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Primary aldosteronism and pregnancy

Hyperaldostéronisme primaire et grossesse

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Abstract

Hypertension (HT) is a complication of 8% of all pregnancies and 10% of HT cases are due to primary aldosteronism (PA). There is very little data on PA and pregnancy. Given the changes in the renin angiotensin system during pregnancy, the diagnosis of PA is difficult to establish during gestation. It may be suspected in hypertensive patients with hypokalemia. A comprehensive literature review identified reports covering 40 pregnancies in patients suffering from PA. Analysis of these cases shows them to be high-risk pregnancies leading to maternal and fetal complications. Pregnancy must be programmed, and if the patient has a unilateral form of PA, adrenalectomy should be performed prior to conception. It is customary to stop spironolactone prior to conception and introduce antihypertensive drugs that present no risk of teratogenicity. When conventional antihypertensive drugs used during pregnancy fail to control high blood pressure, diuretics, including potassium-sparing diuretics may be prescribed. Adrenalectomy can be considered during the second trimester of pregnancy exclusively in cases of refractory hypertension. A European retrospective study is currently underway to collect a larger number of cases.

Keywords: Pregnancy; Primary aldosteronism preeclampsia; Spironolactone

Résumé

Huit pour cent des grossesses se compliquent d'hypertension artérielle (HTA) et 10 % des HTA sont dues à un hyperaldostéronisme primaire (HAP). Il y a très peu de données sur l'HAP et la grossesse. Au vu des modifications du système rénine angiotensine pendant la grossesse, le diagnostic d'HAP est difficile à établir en per gestationnel. Il peut être suspecté devant une hypokaliémie. Une revue exhaustive de la littérature a permis d'identifier 40 grossesses chez des patientes atteintes d'hyperaldostéronisme primaire. L'analyse de ces cas rapportés dans la littérature montre qu'il s'agit de grossesses à haut risque conduisant à des complications maternelles et fœtales. La grossesse doit être programmée et si la patiente a une forme unilatérale, la surrénalectomie doit être réalisée en préconceptionnel. Il est recommandé d'arrêter la spironolactone en préconceptionnel et d'introduire des antihypertenseurs ne présentant pas de risque de tératogénicité. Cependant, lorsque les antihypertenseur usuels ne permettent pas de contrôler l'hypertension artérielle, les diurétiques, y compris les diurétiques épargneurs de potassium peuvent être prescrits. La surrénalectomie peut être envisager au second trimestre de la grossesse en cas d'HTA réfractaire. Une étude rétrospective européenne est actuellement en cours afin de colliger un nombre plus important de cas.

Mots clés : Grossesse ; Hyperaldostéronisme primaire ; Préclampsie ; Spironolactone

1. Introduction

Primary aldosteronism (PA) is a form of hypertension caused by over-secretion of aldosterone by the adrenals. It was described for the first time by Jerome Conn in 1955 [1]. PA is currently the leading cause of secondary hypertension, with an estimated prevalence of ∼ 10% of all hypertensive patients [2–5].

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Guidelines have been published for the diagnosis and management of PA [6]. However, during pregnancy, physiological changes of the renin angiotensin aldosterone system make diagnosis more difficult. The issue of hypertension management during pregnancy in patients with a diagnosis of PA arises regularly. While there are guidelines for the management of hypertension during pregnancy, there are no specific guidelines for pregnant patients with PA. Analysis of the literature can provide some elements to guide the management of PA during pregnancy.

2. Physiology of the renin angiotensin system during pregnancy and diagnostic difficulties

During pregnancy, all components of the renin angiotensin system (RAS) are stimulated [7,8]. In addition, a local RAS is set up in both the placenta and the ovaries, and the different genes of the RAS are expressed in the human fetus in the fifth week after conception [9].

2.1. Role of estrogen

Estrogen during pregnancy stimulates the hepatic synthesis of angiotensinogen, the precursor of angiotensin I. In addition, estrogen and progesterone increase the secretion of renin and angiotensin-converting enzyme [10]. This leads to an increase of angiotensin II secretion, which stimulates the glomerulosa zone and increases aldosterone levels.

2.2. Renin

During pregnancy, two sources of renin should be considered: uterus and kidney. The factors that regulate renin production by the uterus are unknown [11]. Renin activity increases during pregnancy (four-fold at 10 weeks gestational age [wGA], reaching a plateau at 22 wGA). It is estimated that half of the increase of renin activity is explained by the increased rate of angiotensinogen synthesis. Prorenin is produced by the uterus, ovaries, and placenta (circulating levels increase fivefold during the first four weeks of pregnancy). The physiological role for the elevation of prorenin is not known, as there is no evidence that it is converted into renin in the vessels. The fetal kidney is the primary source of renin in the fetus and the concentration of renin in the cord blood is higher than in the newborn at term, and also higher than in maternal blood [12,13].

2.3. Angiotensin II

The level of angiotensin II increases three fold during pregnancy. Concurrent with the increase of angiotensin II levels is the development of resistance to its vasopressor effect (more angiotensin II is required to obtain the same increase in blood pressure), starting at 12 wGA and reaching its maximum at 30 wGA. This resistance decreases after 32 wGA but does not return to the levels of non-pregnant women until term. Increased production of prostaglandin E2 and progesterone contribute to this resistance.

2.4. Aldosterone and its physiological effects during pregnancy

Aldosterone levels increase during pregnancy and can reach concentration levels 10-fold higher than baseline by the end of pregnancy. This increase is due to the rise of renin and angiotensin levels. Aldosterone production remains sensitive to physiological stimuli (such as changes in intravascular volume) but less so than outside of pregnancy. The decrease in sodium excretion mediated by aldosterone in the standing position is greater during pregnancy. Progesterone levels are positively correlated with the levels of aldosterone. Progesterone is a competitive inhibitor of aldosterone in the distal convoluted tubule. The physiological effects of increased aldosterone are thus attenuated during pregnancy [14]. Aldosterone, the final step of the cascade, leads to fluid overload and increased cardiac output. Hypervolemia starts during the first quarter of pregnancy. These physiological changes are necessary to obtain good placental perfusion [15]. Despite the marked increase in blood volume, pregnant women are usually normotensive, because of the antagonizing effect of progesterone on the mineralocorticoid receptor and peripheral vasodilation [16]. Another possible explanation is the resistance to the pressor effect of angiotensin II in the maternal vessels. Prostaglandin or a prostaglandin-like substance appears to mediate this process as inhibitors of prostaglandin synthase (for example, indomethacin or aspirin) restore the response to angiotensin II. The contribution of the resistance to angiotensin II in pregnancies of bilateral adrenal hyperplasia patients appears to be variable [10]. During normal pregnancy, there is no hypokalemia despite the increase in the concentration of aldosterone [17].

2.5. Mineralocorticoid precursors

The primary source of increased mineralocorticoid activity comes from the increase in the production of deoxycorticosterone (DOC). During pregnancy, DOC is mostly produced from progesterone from outside adrenal source [18]. There is also an increase of the protein carrier which complicates the interpretation of DOC and cortisol measurements.

2.6. Diagnosis of PA during pregnancy

The diagnosis of PA during pregnancy is difficult to establish due to the physiological changes of the RAS. Additionally, hypertension, is a common complication of pregnancy (6 to 8% of pregnant women). The percentage of PA in pregnant women is difficult to estimate. Taking into account the 10% prevalence of PA in patients with hypertension, one can speculate that 0.6 to 0.8% of all pregnant women suffer from PA.

3. Antihypertensive medications and pregnancy

During pregnancy, the primary goal of antihypertensive therapy is the prevention of acute complications such as