Management of PCOS Women Preparing Pregnancy

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11.1 Introduction

As well known, infertility is a prevalent presenting feature of PCOS with ~75% of these women suffering infertility due to anovulation, making PCOS the most common cause of anovulatory infertility. Women with PCOS often have many concerns about childbearing including whether they could become pregnant and what they should do before they try to become pregnant. Polycystic ovary syndrome (PCOS) is a common female reproductive endocrine disease. The prevalence in premenopausal women ranges from 6 to 20%, possibly making this syndrome as the most common endocrine and metabolic disorder in women of reproductive age [1–3]. According to the reports in specialized departments of China like in our "Department of Gynecological Endocrinology," it stands as the most important disease – in our daily clinic from more than 500 outpatients, at least 50% are diagnosed with PCOS, and more than 50,000 per year of our PCOS patients get treatment as described in this chapter. The disease can begin in early adolescence, the etiology is not yet clear, the pathogenesis is complex, and it is related to environmental (especially nutrition) factors. Particularly, genetical factors may also play an important role in the development of the disease and differences in type and outcome [4]. Changes of endocrine and metabolic markers are often associated with PCOS although are not decisive for the diagnosis. In 2003, the "European Society for Human Reproduction and Embryology (ESHRE)" and the "American Society of Reproductive Medicine (ASRM)" revised the diagnostic criteria for PCOS at the Rotterdam meeting [5]: (1) rare ovulation or anovulation; (2) abnormal clinical manifestations and/or

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biochemical indicators of hyperandrogenism; and (3) polycystic ovarian morphology (PCOM): follicle number of 2–9 mm in diameter in one or both ovaries ≥12 and/or ovarian volume >10 cm^3. In 2018 the cut-off for follicle number was raised to 20 or more in either ovary [2]. If at least two of the three abovementioned criteria are met, "PCOS" can be diagnosed, whereby diseases such as thyroid dysfunction, Cushing's syndrome, androgen-secreting tumors, hyper-prolactinemia, pituitary gland diseases, and premature ovarian failure must be excluded.

Currently there is controversial discussion about the value of the assessment of anti-Müllerian hormone (AMH) in context with the diagnosis of PCOS. However, according to our own and other recent research, we conclude that AMH may be a useful parameter to assess the severity and prognosis of PCOS and may help to differentiate the main phenotypes of the disease, being higher in PCOS patients compared to controls especially in non-obese women [6–8]. However, the mechanisms resulting in increased AMH in PCOS are poorly understood and have been attributed to obesity, insulin resistance (IR), hyperandrogenism, complex interactions with gonadotrophins, etc. [9].

PCOS is characterized by biochemical and clinical hyperandrogenic features and menstrual and ovulation disorders. Related metabolic disorders include IR, abnormal glucose, and abnormal lipid metabolism, which can increase the risk of cardiovascular disease [10]. Primary disease characteristics of PCOS, mainly hyperandrogenism and impaired glucose tolerance, also predict suboptimal obstetric and neonatal outcomes. Increased rates of gestational diabetes mellitus, pregnancy induced hypertension, preeclampsia, caesarean section delivery, and preterm birth have been reported among pregnant women with PCOS.

It is very important to strengthen the need of the individualized long-term management of PCOS patients. Thus, this article will elaborate preferably on the long-term complications of PCOS and new developments in long-term management.

11.2 Pathophysiology of PCOS

The pathophysiology of PCOS is complex and not fully understood [11–14]. Women with PCOS experience an increase in frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses which, in turn, results in an increase in the luteinizing hormone (LH)/follicle stimulating hormone (FSH) ratio. The dominance of LH over FSH increases ovarian androgen production and decreases follicular maturation. This leads to an increase in the level of biologically active testosterone and contributes to the clinical consequences of hyperandrogenemia in PCOS [15]. Abnormalities in both androgen metabolism and the control of androgen production, when accompanied by anovulation, increase the likelihood of metabolic dysfunction [16]. The majority of women with PCOS have insulin resistance and/or are obese [16]. Their elevated insulin levels increase GnRH pulse frequency and either contribute to or cause the abnormalities seen in the hypothalamic–pituitary–ovarian axis that lead to PCOS [15]. Normal patterns of gonadotropin secretion are essential for reproduction, and any imbalance may contribute to decreased fertility and

pregnancy problems [17]. The pathological imbalance of LH and FSH, present in women with PCOS, explains the rationale for pretreatment with combined hormonal contraceptives to increase fertility and improve pregnancy outcomes; however, more studies are needed regarding this important topic.

11.3 Long-Term Consequences of PCOS

Studies show a link between hyperandrogenic PCOS and disturbances in metabolic parameters which could lead to an increased risk of cardiovascular disease (CVD) [12, 16]. Obesity, impaired glucose tolerance, and type 2 diabetes are all more prevalent in women with PCOS when compared with the general population [18]. Although conventional cardiovascular risk calculators such as the Framingham Index have not been validated within this patient population and there is no real proof of an increased risk of CVD as main endpoint in studies, there is clear evidence of higher incidence of hypertension, impaired lipid and glucose metabolism, and increased risk of developing gestational diabetes and type 2 diabetes, which indeed all can increase the risk of CVD [12, 16]. In addition, polycystic ovary syndrome is associated with poorer pregnancy outcomes, for example, an increase in risk of pre-term delivery and preeclampsia. Decreased quality of life, including an increased risk of depression and anxiety, is also an important risk in untreated PCOS patients [11].

11.4 Treatment Targets

11.4.1 Lifestyle

Lifestyle modification involving a healthy diet and exercise and achievement of optimal BMI is important for all women affected by PCOS. Evidence from observational studies shows that moderate weight loss (5–10%) in women with PCOS can improve insulin resistance as well as androgenic and reproductive outcomes.

11.4.2 Hyperandrogenism

Pharmacological treatment of PCOS is aimed to reduce the level of circulating androgens and to control their effect at tissue level in order to ameliorate symptoms such as hirsutism and acne and reduce the risk of long-term metabolic consequences. Combinations of ethinyl-estradiol (EE) and progestogens, especially those containing antiandrogenic progestogens such as cyproterone acetate (CPA), chlormadinone acetate (CMA), and drospirenone (DRSP), have traditionally been the first choice for management of PCOS [19]. Almost all combined oral contraceptives (COCs) and other estrogen/progestogen combinations like vaginal rings and contraceptive patches contain EE as the estrogenic component. Reason for this is the good cyclical

stability because of the long half-life of EE which can stabilize the endometrial situation during the use of those combined contraceptives. Only two newer COCs available in many Western countries contain estradiol instead of EE, in combination with newer special progestogens, dienogest (DNG) or nomegestrol acetate (NOMAC), respectively, which due to their strong endometrial efficacy can avoid breakthrough bleedings in contrast to other combinations with estradiol (E2) which have been tested for their potential use in contraception.

The antiandrogenic effect of the estrogen/progestogen combinations is achieved via a number of different mechanisms, which mainly are (1) increase in hepatic SHBG production with all estrogens in a dose-dependent manner; however, the effect is much stronger using EE compared with E2; (2) suppression of LH secretion and thereby ovarian androgen production, achieved with all progestogens (including androgenic progestogens such as levonorgestrel [LNG]) if used in ovulatory inhibition dosages; (3) competition at the 5-alpha-reductase and androgen receptors by progestogens, effect strongest when using CPA; (4) competition at the androgen-receptor with antiandrogenic progestogens like CPA, CMA, DNG, and DRSP can block the action of testosterone; (5) in addition the ovarian androgen production can be blocked directly, especially when using EE/CPA combinations.

11.4.3 Identifying Treatment Priorities in PCOS

The management of PCOS should be tailored to each woman's specific goals, reproductive interests, and particular symptomatic presentation. The presenting primary complaint may vary depending on age or ethnic variation. Treatment may primarily focus on the symptom generating the greatest level of distress, such as hirsutism or infertility, and often require a multidisciplinary approach. When discussing long-term management of PCOS, women should be advised regarding the risks and benefits of treatment and the elements of lifestyle management to reduce the metabolic and cardiovascular consequences of the syndrome. Recognition of the symptoms of venous thromboembolism (VTE) and knowledge how to respond are also important.

11.4.4 Obesity

Obesity is a common problem in patients with PCOS. In the United States, 80% of women with PCOS suffer from obesity. According to a recent meta-analysis [20], women with PCOS had an increased prevalence of overweight [RR (95% CI): 1.95 (1.52, 2.50)], obesity [2.77 (1.88, 4.10)], and central obesity [1.73 (1.31, 2.30)] compared with women without PCOS; Caucasian women with PCOS had a greater increase in obesity prevalence than Asian women with PCOS compared with women without PCOS [10.79 (5.36, 21.70) versus 2.31 (1.33, 4.00), $P < 0.001$]. Numerous studies have shown that centripetal obesity and visceral hypertrophy are associated with PCOS. High insulin levels due to hyperandrogenism and IR in PCOS can lead to centripetal fat distribution, mainly manifested as an increase in the ratio of waist

circumference to hip circumference [21, 22]. Moreover, non-targeted and targeted studies suggest that the genomic, transcriptomic, and proteomic profiles of visceral adipose tissue from women with PCOS are quite different from those of healthy women and resemble those of men, indicating that androgen excess contributes to their adipose tissue dysfunction.

In addition to reducing ovulation, obesity is also associated with endometrial changes associated with IR, which reduces the rate of implantation and increases the rate of abortion and is closely related to complications in the third trimester of pregnancy, leading to low fertility. At the same time, obesity is likely to aggravate the hyperandrogenism of PCOS and menstrual disorders to form a vicious circle. It can also lead to psychological complications of women with PCOS, such as anxiety and depression. The accumulation of abdominal fat can induce IR and hyperinsulinemia, and insulin can stimulate the production of ovarian androgens, further aggravating hyperandrogenism. Overweight and obesity are prone to increase the risk of type 2 diabetes (T2DM) [23]. Some studies have shown that for every 1% increase in body mass index (BMI), the risk of T2DM can increase by 2%. The amount of visceral fat and abdominal fat is positively correlated with the risk of IR, inflammation, T2DM, dyslipidemia, metabolic syndrome (MetS), and cardiovascular disease, but metabolic disorders can also be seen in some nonobese PCOS women [24].

Weight management is crucial for treatment of PCOS patients. Weight loss is beneficial for improving the menstrual cycle and restoring ovulation. In a randomized trial of PCOS female infertility, it was found that both COC or separate lifestyle changes aiming for weight loss significantly improved ovulation rates compared with immediate clomiphene citrate treatment, i.e., live birth rates increased more [25].

We found that letrozole combined with low-dose highly purified human menopausal gonadotrophin (HMG) may be an effective and safe choice for reducing hyperstimulation and can increase the pregnancy rate by ovulation induction of clomiphene-resistant women with PCOS [26]. However, a recent randomized trial found that weight loss even is superior to oral contraceptive pretreatment in improving induced ovulation in overweight and obese PCOS women, providing additional evidence for the importance of weight loss to improve the reproductive function of PCOS [27]. As “COC” in China mostly EE plus CPA is used, although according to the new labeling the indication now only is “for treatment of biochemical and clinical signs of hyperandrogenism.” Indeed in our department thousands of PCOS patients every year are treated with EE/CPA, and only since recently we use more EE/DRSP in obese patients, mostly together with lifestyle changes. Within a large cohort study using EE/CPA together with standardized lifestyle change, we observed significant improvement in physical aspects like weight loss associated with increased quality of life and a decrease of depressive symptoms and anxiety [28]. Weight loss is also beneficial for improving metabolism [29]. Lifestyle improvement can be achieved with diet, exercise adjustment, etc. Existing dietary and reproductive physiological data suggest that specific dietary improvements may help to counteract the chronic low-grade inflammatory process in the disease. The

reproductive outcome of these patients is improved [30]. It was recommended that for overweight PCOS patients the diet should be controlled keeping it at 1200 ~ 1500 kcal/day, and moderate-intensity exercise for more than 5 days per week during at least 30 minutes should be performed. A specific recommendation is to increase whole grain intake and avoid refined carbohydrates, including oats, brown rice, and quinoa. Encouragingly, it was found that women who received in vitro fertilization and had a nutrition with higher content of grains had higher live birth rates. Within a large prospective cohort study including more than 5000 women, it was demonstrated that for obese women any form of exercise is beneficial to improve the fertility [31]. Recent studies have shown that weight loss in the first 2 months is a good predictor of prognosis after 1 year of lifestyle intervention. Therefore, early identifying if individuals will have unsuccessful or successful weight loss may be a promising solution providing tailored treatments for long-term weight loss. For women with obesity who are not able or not really willing to change their lifestyle, as medical treatment the widely used insulin sensitizer metformin may be considered for patients with pre-diabetes or diabetes mellitus. In most countries (like also in China), metformin is labelled only for patients with diabetes mellitus, and if used as "off-label," the patients must be informed. The newest recommendations from the "International evidence-based guideline for the assessment and management of PCOS" suggest that metformin in addition to lifestyle changes could be recommended in adult women with PCOS to treat overweight, hormonal, and metabolic disorders [2]. Metformin may offer especially benefit in high metabolic risk groups including those with risk factors for diabetes or impaired glucose tolerance, whereby with respect to symptoms and treatment effect there could be genetical differences. For the use of metformin, it needs to be considered that adverse effects, including gastrointestinal side effects, are generally dose-dependent, and it is recommended to start with low dose, i.e., with 500 mg increments 1–2 weekly.

We found that the use of EE/CPA can restore the regularity of menstrual cycles and does not deteriorate the glucose and lipid metabolism [32]. To investigate also the new treatment options, we compared metformin, EE/CPA with orlistat, which has the indication to help getting weight loss in obese patients [32, 33]. Within a prospective randomized placebo-controlled four-arm study comparing (a) orlistat combined with EE/CPA vs. (b) metformin plus EE/CPA vs. (c) orlistat plus metformin plus EE/CPA vs. (d) EE/CPA, we found that the combination EE/CPA plus orlistat has been the best choice in reducing weight, reducing androgen levels, improving glucose metabolism, and reducing systemic fat content, with less adverse reactions [33]. According to the newest guideline for the diagnosis and treatment of polycystic ovary syndrome in China, orlistat is recommended in obese women to improve weight loss [3]. However, the first advice always must be to inform the patients about the need of dietary restrictions and "healthy diet," respectively. Moreover, the benefit of orlistat observed in our studies may be dependent on genetical factors, so more research is still needed.

Some studies suggested glucagon-like peptide-1 analogue liraglutide in combination with metformin and lifestyle interventions resulted in significant reduction in

body weight in overweight and obese women with PCOS, which indicates that also liraglutide may be an effective alternative for getting weight loss in such patients. Compared with metformin, short-term exenatide treatment had better efficacy in reducing body weight, improving IR, and reducing inflammation.

However, large and long-term clinical trials are needed to assess efficacy and safety. Patients with difficulty to get weight loss can also consider bariatric surgery, which can effectively alleviate PCOS and its clinical symptoms, including hirsutism and irregular menstruation in severely obese women [34]. A meta-analysis published in 2017 indicated that surgically induced weight loss in women with severe obesity and PCOS resulted in significant decreases in serum levels of total and free testosterone and improvement of hirsutism and menstrual dysfunction in as many as 53% and 96% of the patients, respectively [34].

11.5 Insulin Resistance and Diabetes Mellitus

IR is closely associated with increased risk of pre-diabetes and T2DM in PCOS, with IR in approximately 60–80% of PCOS patients and 95% in obese patients. In a large study of 11,035 patients with PCOS [35], the prevalence of T2DM was 2.5 times that of the age-matched control group. Using a meta-analysis it was calculated that the odds ratio (OR) of Impaired Glucose Tolerance (IGT), T2DM, and MetS in PCOS is 2.48 (95% CI 1.63, 3.77), 4.43 (95% CI 4.06, 4.82), and 2.88 (95% CI 2.40, 3.45), respectively. Subgroup analyses of studies with BMI-matched populations reveal the same risks. The OR for IGT in lean PCOS women has been estimated to be 3.22 (95% CI 1.26, 8.24), whereby the IR of patients with PCOS worsens with increasing age. IR certainly is a key player in the metabolic manifestations in PCOS patients and seems to be partially independent of obesity. Investigations in adolescents found that the frequency of IGT were equal between obese and non-obese PCOS patients. However, there is general agreement that obese women with PCOS have a higher risk to be insulin resistant, and some groups of lean affected PCOS women may have normal insulin sensitivity. A meta-analysis indicates that women with PCOS have a higher risk of IR and glucose intolerance than women of similar age and weight who do not have PCOS [36].

The pathogenesis of IR in patients with PCOS is multifactorial. Investigations on possible mechanisms suggest that there is a post-binding defect in receptor signaling likely due to increased receptor and insulin receptor substrate-1 serine phosphorylation that selectively affects metabolic but not mitogenic pathways in classic insulin target tissues and in the ovary [17]. Consecutive activation of serine kinases in the MAPK-ERK pathway may contribute to resistance in terms of insulin's metabolic actions in skeletal muscles. Insulin functions as a co-gonadotropin through its cognate receptor which can modulate ovarian steroidogenesis. Genetic disruption of insulin signaling in the brain has indicated that this pathway is important for ovulation and body weight regulation [17]. These insights have been directly translated into the novel therapy of PCOS with insulin-sensitizing drugs. Furthermore, androgens contribute to the development of IR in PCOS. IR not only predisposes patients

to metabolic dysfunction and increased risk of type 2 diabetes mellitus but also is important within the pathophysiology of PCOS. High testosterone and SHBG concentrations (indicating a high fraction of the biological active free testosterone) are independently associated with IR, so there is a direct interactive relationship between hyperandrogenemia and IR, i.e., IR may induce an increased androgen action, and vice versa androgens may induce IR, respectively [17]. Androgen exposure at critical periods or intrauterine growth restriction may also have a causal relationship to the development of PCOS [17].

As already described above, lifestyle changes, including diet, exercise, and behavioral changes, are the first-line treatment for all overweight and obese patients with PCOS. In context with changes in glucose metabolism, it has been shown that changes in the diet can improve IR in patients with PCOS. In addition also exercise can improve IR and metabolic profiles and reduce visceral fat in women with PCOS [37]. Such lifestyle changes reduce the risk of IGT progression to T2DM in healthy women and in PCOS patients [37].

For PCOS patients diagnosed with T2DM, there are no specific recommendations for the various available anti-diabetic treatment options. However, metformin and lifestyle changes are suggested as the treatment of choice, and any antidiabetic drug (i.e., sulfonylureas, pioglitazone, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter 2 inhibitors, or basal insulin) can be added to patients who are still unable to achieve their glycemic goals with metformin. Among the available alternative options, pioglitazone appears to improve insulin sensitivity to a similar extent like metformin, and both have synergistic effects on IR in patients with PCOS [38]. However, safety issues, including weight gain and the risk of edema, limit the use of pioglitazone in this population. Limited data also indicate that glucagon-like peptide 1 analogs combined with metformin are more effective in reducing IR and reducing body weight than metformin monotherapy. It is worth noting that only insulin, metformin, and glibenclamide can be safely used in pregnancy. Therefore, patients receiving other antidiabetic drugs should take appropriate contraceptive measures.

11.5.1 Decreased Fertility, Adverse Pregnancy Outcomes

Important long-term consequences of untreated PCOS are decreased fertility and adverse pregnancy outcomes [39, 40]. Infertility in PCOS is due to infrequent or absent ovulation, and no clear evidence exists that factors other than oligo-ovulation or anovulation contribute to reduced fertility. About 75% of women with PCOS have infertility, and PCOS accounts for the vast majority of cases of oligo-ovulation or anovulation requiring fertility treatment [2]. At the same time, women with PCOS are at increased risk of adverse pregnancy and neonatal complications; this information may be vital in clinical practice for the management of pregnancy in women with PCOS. According to various data, the risk of miscarriage in PCOS women is three times higher than the risk of miscarriage in healthy women [40]. Unfortunately, the risk of most frequent pregnancy pathologies is also higher for

PCOS patients, as gestational diabetes mellitus (GDM), pregnancy-induced hypertension and preeclampsia, and for gestational age (GA) children. IGT and GDM in pregnant PCOS patients occur more frequently than in healthy women. A quadruple increase in the risk of pregnancy-induced hypertension linked to arterial wall stiffness has also been observed in PCOS patients [40]. The risk of pre-eclampsia, the most severe of all complications, is also up to four times higher in those suffering from PCOS [40]. A meta-analysis in women with PCOS including 27 studies, analyzing 4982 women with PCOS and 119,692 controls [41], showed a significantly higher risk of developing GDM (OR 3.43; 95% CI: 2.49–4.74), pregnancy-induced hypertension (PIH) (OR 3.43; 95% CI:2.49–4.74), preeclampsia (OR 2.17; 95% CI: 1.91–2.46), preterm birth (OR 1.93; 95%CI: 1.45–2.57), and caesarean section (OR 1.74; 95% CI: 1.38–2.11) compared to controls. Women with PCOS had an increased risk of preterm delivery compared with the background population. The increased risk was confined to hyperandrogenic women with PCOS who had a two-fold increased risk of pre-term delivery and preeclampsia [42]. Our team found that follicular and embryo development and changes in endometrial receptivity in patients with PCOS were associated with adverse pregnancy outcomes [43]. As we always have stressed in our research and publications, based on the literature and our own experience treating during recent years thousands of PCOS patients, individualized comprehensive treatment combining lifestyle changes with pharmacological interventions has a positive effect on pregnancy outcomes in patients with PCOS [28, 33]. These women should be given notice of the additional risks their pregnancies may have, stronger surveillance and attention should be provided, as well as screening for these complications during pregnancy and parturition. According to a meta-analysis evaluating obstetric complications in women with PCOS [41], during pregnancy particularly close checks on a regular basis of glucose metabolism and hormonal status should be performed besides control of lifestyle modification and medical therapy. To reduce pregnancy-related complications, very recently our team found that the use of COC may not be valuable only in patients who want or need contraception but also as pretreatment in PCOS patients who want pregnancy: We evaluated the prevalence of adverse pregnancy outcomes in 6000 healthy Chinese women, selected from 24,566 pregnant women by randomized sampling, and investigated whether these outcomes could be decreased in patients with PCOS by pretreatment with EE/CPA. The result was that patients with PCOS are more likely to develop GDM, PIH, and premature delivery, and 3-monthly pretreatment with the COC was associated with a lower risk of GDM, PIH, and premature delivery [43]. Since this treatment concept has been already proven to be most successful in many of our patients, it is now included in our own routine management for treatment of PCOS patients who want pregnancy, together with individualized lifestyle interventions.

PCOS is a very frequent endocrine disorder. Figure 11.1 summarizes the long-term complications and management of this disease, with symptoms, complications, and risks dependent on the age of the patients. Because of the different symptoms and risks and the broad spectrum of possible symptomatic treatment options, often a multidisciplinary approach is needed. *Obesity* is one of the most

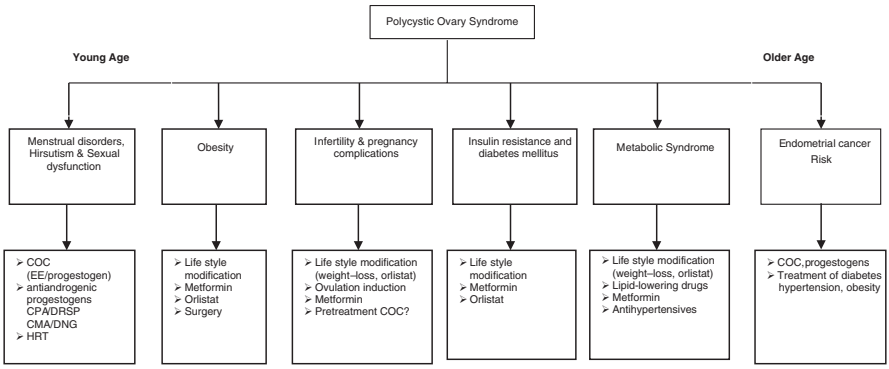

Fig. 11.1 Long-term complications and management of polycystic ovary syndrome; *COC* combined oral contraceptives, *EE* ethinyl-estradiol, *CPA* cyproterone acetate, *DRSP* drospirenone, *CMA* chlormadinone acetate, *DNG* dienogest, *HRT* hormone replacement therapy

common findings in PCOS, and is itself an independent risk factor for many of the symptoms and negative long-term consequences that have been attributed to PCOS. Patients with PCOS are at increased risk of *endometrial cancer*, whereas an association with other types of gynecological cancers like ovarian and breast cancer are controversial or have not been found, respectively. Untreated PCOS patients clearly have an increased long-term risk to develop *diabetes mellitus* and *metabolic syndrome*. In patients who are overweight or obese, lifestyle interventions, principally in terms of diet and exercise, are thought to be the most effective management. If proven to be unsuccessful, metformin is an effective pharmacological treatment and can prevent conversion of IGT to T2DM. At least in Chinese women orlistat combined with COC can help to reduce weight and can lower androgens, blood fat, and glucose, but more research is needed, especially if genetical factors may play a role. PCOS patients may have a *decreased fertility* and/or *adverse pregnancy outcomes*. According own research pretreatment with COC containing an antiandrogenic progestogen can be recommended to increase the fertility and decrease adverse pregnancy outcomes. The most important consideration of management is to tailor treatment choices to the specific needs of the patient.

11.6 Conclusion

Polycystic ovary syndrome (PCOS) is a frequent female reproductive endocrine disease. It has been associated with a number of severe reproductive complications. However, there are still open questions especially regarding the *Management of PCOS women preparing pregnancy*. We summarized the literature focused on the symptoms and negative long-term consequences of untreated PCOS and the existing options for the treatment. We reviewed the Pubmed and China National Knowledge Infrastructure databases and the relevant literature for the last 20 years, including new results of own (published) research and own

experience from treating daily more than 200 PCOS patients. Obesity is one of the most common findings. It can cause abnormal ovulations which can lead to infertility. Important long-term consequences can be adverse pregnancy outcomes. Insulin resistance, important within the pathophysiology of PCOS, predisposes patients to metabolic dysfunction and increased risk of type 2 diabetes mellitus. Lifestyle modifications including dietary changes, exercise and weight loss are first-line interventions for many patients. Well known drug treatments such as metformin, oral contraceptives, etc. should be selected according to the individual situation and patients' needs. Regarding newer methods in the long-term management of PCOS, we found that orlistat may help to achieve weight loss and to improve lipid and glucose metabolism. In addition to pharmacological interventions, long-term standardized individualized management of PCOS patients is needed to achieve fertility and to reduce the risk of metabolic related diseases.

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