

Polycystic Ovary Syndrome

Novel Insights into Causes and Therapy.

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Infertility Treatment in Polycystic Ovary Syndrome: Lifestyle Interventions, Medications and Surgery

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Abstract

Management of patients with polycystic ovary syndrome (PCOS) who wish to become pregnant should include exclusion of other diseases in the woman and additional fertility disorders in the couple. Before the initiation of any pharmacological intervention, the importance of lifestyle modifications should be stressed, particularly weight loss, increased exercise, smoking cessation and reduced alcohol consumption. The pharmacological treatment of choice for the induction of ovulation and for achieving live birth is the combination of metformin and clomiphene citrate. If this combination is unsuccessful, second-line treatments include the administration of gonadotropins and laparoscopic ovarian drilling. Induction of ovulation using clomiphene or gonadotropins leads to single live birth in 72% of cases, whereas laparoscopic ovarian drilling leads to live birth in 50% of cases. In vitro fertilization represents third-line treatment. Finally, individualized interventions can be implemented for the induction of ovulation depending on the specific characteristics of patients with PCOS. These interventions might deviate from the above-designated order of treatments in specific subgroups of patients with PCOS.

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Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women of reproductive age and the most frequent cause of anovulating infertility in developed countries. Common clinical manifestations of PCOS include menstrual disorders, due to the anovulation, and androgen excess signs, including hirsutism, oily skin, acne and androgenic alopecia [1].

A principal characteristic of PCOS is insulin resistance (IR) [1]. Another important feature of the syndrome is obesity. Indeed, 38–88% of patients with PCOS are overweight or obese [2]. The majority of patients of PCOS, regardless of bodyweight,

Table 1. Definition of PCOS phenotypes based on 2003 Rotterdam criteria [5]

PCOS phenotype	Oligo- or anovulation	Biochemical hyperandrogenemia or clinical manifestations of hyperandrogenemia	Polycystic ovaries in transvaginal ultrasonography
1 – severe PCOS	+	+	+
2 – oligo- or anovulation and hyperandrogenemia	+	+	–
3 – ovulatory PCOS	–	+	+
4 – mild PCOS	+	–	+

Phenotypes 1 and 2 were also included in the 1990 NIH criteria [7].

manifest a type of IR that is intrinsic to the syndrome and has uncertain pathogenesis. Obese patients with PCOS additionally have obesity-related IR [3].

PCOS is associated with major metabolic disorders, which are potentially due to the characteristic type of IR that accompanies the syndrome [1]. Indeed, the incidence of type 2 diabetes mellitus (T2DM) in the US is 10 times higher in patients with PCOS compared with healthy women. In addition, 30–50% of obese women with PCOS develop impaired glucose tolerance or T2DM after the age of 30 years [4].

Up to now, three key signs have been proposed for the diagnosis of PCOS. These include chronic oligo- or anovulation, biochemical hyperandrogenemia or clinical manifestations of hyperandrogenemia and polycystic ovaries on ultrasound [5]. It should be emphasized that the diagnosis of PCOS mandates the exclusion of other well-known disorders that cause or mimic the manifestations of PCOS.

There are currently two main definitions of PCOS, which are the subject of intense debate [6]. According to the 1990 criteria of the National Institutes of Health, the diagnosis of PCOS requires the presence of chronic oligo- or anovulation and biochemical or clinical hyperandrogenemia [7]. On the other hand, the 2003 Rotterdam criteria of the ESHRE/ASRM-sponsored PCOS Consensus Workshop Group [5] require the presence of at least two of the following three characteristics for the diagnosis of PCOS: (a) chronic oligo- or anovulation, (b) biochemical or clinical hyperandrogenemia, and (c) polycystic ovaries on ultrasound. The addition of a third diagnostic criterion, namely the presence of polycystic ovaries on ultrasound, results in four different phenotypes of PCOS (table 1).

The Rotterdam definition created several problems with implications in the clinical diagnosis of PCOS and in the design of clinical studies [6]. The Androgen Excess and PCOS Society recently issued guidelines which recommend that PCOS should be primarily considered as a disorder of excess in androgen synthesis, activity or metabolism [8]. Therefore, ovulating patients with biochemical hyperandrogenemia or clinical manifestations of hyperandrogenemia and polycystic ovaries (phenotype 3; table 1)

have a mild form of PCOS. On the other hand, regarding patients with chronic oligo- or anovulation and polycystic ovaries (phenotype 4; table 1), even though preliminary data suggest that they manifest subtle endocrine and metabolic disorders that resemble mild PCOS, their metabolic characteristics are currently considered too mild or not associated with increased risk for metabolic disorders that characterize patients with PCOS.

Causes of Infertility in Patients with PCOS

Infertility in patients with PCOS is due to oligo- or anovulation. PCOS is mainly a cause of oligo-ovulation rather than anovulation. From time to time, due to unknown reasons, a follicle becomes dominant and can escape from the inhibitory intraovarian effect and proceed to ovulation and formation of corpus luteum. Because of these random episodes of ovulation, fertility rates in patients with PCOS without treatment are not zero, even though they are lower than in healthy ovulating women. In addition, some patients with PCOS have regular ovulation (ovulatory PCOS, phenotype 3; table 1) and normal fertility despite the presence of biochemical hyperandrogenemia or clinical manifestations of hyperandrogenemia [9].

Five theories have been proposed for the explanation of anovulation in PCOS: (a) the theory of auto-inhibitory effect on the reservoir of available for selection follicles due to their excessive number [10], (b) the theory of the premature effect of LH on the granulosa cells of the available for selection follicles [11], (c) the theory of follicular unresponsiveness due to the presence of IR and compensatory hyperinsulinemia [12], (d) the theory of increased activity of catechol-o-methyltransferase in the granulosa cells of the follicles [13], (e) the theory of oocyte abnormalities [14], and (f) the theory of elevated anti-müllerian hormone inducing follicular arrest by interacting negatively with follicle-stimulating hormone (FSH) [15].

Besides oligo- or anovulation, other factors also contribute to the infertility in patients with PCOS. It is well established that during the induction of multiple ovulation for in vitro fertilization (IVF), a large number of oocytes is retrieved from patients with PCOS. However, these oocytes are of poor quality, leading to low rates of fertilization, cleavage and implantation and higher miscarriage rates. The latter are not associated with higher rates of fetal aneuploidy. Other non-chromosomal factors are implicated in the increased miscarriage rates in patients with PCOS. The failure of oocyte maturation and fetal development in these patients are probably due to abnormal endocrine and paracrine factors, metabolic disorders and alterations in the intra-uterine environment during folliculogenesis and follicular maturation. Therefore, a better understanding of the association between PCOS and the abnormal extra- and intraovarian factors and of the effects of the latter factors on the cross-talk between granulosa cells and the oocyte, the maturation of the oocyte and the embryonic development. This better understanding will improve clinical stimulation and fertility and increase live birth rates in patients with PCOS undergoing IVF [16].

A substantial proportion of patients with PCOS is obese [2] and has the metabolic syndrome [17]. These two disorders reduce considerably the functionality of the reproductive system. The precise pathophysiologic pathway through which obesity exerts its detrimental action is unclear. However, both animal and clinical studies suggest that obesity has adverse effects on all the levels of the hypothalamus-pituitary-ovary axis. Indeed, obesity affects ovulation, oocyte maturation, endometrial development, uterine responsiveness and fetal implantation and miscarriage. Accordingly, weight loss represents the treatment of choice in obese women with infertility [18–20].

Lifestyle Interventions

Lifestyle change programs, which emphasize behavior control and interventions of diet and exercise, have been shown to be very effective in improving the reproductive as well as the metabolic characteristics of overweight and obese patients with or without PCOS [21, 22]. In an early study in 33 overweight patients with PCOS, weight loss achieved with a low-calorie diet along with exercise resulted in resumption of regular cycles in 18 patients, spontaneous ovulation in 15 patients and spontaneous pregnancy in 10 patients [19]. In a more recent larger study in 143 obese patients with PCOS, weight loss through lifestyle changes improved menstrual frequency [20]. It should be mentioned that there are no data on specific dietary intervention and exercise for PCOS. Lifestyle changes are better defined as behavior modifications and correction of inappropriate dietary habits. Weight loss occurs when energy consumption exceeds energy uptake. Exercise is an integral component of every weight control program. Even though limiting energy consumption with diet is a major driver of initial weight loss, regular exercise contributes to sustained weight loss and reduces the risk for weight regain. Lifestyle changes are an important therapeutic strategy for all overweight and obese patients with PCOS [21, 22].

It is well known that aging is associated with progressive weight gain of approximately 0.5–1.0 kg annually after the age of 30 years. Therefore, maintaining the same weight during aging is considered a success. Weight loss is divided into two phases. A substantial weight loss usually occurs during the first 6 months, and this period is followed by a second phase where it is difficult to achieve further weight loss. This represents a physiologic adaptation and is due to the reduction of energy expenditure (plateau phenomenon) that follows weight loss. The second part of weight loss, which is the most difficult one, aims at maintaining the initial weight loss. The longer the period (ideally, lifelong) that weight loss is sustained, the more effective is the intervention implemented in an obese patient.

The initial target in an obese patient should be a moderate weight loss, i.e. 5–10% of the initial bodyweight. This recommendation is based on the findings of several studies, which showed that moderate weight loss significantly reduces the risk for obesity-related diseases, including cardiovascular disease, T2DM, hypertension,

dyslipidemia, osteoarthritis and sleep apnea syndrome [23]. In addition, weight loss increases pregnancy rates [21, 22].

Dietary Modification

The diet of an obese patient should be balanced, i.e. should be made up of 50% carbohydrates, 20% proteins and 30% fats. Fat intake should be made up of 10% saturated, 10% polyunsaturated and 10% monounsaturated fats. The general rule of weight loss is 0.5–1.0 kg weekly that translates into a weekly caloric deficit of 3,500–7,000 calories. Carbohydrate intake should not be limited excessively, as it happens in the popular Atkins diet, because it might lead to acidosis, water loss, dehydration, cholelithiasis and electrolyte disorders, which might lead to arrhythmias and sudden death. Moreover, low-calorie diets should not include less than 1,200 calories daily, because substantial caloric restriction might lead to rapid weight loss, but this loss is only temporary and weight regain, i.e. relapse, is the rule. The method of very-low-calorie diets, which is rarely used, included a daily intake of 0.8–1.0 g of proteins per kg of bodyweight, 45–50 g of carbohydrates and a small amount of essential fatty acids. Daily calorie intake did not exceed 680–715 calories. Even though very-low-calorie diet is effective, it cannot be implemented because of limited adherence. Weight regain occurs very rapidly and, because the energy expenditure is reduced substantially, there is no further weight loss after an initial fast weight loss [24].

Basic dietary principles should be followed. Calorie intake should be divided into several small meals during the day, i.e. breakfast, lunch, dinner and two to three smaller meals between the main meals. In addition, there should be a balance between the different food categories, and carbohydrates, proteins, fats and minerals should be consumed in the appropriate proportions.

On a personalized basis, it is necessary to determine the daily basal metabolism in calories based on age, height and bodyweight, using basal metabolic rate calculation equations. Afterwards, a low-calorie diet should be administered, based on the calculated basal metabolic rate, with a daily calorie deficit of approximately 500–1,000 calories. In order to calculate the daily calorie intake, the patient's daily energy consumption, based on physical activity, should also be considered.

Exercise

Exercise is defined as any kind of regular activity that increases heart rate above resting levels. This results in increased energy consumption that, when it is not compensated for by increased calorie intake leads to weight loss and is even more important for maintaining bodyweight [25]. Exercise includes for example brisk walking, stair climbing, running, cycling, aerobics and swimming. In addition, participating in

group sports is also considered exercise. Nevertheless, current living and working conditions are mostly sedentary resulting in obesity. Therefore, women can use even more energy than with sports if they include more activities into everyday tasks.

Exercise guidelines issued by the American College of Sports Medicine and the American Heart Association in 2007 [26] recommend moderate-intensity aerobic (endurance) physical activity for a minimum of 30 min on 5 days each week or vigorous-intensity aerobic activity for a minimum of 20 min on 3 days each week or combinations of moderate- and vigorous-intensity activity for promoting and maintaining good health.

The World Health Organization recommends for weight loss moderate-intensity exercise 3–5 days per week, and ideally every day, including walking, swimming, housekeeping and gardening [27]. The duration of exercise should be 30–45 min per day or more than 150 min per week. This moderate-intensity exercise corresponds to approximately 150 calories of energy consumption per day.

Behavior Modification

The treating physician, during his consultations with the obese patient, should try to establish a friendly relationship and to set realistic targets of weight loss, and to have frequent contact with the patient. The medical advice to the obese patient regarding behavior modification should focus on patient self-monitoring (i.e. the patient should record on a daily basis the dietary intake and monitor the bodyweight) and daily exercise. In addition, the treating physician should reward the patient and acknowledge the efforts when weight loss is achieved. The physician should advise the patient to avoid dietary temptations and to focus on important messages. Moreover, the treating physician should offer psychological support to the patient because it has been shown that weight loss improves self-respect and decreases the prevalence of depression, whereas weight regain has the opposite effects [28]. Recently, in the management of obesity, several cognitive and behavioral models have been proposed, which originate from the theory of learning and aim at lifestyle changes. These educational models are particularly useful in obese patients with eating disorders, including bulimia nervosa and the episodic hyperphagia syndrome [29].

Pharmacologic Treatment for Weight Loss in PCOS

Lifestyle changes are ineffective because obese patients who lose weight relapse, thus regaining the lost bodyweight during the following 2–5 years. Therefore, supplementary pharmacological treatment for the management of obesity is frequently necessary, and has been shown to maintain more than 50% of the initial weight loss for a period of 2–4 years. However, after the cessation of pharmacological treatment, a gradual weight regain is observed.

Pharmacological treatment of obesity is recommended in obese patients with a body mass index (BMI) >30 or >27 with concomitant metabolic diseases, including T2DM, which might coexist with dyslipidemia or hypertension. The treatment goal is moderate weight loss, approximately 5–10% of initial bodyweight, because this has been shown to substantially improve fertility and the metabolic risk factors associated with obesity.

The antiobesity agents, depending on their mechanism of action, based on the equation of energy balance, are divided into two categories. The first includes centrally acting agents, which reduce food intake by decreasing appetite and inducing satiety or by increasing energy expenditure [30, 31]. Sibutramine, a centrally acting agent that was recently withdrawn from the market because of adverse cardiovascular effects, reduces bodyweight in patients with PCOS by 4.3% more than diet alone and improves insulin sensitivity and reduces circulating androgen levels [30, 31]. The second category includes agents with peripheral action, which decrease fat absorption [32, 33]. The main representative of this class is orlistat, which was shown to reduce bodyweight and also to reduce IR and hyperandrogenemia in patients with PCOS [32, 33].

Bariatric Surgery

Two small studies in severely obese patients with PCOS (n = 24 and 17, respectively; mean baseline BMI 50.0 ± 7.5 and 50.7 ± 7.1 , respectively) reported a considerable weight loss ($56.7 \pm 21.2\%$ and 41 ± 9 kg, respectively). In addition, the majority of patients achieved resolution of hirsutism, improvement in IR and restoration of normal menstrual cycles and ovulation; pregnancy was also reported in some patients [34, 35]. However, bariatric surgery for the management of PCOS should be recommended with great caution and only when specific strict criteria are fulfilled [36, 37].

Pharmacological Treatment for the Induction of Ovulation

Clomiphene Citrate

It has been suggested that clomiphene citrate represents first-line treatment for the induction of ovulation and pregnancy in anovulatory patients with PCOS. Treatment cost is low, the drug is convenient to use, adverse effects are relatively few and mild, and there are important clinical data on the effectiveness of the agent [38].

Clomiphene citrate acts by inhibiting the estrogen-negative feedback regulatory mechanism resulting in increased secretion of FSH and LH. The ensuing ovulation is the result of hormonal and morphologic changes in the developing follicles. Thus, treatment with clomiphene does not induce ovulation but restores and augments the sequence of events of normal menstrual cycle. However, it is not certain whether the