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Commentary

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Are antihypertensives pro or con for pathophysiology of preeclampsia?

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Preeclampsia is an important cause of severe morbidity, long-term disability and death among both mothers and their babies. Recently oral antihypertensives- methyldopa, nifedipine, and labetalol- are recommended for treating severe preeclampsia patients [1]. This study showed a multicenter, parallel-group, open-label, and randomized controlled trial in 894 severe preeclampsia patients that compared the effects on the reduction of blood pressure among nifedipine, labetalol and methyldopa. All the oral antihypertensives reduced blood pressure in most patients. As a single drug, nifedipine resulted in a greater frequency of the blood pressure improvement than labetalol or methyldopa. However, intensive care unit admissions were significantly more frequent in the nifedipine treatment. In WHO recommendations for prevention and treatment of preeclampsia and eclampsia in 2011, the lack of benefits with the use of antihypertensives over placebo was consistent for critical outcomes of preeclampsia across various hypertensive disorders in pregnancy [2]. The real-world implications and worldwide generalizability of these studies [1,3] are where we must pursue the mechanism of this disease. Obstetricians understand that the ultimate treatment is the interruption of pregnancy: intra-uterine fetal death or early delivery irrespective of gestational age. The background of preeclampsia is the surviving fetus in utero itself. It is well known that fetal blood pressure is low, between 40 and 50 mmHg. Feto-placental circulation is composed of fetus and placenta. Placental circulation is 40% to 50% of this circulation at late pregnancy, and the exchange of fetal vital substances such as oxygen and wastes between fetus and mother occurs under very low blood pressure (about 10 mmHg) at the capillary of the umbilical artery in the chorionic villi which is floating in maternal blood. The capillary is bordered with syncytial cells and directly contacted with maternal blood. The sufficient supply of maternal blood into this space is essential for survival of fetus [4].

Concentration of highly vasoactive hormones such as vasopressin and angiotensin II in the feto-placental circulation is higher than that in maternal circulation. Devane and Porter reported that increased amniotic vasopressin levels indicated fetal acidosis [5]. Vasopressin constricts not only arterioles, which increases peripheral vascular resistance, but also is uterotonic. Broughton Pipkin & Symonds reported a significant difference in angiotensin II concentrations between umbilical venous and arterial blood during preeclampsia, suggesting increased angiotensin II release from the stressed and hypoxemic fetus [6]. These observations indicate that vasoconstrictive hormones are elevated in the feto-placental circulation in preeclampsia. It is thus reasonable to speculate that fetus makes effort to keep the exchange of fetal vital substances via maternal blood, which is decreased due to uterine artery constriction in preeclampsia. Importantly, while fetus in preeclampsia makes effort to increase its blood pressure, antihypertensive treatment results in the decreased blood pressure in both feto-placental and maternal circulation.

Since the increased fetal vasoconstrictive hormones are highly biologically active, the leak of these hormones into the maternal circulation is strictly regulated by placental aminopeptidases in order to maintain maternal blood pressure and to keep uterine tonus under control. Placental leucine aminopeptidase (P-LAP) is responsible for degradation of vasopressin and oxytocin [7], while placental aminopeptidase A is responsible for degradation of angiotensin II [8]. In normal pregnancy, these enzyme levels in maternal blood increase with advancement, whereas these enzyme levels in mild preeclampsia increase much higher than in normal pregnancy with advancing gestation. However, in severe preeclampsia these enzyme activities decrease with advancing gestation and fell to very low levels accompanied with approaching fetal jeopardy [9].

In 1940, Smith & Smith reported a favorable outcome of the treatment during 1 week by using estradiol benzoate accompanied with progesterone in severe preeclampsia without any antihypertensives. Taken a hint from Smith's case reports, a modified sex steroids treatment was performed in severe preeclampsia on a dose increase by gestational week method without any antihypertensives by measuring maternal blood P-LAP levels [10,11], because P-LAP is regulated by estradiol and progesterone. Owing to alleviation of clinical symptoms, prolongation of gestation at least for 3 weeks was witnessed, and the treatment was proved successful.

Growing out antihypertensive treatment for preeclampsia should be further evaluated [9], since antihypertensives might be thus burden of fetal well-being. The sex steroid treatment for severe preeclampsia could be candidates replacing antihypertensive treatment [10,11].

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