансів, його стандартну похибку та 95% довірчий інтервал, відповідно до Altman (1991). Значущих превентивних відмінностей для фенотипів прееклампсії в досліджуваних групах нами не було визначено. Аспірин у дозі 75 мг/добу та кальцій у дозі до 1г/добу, враховуючи нерегулярність прийому (4-5-6 раз на тиждень), не залежно від фенотипу прееклампсії, профілактичної дії не чинять. Превентивна терапія прееклампсії потребує чіткого терміну початку (до 12 тижнів) та систематичного прийому препаратів (щоденно). У майбутньому необхідно визначити ідеальну дозу аспірину та добавок кальцію для профілактики прееклампсії та гіпертензивних розладів під час вагітності.

Ключові слова: *превентивна терапія, прееклампсія, аспірин, кальцій.*