Chapter

Polycystic Ovary Syndrome Phenotypes and Infertility Treatment

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Abstract

The polycystic ovary syndrome (PCOS) includes different clinical, endocrine, metabolic, and morphological criteria in women of reproductive age and consequently different health risks in later life of a woman. Controversy and debates related to diagnostic criteria are constant and current worldwide. As a result of many proposals for PCOS diagnostic criteria, clinicians recognize four phenotypes of PCOS. PCOS is a frequent cause of infertility with an overall prevalence of 5–15% and counts for approximately 70% of all cases of ovulation disorders. There are many aspects of studying differences between PCO phenotypes and problems in infertility treatments. Ovulation induction is often used to treat anovulatory patients with PCOS, but many of these women fail to conceive and the next step in the treatment is assisted reproduction. The contribution of oocyte health to reproductive potential varies and largely depends on the PCOS phenotype and comorbidities associated with PCOS. Contrary to the previous one, PCOS phenotype is not significantly associated with the morphological quality of oocytes. It seems that a combination of hyperandrogenism and chronic anovulation is associated with a negative impact on the cumulative pregnancy rate in medically assisted reproduction.

Keywords: PCOS, PCOS phenotype, ART, ovulatory failure, reproductive hormone, *in vitro* maturation

1. Introduction

Management of PCOS (polycystic ovary syndrome) related to infertility, includes lifestyle changes, ovulation induction by pharmaceuticals, or assisted reproductive technology (ART) as an *in vitro* fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) and *in vitro* maturation (IVM) of the oocyte. It can be followed by a "freeze-all" procedure. PCOS patients have a higher risk of developing ovarian hyperstimulation syndrome (OHSS), a life-threatening condition, therefore ART is no favored procedure in current international guidelines.

Hyperandrogenism, anovulation, and ovarian morphology are the basic determinants in the diagnosis of the polycystic ovarian syndrome (PCOS) according to international guidelines. Given the different clinical presentations in patients, the

criteria for the diagnosis of this condition are still discussed, as well as whether the syndrome involves several different diseases with the same clinical picture, as well as discussions about what is really a clinical picture of the polycystic ovary. Therefore, different approaches in the diagnosis and treatment of patients, have been proposed for different phenotypes of PCOS. The criteria for pre-recognition of this condition have been adopted for years by various authoritative bodies at international meetings, such as the National Institute for Health (NIH), Rotterdam consensus, Androgen Excess, and PCO Society, but there has been a constant difference over the mandatory criteria for PCOS [1]. An important starting point in the diagnosis was to exclude diseases of other endocrine glands (pituitary gland, thyroid, and adrenal gland), which give a similar clinical picture and can be confused with PCOS.

Ovulation disorder in the general population of women is estimated at 15% (12–18%) [2]. Regular menstrual cycles are not the exclusive evidence of ovulation, since in some women there is a "subclinical disorder" of ovulation that is proven only by serum values of progesterone in the middle lutein phase of the cycle (21–24.d.c. which must be >5 ng/mL). In the case of PCOS, almost 80% of patients have ovulation disorder [3].

Hyperandrogenism (hyperandrogenemia) implies clinical and/or biochemical evidence of elevated serum androgens, but the incidence in the general population of women is unknown. Hirsutism, androgenic alopecia, and acne are clinical manifestations of hyperandrogenism. The intensity of hirsutism differs ethnically and geographically, and it is desirable to develop population-specific criteria for hirsutism. Almost 70% of women with hirsutism have PCOS, 40% have severely expressed acne, and only 22% have androgenic alopecia [4]. Hyperandogenemia (biochemical hyperandrogenism) is determined by free testosterone and free androgen index (FAI—free androgen index) [5]. A total of 78% of patients with PCOS have hyperandrogenism and 40% in an unselected population of patients with BMI >25 [6].

Polycystic ovary morphology (PCOM) is evaluated by ultrasound examination based on the number of antral follicles (> of 20 per ovary) and/or on the basis of total ovarian volume (> 10 mL), where the frequency of the ultrasonic probe is an extremely important parameter. Based on these international criteria, the prevalence of PCOM in the population is 12.5% [7, 8]. Ultrasonic examination of nonselective population, based only on PCOM, significantly increase the incidence of PCOS and vice versa.

Thus, on the basis of the described criteria, four PCOS phenotypes with different prevalence in the general and separate population are defined, which are as follows [5]:

- Phenotype A (hyperandrogenism, anovulation, PCOM).
- Phenotype B (hyperandrogenism, anovulation).
- Phenotype C (hyperandrogenism, PCOM), ovulatory PCOS.
- Phenotype D (anovulation, PCOM), non-hyperandrogenemic PCOS.

Compared to phenotype C and D, patients with phenotype A and B (classical phenotype) are more often obese, with hirsutism, more likely to have insulin resistance, dyslipidemia, fatty liver, and metabolic syndrome in later life. The frequency of individual phenotype differs significantly in different populations with symptoms

of PCOS and also in the general population [9]. Each of the PCOS phenotypes has its own specifics in the treatment of impaired fertility.

2. PCOS phenotype and complications of treatment with medically assisted reproduction procedures

The first line of treatment of patients with PCOS is the induction of ovulation with clomiphene citrate or letrozole. *In vitro* fertilization (IVF) procedures are indicated when this initial treatment fails or in cases where the patient's partner has severe male infertility. Patients with PCOS phenotype A have significantly more frequent resistance to clomiphene despite increasing the dose of the drug through three consecutive stimulation cycles, compared to phenotype D (non-androgenic phenotype) [10].

Gonadotropin stimulation in patients with PCOS is associated with the development of a significantly higher number of follicles in the ovaries, as well as oocytes, a significantly higher number of developed embryos and embryos in excess for cryopreservation. Ovarian stimulation in these patients lasts longer and higher doses of gonadotropin are often required, which is associated with disorders of folliculogenesis caused by hyperandrogenism. Estimating the right dose of gonadotropin is the biggest challenge in the phase of ovarian stimulation and is often insufficient. The follicles do not grow, due to hyperandrogenism, and by increasing the dose, the ovary enters in hyperstimulation, which is an extreme of the ovarian response. A newer approach to ovarian stimulation with follitropin delta, based on the patient's body mass and AMH value, proved to be the best, especially in the PCOS patient population and has a significant reduction in the risk of ovary hyperstimulation. Patients with hyperandrogenism and polycystic ovarian morphology (phenotype A and C) have the highest risk of ovary hyperstimulation [11].

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovarian stimulation, and PCOS patients have the highest risk for complications during the IVF (*in vitro* fertilization) procedure. The frequency of OHSS is from 3 to 6% of IVF cycles. Patients with antral follicles count >24, AMH concentration > 3.5 ng/mL, or estradiol concentration > 3500 pg., have a risk of developing OHSS. Clinical OHSS is recognized in three stages, and depending on the severity of symptoms, we distinguish between mild, medium severe, and severe types of hyperstimulation. Severe ovarian hyperstimulation can be a life-threatening condition, requiring hospitalization and treatment to maintain vital circulatory and pulmonary functions, and can also end with the death of a patient. Identification of patients at risk for OHSS is the basis of the strategy for the prevention of this serious iatrogenic condition and the safety of IVF procedures.

The protocol of choice for ovarian stimulation in patients with PCOS and risk for OHSS is an antagonistic protocol that can be fixed or flexible. In this stimulation, it is possible to achieve the final maturation of oocyte with GnRH (gonadotropin-releasing hormone) agonists, thereby avoiding the administration of hCG (human chorionic gonadotropin) injection, which is the basic molecule in the mechanism of development of OHSS in at-risk patients. In this way, the basic mechanism of vascular permeability and compromising circulation by leaking plasma from the vascular system into extracellular spaces are avoided. Those are signs of a more severe form of OHSS. Likewise, the stimulation cycle is abruptly "extinguished." Menstrual bleeding occurs within a few days after the application of the GnRH agonist. Harvested oocytes are fertilized by IVF/ICSI procedure and developed embryos are cryopreserved, most

often in the blastocyst stage, which represents the so-called "freeze-all" strategy that gives safety to the treatment of patients with PCOS. Embryo transfer is planned in the next cycle in which signs of hyperstimulation do not exist. Hormonal preparation of the endometrium, and ovarian stimulation, in this case, is not required.

Additional treatment of PCOS patients involves the use of various medications that have metabolic effects and that could significantly improve the treatment of these patients in IVF procedures by individualizing therapy. The fact is that within the PCOS population with the same PCOS phenotype, an individual woman may have a significantly different response to different types of treatments with respect to the unique hormonal/metabolic status associated with the PCOS phenotype as well. There is a large gap in the literature that indicates the need for new research and the need for an individual approach in the treatment of infertility of these patients.

Spontaneous abortions in patients with PCOS are more common compared to the general population and they are associated with insulin resistance, hyperandrogenism, and obesity. These conditions are very often associated with PCOS, but they are also separate risks for the spontaneous loss of pregnancy. Studies link spontaneous abortion to impaired endometrial receptivity and to more frequent embryo aneuploidy of patients with PCOS. In the Asian population of women with PCOS phenotypes who have hyperandrogenism (A, B, C types), a higher risk for spontaneous miscarriage after IVF procedures was observed than in phenotype D [12]. Impaired glucose and insulin metabolism at the endometrial level and excessive expression of androgen receptors in the endometrium are associated with a signal transduction disorder during the implantation process in patients with PCOS [13]. The causes of more frequent embryo aneuploidy in PCOS patients have not yet been clarified. There are assumptions that impaired glucose metabolism and steroidogenesis lead to DNA molecule instability [14].

3. PCOS phenotypes and the outcome of medically assisted reproduction procedures

During the stimulated IVF cycle, various indicators of quality and success of treatment are monitored. Among other things, these are the total dose of gonadotropin used for stimulation, the number of aspirated oocytes, the number of oocytes in metaphase II, the percentage of fertilization, the number of developed embryos on the 3rd day, the number of developed blastocysts on the 5th day, the number of cryopreserved embryos, the proportion of conceived pregnancies, the number of born children, etc. Since PCOS phenotypes imply hormonal and metabolic differences, the question arises whether the indicators of the course of treatment are different in patients with different PCOS phenotypes.

The results of the studies so far indicate significant differences in treatment between PCOS patients and women who do not have this syndrome and who in studies represent the usual control group. Studies most often follow PCOS patients as a single group. Different criteria for defining PCOS phenotype are associated with problems of analysis and comparison of parameters that monitor the course and outcome of the IVF procedures in different studies [15]. There are two fundamental factors that are most often analyzed and compared in patients with PCOS—hyperandrogenism and PCO morphology of the ovaries, which are clinically very important factors in decision-making during the treatment of infertility by medically assisted fertilization procedures. The role of androgens in folliculogenesis is still unclear and

there are conflicting results of studies dealing with this problem. The results of studies analyzing differences in treatment outcomes among defined PCOS phenotypes indicate a negative effect of hyperandrogenism in IVF procedures, and a higher incidence of complications later in pregnancy [16]. In patients with phenotype A and B, for every 1 pg./ml increase in free testosterone concentration, the proportion of clinically confirmed pregnancies decreases by 50–60% as well as the proportion of live births [17]. According to recent findings, the differences between PCOS phenotypes refer only to the number of good embryos for transfer, which is significantly higher in patients with hyperandrogenism and ovulation disorder, but without the typical PCO morphology of the ovaries (phenotype B). The proportion of biochemical and clinically confirmed pregnancies, as well as the number of couples with born children, do not differ significantly among phenotypically different PCOS patients [17, 18]. In addition, studies indicate that the proportion of clinically confirmed pregnancies, is significantly lower in women with PCOS phenotypes A, B and C compared to control patients [17]. The number of children born does not differ in different PCOS phenotypes. In some areas of the world, certain PCOS phenotypes have not been found at all, for example, there are no phenotypes B and C among Vietnamese women with PCOS [19]. Since the anti-Müller hormone (AMH) is often elevated in patients with PCOS, it has become a powerful factor that should have prognostic value in clinically assessing the outcome of treatment with medically assisted fertilization, however, it has been proven useful only in the group of patients with phenotype B. The proportion of clinically confirmed pregnancies and the proportion of babies born increases by 1.3 times for each 1 ng/ml serum AMH concentration increase [17].

4. PCOS phenotypes and the impact on oocytes and embryos quality

PCOS patients' oocytes quality can be associated with the hormonal and metabolic conditions, and therefore, consequently with the quality of the embryo. Poorer oocyte quality is part of the problem of subfertility in patients with PCOS. There is evidence that oocyte quality depends on PCOS phenotype and accompanying diseases and conditions that are more common in PCOS patients. Oocyte quality is defined by the morphology and morphology of associated structures, such as zona pellucida, cumulus oophorus, and corona radiata. An ovarian microenvironment in which follicles and oocytes grow and mature is exposed to multiple hormonal abnormalities in patients with PCOS. Well-known disruptive mechanisms include elevated concentrations of LH (luteinizing hormone) and FSH (follicle-stimulating hormone), impaired ratio of these hormones, elevated AMH values, impaired insulin-like growth factor secretion, and enzymes involved in the conversion of androgens to estrogens.

Hyperandrogenism interferes with the normal feedback loop between the ovaries, pituitary gland, and hypothalamus, which leads to an increased frequency of excretion of the releasing hormone for gonadotropins, and consecutively results in premature luteinization of granulose cells and abnormal maturation of the oocytes. There is also a direct effect of hyperandrogenism on the oocyte by activating its proapoptotic mechanism [20]. Hyperandogenic ovarium microenvironment interferes with the oocyte in the continuation of meiosis, promotes mitochondrial abnormalities and oxidative stress, and interferes with lipid metabolism in the oocyte [21].

High concentrations of AMH synthesized by granulosa cells, inhibit the recruitment of follicles, and therefore, the selection of follicles that will ovulate, leading to a vicious cycle of anovulation and hyperandrogenism. In addition, by blocking

the action of FSH on follicle growth and blocking the action of aromatase in charge of converting androgens synthesized in theca cells to estrogens in granulosa cells, the chronic state of hyperandrogenism is again supported. There is evidence that in patients with PCOS an increased concentration of AMH in follicular fluid exists along with oocytes of low quality. Molecular mechanisms that lead to disruption in the growth and maturation of oocytes are not known [22]. Significantly lower follicular fluid AMH levels were observed in follicles of fertilized MII oocytes than in non-fertilized non-PCOS patients [23]. Also in our non-PCOS patients with sterility and impaired fertility, gene for the AMH and androgen receptor in human cumulus cells surrounding morphologically highly graded oocytes are underexpressed [24].

Hyperinsulinemia, insulin resistance, and obesity are metabolic disorders associated with PCOS that intertwine with hormonal disorders and further worsen the conditions of oocyte microenvironments. Hyperinsulinemia reduces the synthesis of binding globulin for sex hormones (SHBG), and insulin also competes with androgens for binding sites on this carrier, which means that it promotes hyperandrogenism and all its negative effects. The direct effect of hyperinsulinemia on oocytes has been proven to disrupt the expression of genes associated with the dynamics of the division spindle and the function of centrosomes. In the case of insulin resistance, there is a change in gene expression for glucose carriers in granulose cells, and therefore, a possible decrease in energy sources for the metabolism of the oocyte itself and the processes of meiosis [25].

Based on PCOS phenotype in the population of women being treated with medically assisted reproduction procedures, no difference has been found so far in the proportion of oocytes in metaphase II, percentage of fertilization, or the evaluation of quality embryos for transfer [17, 26]. According to available data to date, patients who have a classic PCOS phenotype (A and B) associated with insulin resistance and obesity also have the highest risk for low-quality oocytes [27].

Besides poor quality oocytes, PCOS patients can have larger numbers of germinal vesicle stages – metaphase I oocyte collected from IVF, due to their elevated antral follicles count. Those are commonly maturated with unsatisfactory results. When optimized maturation procedure will serve, not only for PCOS and infertile patients but also in cancer patients for the preservation of fertility and as a more patient-friendly alternative than standard controlled ovarian stimulation. PCOS patients are not the only ones that could benefit from *in vitro* maturation (IVM) technology. IVM has numerous clinical applications. Under proper culture media additives, immature oocytes in the stage of metaphase I go to the final stage of maturation [28]. Although the IVM seems to have improved lately [29], still a success rate remains lower than traditional IVF [30]. International guidelines do not favor IVM over the other options due to lack of evidence [5] but conceived children are not endangered after IVM procedure [31]. Improving the IVM techniques can definitely increase the success of IVF/ICSI procedures in PCOS patients and lower the risk of OHSS.

5. Conclusion

The definition of phenotypes of polycystic ovarian syndrome stemmed from a diverse and complex clinical picture of this endocrine disorder. Diagnostic criteria of individual phenotype, contribute to new concepts of research into the effects of obesity, hyperandrogenism, and metabolic disorders on reproduction in humans. According to the outcomes of the treatment of infertility of patients with this disorder,

significant differences in the chances of conception compared to the population of infertile women who do not have polycystic ovary syndrome have been clearly proven. Less clear is the difference in infertility treatment outcomes between women with a defined polycystic ovarian syndrome phenotype, which is the area of new research. In cases of classical phenotype polycystic ovarian syndrome (A and B) associated with obesity and insulin resistance, negative effects of this disease on gametes and embryos are possible due to cellular process disorders related to glucose and androgen metabolism.

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Conflict of interest

Authors have no conflict of interest.

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