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Literature overview regarding fertility, pregnancy, and neonatal outcome in patients with polycystic ovary syndrome

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ABSTRACT

Polycystic ovary syndrome (POCS) is the most common endocrine disorder and affects women in each stage of their life, lowering the quality of life and lifespan. After they overcome infertility and succed to conceive, they will not be exposed just at severe obstetrical outcomes such as miscarriage, preterm birth, gestational diabetes, gestational hypertension, but at poor neonatal outcome as well such as increased perinatal mortality, congenital anomalies, extended stays in neonatal intensive care unit (NICU), low Apgar score, macrosomia, and growth restriction. Also, the children born from mothers with polycystic ovary syndrome, during childhood and adolescence will have a decreased quality of life, being forced to experince multiple episodes of hospitalisation, metabolic disorders, and asthma.

The porpose of this article is to make a literature review, in order to obtain a clearer picture over the impact of the POCS on fertility, pregnancy, and neonate. The analysis was limited to articles written in English and published between October 2014 and August 2021 on PubMed, NCBI and medical journals.

In conclusion this article aims to present the importance of an apparent inoffensive endocrine disorder, which generates high risk pregnancys, with poor obstetrical and neonatal outcome.

Keywords: infertility, hyperandrogenemia, miscarriage, insulin resistance, gestational diabetes, gestational hypertension

INTRODUCTION

First described in 1935 by Stein and Leventhal, polycystic ovary syndrome (POCS) is the most common endocrine condition in reproductive aged women causing infertility (1,2). PCOS affects fertility and reproduction at many levels, starting with anovulatory infertility, and continuing with many serious pregnancy adverse outcomes such as gestational diabetes, gestational hypertension, preterm birth but early pregnancy loss also. Regarding the neonates, those born from mothers with PCOS, are at higher risk of developing macrosomia, meconium aspiration, or to receive low Apar score at birth (3,4). All the things mentiond above will be further detailed.

MATERIALS AND METHODS

PubMed, NCBI and medical journals were searched for studies written in English that analyzed the impact of POCS over the women's fertility and pregnancy and neonatal outcome. The studies have been published between October 2014 and August 2021.

The publications were selected taking in account the year of publication and the novelty they came with. The keywords used were: infertility, hyperan-

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drogenemia, miscarriage, insulin resistance, gestational diabetes, gestational hypertension.

DEFINITION AND EPIDEMIOLOGY

Regarding the definition, although they are older than 10 years and not consented by all, Rotterdam criteria are most frequently used (2). The criteria are: chronic anovulation (more than 35 days between periods), hyperandrogenism and ultrasound changes in both ovaries such as multiple small follicules (12 or more, with diameters between 2-9 mm) or increased ovarian volume (over 10cm³) (3-5). The frequency of PCOS is evaluated as being 12-20% from reproductive aged women. The affected ones will present signs and sympthoms of hyperandrogenism, irregular menstruations and infertility; obesity, is also present in 50-80% of patients (3,5). Many women present signs of glucose intolerance and insulin resistance, with a prevalence of 30-35% in the U.S. which are the promotors of type II diabetes. Cases of type II diabetes mellitus were reported in 8 to 10% of women with POCS (3,6).

HYPERANDROGENISM AND INSULIN RESISTANCE

POCS is a disease which affects women in a reproductive, hormonal, metabolic, and psychological way. Insulin resistance and hyperandrogenism are the fundamental pathophysiologic mechanisms, but the chronic inflammation generated by the syndrome itself, isn't neglectable (7). The abdominal obesity is an important contributer in the process via adipocytokynes (8). In women with POCS the adipocite is hypertrophied, and also contains a higher concentration of inflammatory markers especially high-sensitive C-reactive protein (hs-CRP), IL6, TNF-α and adipokines like adiponectin, visfatin and omentin. This kind of adipocites is more sensitive, and more predisposed to undergo apoptosis. This is how the pathonenesis circle stars, the inflammatory markers released during apoptosis trigger an inflammatory cascade which will induce insulin resistance and hyperandrogenism. Also, the rised androgen levels will determinine adypocite hypertrophy (7). Biocheminal speaking, it seems that the insulin resistance is generated by the drop of insulin receptor-β subunit which is located in the visceral adipose tissue cells (8). Regarding hyperandrogenemia, the androgens involved are testosterone, dihydrotestosterone (DHT), androstenedione (A4), dihydroepiandrosterone sulfate (DHEAS), as well as 3β-hydroxysteroid dehydrogenase (3β-HSD), the enzyme responsible for pro-androgens conversion to bioactive androgens (8,9). Lately have been discovered some new species of androgens such as 11-ketotestosterone and 11-keto dihydrotestosterone (11-oxygenated C19 steroids), the last being considered the most bioactive androgen in women with POCS.

In which concerns the sources of androgens, these are: ovarian theca cells, adrenal cortex, abdominal subcutaneous adipose store, and other extra ovarian sources (10). These steroids have a stimulating effect on the ovarian thecal cells, which determines ovary sensitization to LH stimulus, and in the end androgens hyperprouduction. Both, androgens and insulin, reduce sex hormone binding globulin (SHBG) production, increasing thereby free circulating androgens, and worsening their clinical effects (11).

POLYCYSTIC OVARY SYNDROME – OBESITY – AMENORHEEA – INFERTILITY

Inferitility is defined as the inability of procreate after twelve months or more of spontaneous conception. According to WHO this affliction affects approximately 50-80 millions of women (12).

POCS is one of the major infertility causes (13). As we discussed above insulin resistance and hyperinsulineamia plays a significant role in the pathogenesis of this affection characterisezd by oligomenoeehea and hyperandrogenism (14). It has to be mentioned that insulin resistance appears only in certain tissues, more precisely in fat tissue and skeletal-muscle. Hyperinsulinemia has a promotor effect over the ovary and adrenal glands, leading to greater steroid synthesis. These biochemical changes will manifest through follicular arrest and anovulation (12). The increased level of androgens, on the other hand, determines the storage of visceral adiposity, which together with obesity will highten insulin resistance and hyperinsulinemia (14). Obesity has a major role in infertility through the adipocyte capacity of aromatization androgens to estrogens, estradiol to estrone and dehydroepiandrosterone to androstenediol (13) determining a hyperestrogenic enviorment which will exert a negative feedback on the hypothalamic – pituitary – ovarian (HPO) axis (14).

Also, in POCS patients, the LH secretion is characterized by an elevated pulse frequency and amplitude but, with a declined degree (15). In addition it has been noticed a gucotoxic effect on the hypothalamic neurons, which will lessen the LH response to GnRH stimulus. Furthermore, the metabolic products of the glucose will accumulate in the ovary, affecting the gonad as well (14).

In conclusion one of the POCS induced infertility mechanism is that the steroid storage is greater in obese women, most of the sex hormones having greater affinity for the adipocyte than for blood

stream. The second presumed mechanism is the signalization via adipokines like leptin, adiponectin and resistin. These molecules are produced by the adipocyte and have the ability to block ovulation (13).

RESTORING FERTILITY IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

Looking at the metabolic consequences of obesity, it appears appropriate that first step in the management of infertility to be considered lifestyle change (16,19). Lifestyle change reffers especially to weight loss, the recommendations in this direction being to obtain an energy deficit of 30% and physical activity minimum of 150 minutes per week, during a period of 3-6 months (18,19). It seems that a weight reduction with approximately 10% improves menstrual cycle in 80% and increases the chances to spontaneously conceive with 29%. Bariatric surgery is another therapy option, the eligible candidates are patiens with a BMI> 40 kg/m². It has to be mentioned that pacients who undergone bariatric surgery will have high-risk pregnancys and will need a carefull and closer monitoring (18).

Others steps in infertility management are pharmacotherapy, surgery and assisted reproductive technologies (ART) (17,19). Metformin is a drug used in the treatment of diabetus mellitus. The drug has the role of decrease insulin resistance and in concequence to restore the balance between circulating androgens concentration and SHBG synthesis. Furthermore, it has insulin sensitizing effect not only on the ovary and fat tissue but on the liver, skeletal muscle and endothelium too. It was observed that patients treated with Metformin had a lower abortion rate. Despite all its positive effects, it has been noticed that Metformin is more effective in the treatment of adolescents with POCS than in adult ones (16).

In fact, in adult ones the first choice treatment is clomiphen citrate. The drug acts by blocking the hypothalamic estrogen receptor sites, which will lead to an augumented secretion of GnRH, and implicit an increase of FSH, LH secretion, follicular growth and ovulation (16,18). Clomiphene citrate is associated with a rise of conception rate per cycle with 22% and until now no teratogenic effects have been noticed after the administration (18).

With an efficacy comparable with that of clomiphen citrate, but with more side effects, Letrozole is an aromatase inhibitor, which reduces ovarian estradiol production. Although the drug is considerd a line 2 ovulation inductor, it has proven its effectiveness even when clomiphen citrate didn't (18,19). Gonadotrophin therapy is also used as an ovulation inductor in POCS patients. This method requires a close follow-up of follicles, in order to prevent multiple pregnancy and ovarian hyperstimulation syndrome (OHSS) (18).

Patients with POCS who fail to respond to pharmacological therapy are candidates for assisted reproductive technologies (ART) ten times more comparing with those without of PCOS. These techniques are IVF, ICSI and *in vitro* maturation (17,19).

Regarding the surgical techniques, laparoscopic ovarian drilling is another treatment option for women who didn't respond at pharmacological treatment. The techniqe consists in ovary theca perforation in 5-10 elective points with the porpose to destroy the androgen secretory tissue, in order to restore the hormonal balance (19).

Besides the options mentioned above are also worth to be mentioned vitamin D, inositol and minerals administration (18,19).

MISCARRIAGE AND PRETERM BIRTH

The connection between POCS and miscarriage has been studied and debated for many years in specialty literature (20).

According with recent studies it's known that patients who were diagnosed before pregnancy with POCS will have an increased risk of miscarriage comparing with those without this diagnosis. One of the possible mechanisms could be the association between PCOS and autoimmune and genetic disorders but also decreased circulating progesterone and estradiol levels in these patients (5,20). Another presumed mechanism involves the following: disruption of hypothalamic-pituitary-ovarian axis, diminished oocyte quality, deficiency of the endometrial decidualization, poor oocyte quality and impaired endometrial receptivity (21).

Insulin resistance and hyperinsulinemia, are independent risk factors for miscarriage. The researchers found a prevalence of 27% of insulin resistance in POCS patients who suffered miscarriages (21). Comparing with non-obese controls, it seems that obesity is strongly associated with miscarriage (20).

Despite all things, the incidence of miscarriage in POCS patients still remains unclear, especially when in some studies is described as 10%, while in another is 80% (20).

Preterm birth is another important obstetrical complication in women with PCOS. Comparing with healthy pregnant women, the POCS ones have a double risk of developing spontaneous preterm labour and delivery. It seems that the risk of very preterm birth (< 32 weeks) is higher than that of moderate preterm birth (32-36 weeks). Regarding the extremely preterm delivery (<28 weeks) the risk is three times higher in these patients (22).

GESTATIONAL HYPERTENSION AND PREECLAMPSIA

Pregnant women with POCS are at higher risk of developing gestational hypertension and preeclampsia (25).

Regarding the involvement of hyperanrogenism in the pathophisiology, it seems that women with preeclampsia have testosterone levels 1.5-2.4 fold higher comparing with control group (25).

Literature has shown that insulin resistance, one of the main pathophysiologic pathways of POCS, has a major role in the development of hypertensive disorder in pregnancy. The cells of both, artery muscle layer and endothelial layer are insulin-sensitive cells. Under the stimulus of hyperinsulinemia, nitric oxide (NO) and Prostaglandins (PG) synthesis are reduced, which will lead to an increased peripheral vascular resistance. Histologically the changes are the following: endothelial dysfunction, lumen stenosis and hypertrophy of the muscular layer. All these processes will contribute to peripheral vascular resistance and increased blood pressure (23).

According to literature, the women with POCS and without other risk factors for gestational hypertension, are 62% more likely to develop the disease comparing with non-POCS control group (24).

GESTATIONAL DIABETES

Gestational diabetes mellitus (GDM) is the most frequently reported pregnancy complication in women with PCOS. Early diagnosis and accurate treatment are the key of improving maternal and neonatal outcome (28).

According to WHO 2013 criteria, POCS patiens have a greater risk of developing gestational diabetes, with an incidence of 40% more than healthy ones (26). Most of these patients are diagnosed in the first trimester and the causative factor it's supposed to be the inadequate pancreatic β-cell response to the abnormal placental mediators on the backgroung of insulin resistance (27).

Also, Danish researchers found out that obesity is a major risk factor in what concerns the development of GDM, the non-obese ones having the same risk as the pregnant women who didn't have POCS (26). Literature reveals that pregnant patients with POCS and BMI higher than 30, had an increased incidence of GDM with stronger insulin resistance and more alterated results at fasting insulin, Homeostatic Modes Assessment for Insulin Resistance (HOMA-IR) and Homeostatic Modes Assessment for Insulin Resistance to quantify β-cell function (HOMA-β). The impaired pancreatic function was observed even before of conception (27).

MATERNAL AND NEONATAL PROGNOSIS

According to recently literature, POCS can start since intrauterine life. Factors like low birth weight or high birth weight can generate premature puberty and metabolic syndrome. These events will lead during adolescence to hyperandrogenism and anovulation (31).

Regarding the neonatal outcome, it was found that the neonates born from mothers with POCS had an increased perinatal mortality, some are due to congenital anomalies such as cardiac, neural tube, urogenital and gastrointestinal anomalies (29) (5). Also, the period they stay in Neonatal Intensive Care Unit is longer (29). Lower Apgar Score, increased anogenital distance and seborheea, macrosomia and growth restriction are some of the main neonatal complications (26,29).

The outcome can be poor after the baby goes through the neonatal period too. The researchers found out that during childhood and adolescence, these children will have a higher number of hospitalisations, and also will develop metabolic disorders and asthma (27).

Women with POCS too, are prone to develop severe conditions such as cardiac disease, and gynecologycal neoplazic diseases like endometrial, ovarian and breast cancer (30).

CONCLUSIONS

Polycystic ovary syndrome remains a controversy and complex endocrine disorder, characterised by impaired hormonal function and metabolic alterations with impact over many stages of reproductive life.

Despite women with polycystic ovary syndrome encounter difficultes regarding conceiving, these can be overcome through lifestyle change, diet, medication, assisted reproductive technology (ART) and surgical procedures.

Regarding pregnancy and the fetus, pregnancies of POCS patients are considered high risk pregnancies, these patients heaving not only a great incidence of miscarriage, gestational hypertension, gestational diabetes, preterm birth, but poor neonatal outcome also.

Insulin resistance and hyperandrogenism as the main pathophysiologic mechanisms of POCS are the leading cause of all complications mentioned above.

In conclusion, POCS is a fascinating, mysterious and complex endocrine disorder which involved not only gynecological affections, but obstetrical, neonatal, cardiological and oncological as well.

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