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COMMENTARY

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Hypertension in pregnancy: Role of body mass index, insulin resistance, aldosterone, and calcium homeostasis

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In a recent study, Zhuang and coll.[1] have reported that body mass index (BMI) and calcium supplementation during pregnancy play an important role in the development of pregnancy-induced hypertension (PIH) in a large cohort of Chinese women. In particular, the authors reported that overweight and obese women before pregnancy had an increased prevalence of PIH, delivery before 34 gestational weeks, and other obstetric outcomes of PIH. On the contrary, calcium supplementation (about 600 mg per day) during pregnancy was associated with a significant reduction in PIH and other adverse pregnancy-related outcomes. The authors suggested that the reduction in BMI prior pregnancy and the supplementation of calcium during pregnancy could be useful to prevent the risk of hypertension and of its related complications.

Several studies have reported that pre-existing maternal hypertension and increased BMI are strongly associated with negative maternal and fetal outcomes.[2] These conditions increase the onset of gestational diabetes, PIH, and preeclampsia, leading to an increased risk of later-life cardiovascular and metabolic disorders.[3] One of the main factors involved in the pathogenesis of all these disorders is insulin resistance. This is a complex pathological condition characterized by an inappropriate sensitivity to insulin hormone in insulin-dependent tissues, due to different and not completely known mechanisms, including oxidative stress, inflammation, insulin receptor mutations, postreceptor defects, and mitochondrial dysfunction.[4] Insulin resistance plays a key role in the pathogenesis of many metabolic disorders, such as type 2 diabetes mellitus, metabolic syndrome, and polycystic ovary syndrome (PCOS). In particular, insulin resistance is often present even in lean PCOS patients[5] and is involved in the increased risk of PCOS women for developing gestational diabetes mellitus, PIH, preeclampsia, and other obstetrics and cardiovascular events during pregnancy compared with healthy controls.[2]

For all these reasons, the treatment of insulin resistance must be considered in all women, especially with PCOS or metabolic syndrome, to prevent or reduce the possible related complications. Metformin is one of the most widely used treatments for type 2 diabetes and other comorbidities associated with insulin resistance. It has been shown to improve ovary function and fertility outcomes in women with PCOS and insulin resistance even underwent to assisted reproductive technologies (ART).[6] Even if its use is safe, the exposure of metformin in pregnancy has still not been elucidated. Recent evidence reported inositol as an effective insulin sensitizer that can be used before and during pregnancy, improving not only the metabolic profile, but also the ovulatory functions[7] and preventing the onset of gestational diabetes.[8]

The treatment with adequate diet and insulin sensitizers and the reduction in BMI within normal range must be considered in all women, especially if seeking pregnancy, to prevent the complications related with the pregnancy and their future metabolic and cardiovascular risk.

Preeclampsia is the most severe form of hypertension in pregnancy. It is promoted by genetic and epigenetic factors, and as already reported, it is frequently associated with overweight, PCOS, uterine fibroids, endometriosis, and metabolic syndrome. Beyond insulin resistance, aldosterone has been proposed to play a role in its pathogenesis.[9] During pregnancy, the renin-angiotensin-aldosterone system (RAAS) is activated to maintain the salt and water balance both in the mother and in the placenta, even through the presence of placental 11beta-hydroxysteroid dehydrogenase type 2 (HSD2) enzyme. In a previous study, we evaluated the differences in the mineralocorticoid effector mechanisms in the etiology of preeclampsia.[10] We have measured the subtraction potential difference between rectal mucosa and oral, showing a hyperfunction

of aldosterone only in preeclampsia while in the normal pregnancy the potential difference was normal notwithstanding the high values of aldosterone. These results suggested that in normal pregnancy, some placenta factors blunt the biological function of aldosterone, not inducing hypertension or hypokalemia, while this effect is lacking in preeclampsia. We previously reported that the number of mineralocorticoid receptor (MR) in the mononuclear leukocytes (MNL) is low in primary aldosteronism and this down-regulation is involved in the escape of the kidney to the action of aldosterone[11] and this mechanism could also characterize the etiopathogenesis of preeclampsia. Inflammation starts in MNL and macrophages and, as reported in a previous study incubating MNL with aldosterone, it is blocked by coincubation with canrenone, a MR blocker derived from spironolactone.[12]

Aldosterone is a major factor in the genesis of many gynecological problems associated with inflammation and autoimmunity[13] A possible link between PCOS and preeclampsia is the finding of activation of RAAS in both these conditions. Aldosterone or aldosterone-to-renin ratio (ARR) is increased in PCOS[14] and other gynecological diseases, as endometriosis and uterine fibroids.[15] Actually, the most used treatment of PCOS is hormonal contraceptives (HCs) containing progestin with low or antiandrogen activity, able to block ovarian androgen secretion and resume menstrual abnormalities. However, data are conflicting about their effects on insulin resistance, BMI, and further complications. A possible alternative treatment is the association of spironolactone to enhance the antiandrogen effects and to reduce some risks related to HCs, such as the activation of RAAS with water retention and hypertension, the systemic inflammation, and the future metabolic and cardiovascular risk.[16] If spironolactone is not associated with HCs, barrier contraceptives are necessary during the treatment given the potential fetal toxicity of its antiandrogen action; canrenone and potassium canrenoate have a weak antiandrogen activity, but that can still disturb the sexual development of a male fetus; only eplerenone is devoid of antiandrogen activity, but isolate reports about its use in pregnancy are reported, requiring further studies.[17] Recently, the presence of autoantibodies stimulating the angiotensin II type 1 receptor has been reported in preeclampsia[18] and in primary aldosteronism, supporting the role of RAAS in the pathogenesis of these conditions([19]).

Another interesting finding of the study of Zhuang and coll.[1] was the protective effect of calcium supplementation for the risk of PIH. Calcium is essential for bone mineralization and for signaling and regulation of cell function. Its levels are regulated by dietary intake, renal excretion, and vitamin D values. However, calcium intake and vitamin D status are frequently reduced in the population, especially in the elderly and in pregnant women. In particular, in these patients, the alterations of calcium balance can cause osteopenia and different symptoms such as numbness, tremors, and muscle cramps in the mother and contribute to delayed growth and poor mineralization in the fetus.[20] Moreover, recent evidence suggests that women with low calcium intake show a higher risk of developing PIH and preeclampsia.[21] In fact, women with preeclampsia have reduced serum levels of calcium and magnesium compared with normal pregnant women.[22] Reduced serum levels of calcium increase the release of parathyroid hormone (PTH) and renin, which in turn cause increase in intracellular calcium in vascular smooth muscle, inducing vasoconstriction and increasing blood pressure values.[23] Vitamin D deficiency has been associated with hypertensive disorders of pregnancy,[24] and this could be related not only to the secondary increase in PTH but also to its pleiotropic effects. Magnesium is also involved in calcium homeostasis, acting as a calcium channel blocker, and its deficiency during pregnancy can induce maternal and fetal outcomes and preeclampsia.

The study of Zhuang[1] supports a protective role of calcium supplementation for preeclampsia and PIH that could be related to the increased need of calcium during pregnancy due to physiological adaptations of this particular situation.

However, results are still conflicting and further studies are necessary to clarify the role of calcium in the development and prevention of PIH.

CONFLICT OF INTEREST

The authors report no conflicts of interests.

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