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Review Article

Etiology, Management, and Treatment of Polycystic Ovary Syndrome: A Systematic Review

Marwa B Bakir[1], Samir M Abdel-Mageed[2] and Ehab I Mohamed[3]*

[1]Pharamcology Department Medical Research Institute, Alexandria University, Alexandria, Egypt

[2]Physics Department, Faculty of Science, Alexandria University, Alexandria, Egypt

[3]Medical Biophysics, Medical Research Institute, Alexandria University, Alexandria; Egypt

***Corresponding Author:** Ehab I Mohamed, Medical Biophysics, Medical Research Institute, Alexandria University, Alexandria; Egypt.

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Abstract

Polycystic ovary syndrome (PCOS), which affects 5-20% of women in their reproductive age, is the most common endocrinopathy affecting women worldwide. It is a condition characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology, with excessive ovarian androgen production being a key feature of PCOS. Metabolic dysfunction characterized by insulin resistance and compensatory hyperinsulinaemia is evident in the vast majority of affected women. PCOS increases the risk for cardiovalscular diseases, type-2 diabetes mellitus, gestational diabetes and other pregnancy-related complications, venous thromboembolism, cerebrovascular and cardiovascular diseases and endometrial cancer. PCOS is a diagnosis of exclusion, based primarily on the presence of hyperandrogenism, ovulatory dysfunction and polycystic ovary morphology. Treatment should be tailored to the complaints and needs of the patient and involves targeting metabolic abnormalities through lifestyle changes, medication and potentially surgery for the prevention and management of excess weight, androgen suppression and/or blockade, endometrial protection, reproductive therapy and the detection and treatment of psychological features. This review summarizes the current state of knowledge regarding the etiology, mechanisms and pathophysiology, diagnosis, screening and prevention, management and future investigational directions of PCOS.

Keywords: Polycystic Ovary Syndrome (PCOS); Insulin Sensitizer; Metformin; Clomiphene Citrate (CC); Letrazol

Abbreviations

ACTH: Adrenocorticotropic Hormone; AE-PCOS: Androgen Excess and Polycystic Ovary Syndrome; AFC: Antral Follicle Count; AMH: Anti-Müllerian Hormone; AMPK: Adenosine Monophosphate Activated Protein Kinase; ASRM: American Society for Reproductive Medicine; BMD: Bone Mineral Density; BMI: Body Mass Index; BMR: Basal Metabolic Rate; CC: Clomiphene Citrate; CCK: Cholecystokinin; COCP: Combined Oral Contraceptive Pill; CRP: C-Reactive Protein; CVD: Cardiovascular Diseases; DHT: Dihydrotestosterone; DM: Diabetes Mellitus; E2: Oestradiol; ESHRE: European Society of Human Reproduction and Embryology; FI: Flow Index; FSH: Follicle-Stimulating Hormone; GLUT4: Glucose Transporter 4; GnRH: Gonadotropin-Releasing Hormone; hCG: Human Chorionicgonadotropin; HDL: High Density Lipoprotein; hMG: Human Menopausal Gonadotropin; IGF: Insulin-Like Growth Factor IGFBP-1; IGF: Binding Protein 1; IGT: Impaired Glucose Tolerance;

IUI: Intrauterine Insemination; IVF: *In-Vitro* Fertilization; IVF/ICSI: *In Vitro* Fertilization/Intracytoplasmic Sperm Injection; IVM: *In Vitro* Maturation; LH: Luteinizing Hormone; LKB1: Liver Kinase B1; LOD: Laparoscopic Ovarian Drilling; NAC: N-Acetyl Cysteine; NICE: National Institute for Health And Clinical Excellence Guidance; OCPs: Oral Contraceptives; OGTT: Oral Glucose Tolerance Test; OHSS: Ovarian Hyperstimulation Syndrome; OI: Ovulation Induction; OV: Ovarian Volume; COS: Polycystic Ovary Syndrome; PPAR: Peroxisome Proliferator-Activated Receptor; RCT: Randomised Controlled Trial; SHBG: Sex Hormone-Binding Globulin; T2DM: Type-2 Diabetes Mellitus; TZDs: Thiazolidinediones; VEGF: Vascular Endothelial Growth Factor; VFI: Vascularization Flow Index; VI: Vascularization Index; WHO: World Health Organization

Introduction

Polycystic ovary syndrome (PCOS), which is a heterogeneous complex genetic trait of unclear etiology, is an important cause of ovulatory and menstrual irregularity, subfertility and infertility, clinically evident hyperandrogenism, and metabolic dysfunction for women. It is recognized as one of the most common endocrine/metabolic disorders for women of reproductive age [1]. Rates vary by PCOS diagnostic criteria; reported in 5%-10% of women based on NIH criteria, 10%-15% of women based on Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society criteria and 6%-21% of women based on Rotterdam ESHRE/ASRM Criteria [2].

Polycystic ovary syndrome pathophysiology and etiolgy

PCOS is now thought to be a complex genetic trait, similar to cardiovascular diseases (CVD), type-2 diabetes mellitus (T2DM), and metabolic syndrome, where multiple genetic variants and environmental factors interact to foster the development of the disorder (Figure 1). Etiology is unclear, although PCOS is thought to develop from the interaction of genetic, fetal, and environmental factors, with the relative importance of each factor varying for women with PCOS [3]. The inherited basis of PCOS was established by twin studies and reports demonstrating an increased prevalence of PCOS in female first-degree relatives of affected women [4]. Excessive exposure of a female fetus to androgens, including testosterone, in an intrauterine environment, might contribute to reproductive and metabolic consequences of PCOS (Figure 2) [3,5]. The most likely environmental factor affecting the development of PCOS is diet and its association with obesity [6].

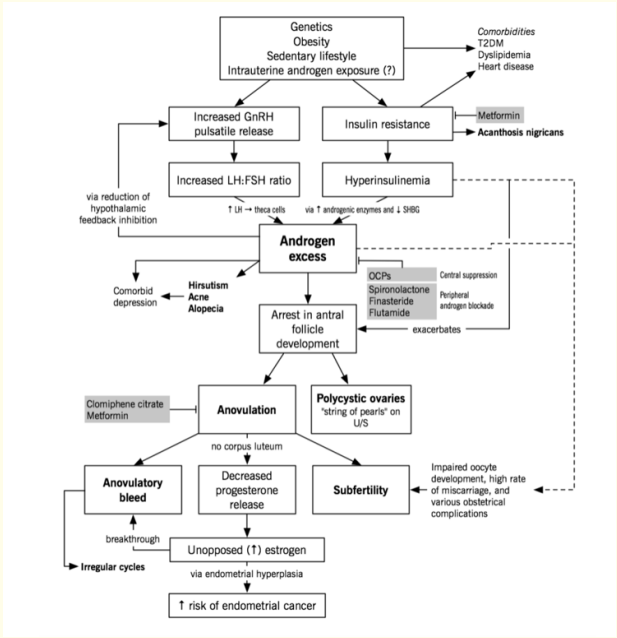

Figure 1: Pathophysiology of Polycystic Ovary Syndrom (PCOS), the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus is often disturbed in polycystic ovary syndrome (PCOS), leading to the hypersecretion of luteinizing hormone (LH) by the pituitary gland, which induces ovulary dysfunction and hyperandrogenism. This disturbed secretion of LH is thought to occur early in puberty and is related to the disturbed inhibition of GnRH secretion by progesterone. Although serum follicle-stimulating hormone (FSH) levels are generally normal, follicles seem to be more resistant to FSH for women with PCOS than in controls. This effect might be due to increased levels of intra-ovarian anti-Müllerian hormone (AMH). Notably, genetic and epigenetic variants contribute considerably to most of these alterations. Environmental factors contribute somewhat less, most by exacerbating insulin resistance and dysregulated gonadotropin secretion [1].

PCOS is associated with abnormalities in ovarian steroidogenesis, since the hypothalamus is resistant to negative feedback from progesterone, which is the main regulator of gonadotropin-releasing hormone (GnRH) pulse frequency, as shown in the PCOS

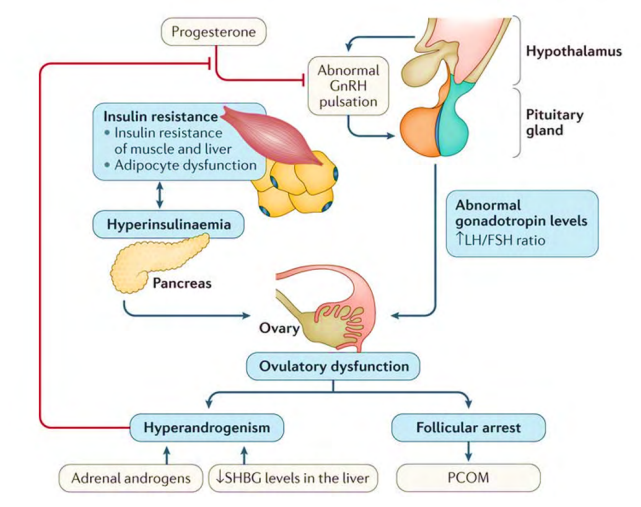

Figure 2: Polycystic Ovary Syndrom (PCOS) is a chronic hyperandrogenic state that has many significant short-term and long-term implications for patients such as oligomenorrhea, amenorrhea, infertility, diabetes mellitus, cardiovascular disease, increased risk of endometrial cancer, and excessive body hair (hirsutism). It is characterized by the following: a) a menstrual cycle that ranges from > 35 days or < 8 cycles/year to complete absence of menses (amenorrhea); b) evidence of androgen excess, such as acne, hirsutism, alopecia, acanthosis nigricans, or increased androgen levels on laboratory testing; and c) all other causes of hyperandrogenism and anovulation have been excluded (3).

pathophysiology scheme of Figure 1. High GnRH pulse frequency increases luteinizing hormone (LH) and decreases follicle-stimulating hormone (FSH), which promotes androgen production and interferes with normal follicular development. Besides, there is evidence of resistance to the effects of FSH at the follicular levels in the ovaries of PCOS women, possibly in part secondary to excess local anti-müllerian hormone (AMH) production [1,7].

It was first observed that patients with PCOS were hyper-insulinemic in response to an oral glucose tolerance test, a condition which is now known as insulin resistance (Figure 2). Insulin resistance is highlighted by the administration of insulin-sensitizing agents, principally, thiazolidinediones (e.g., metformin), which has been found to improve PCOS patients [8]. Insulin action decreases, *in vivo*, in skeletal muscle due to signaling defects moreover, hepatic insulin resistance occurs only in obese women with PCOS. Overall, 50-70% of women with PCOS show clinically measurable insulin resistance, beyond that determined by their body weight (i.e., degree of obesity) [4].

Hyperinsulinemia contributes to excess androgens in several ways [8]:

- Augments LH-stimulated androgen synthesis by ovarian theca cells.
- Potentiates corticotropin-mediated adrenal androgen synthesis.
- Inhibits hepatic synthesis of sex hormone-binding globulin (SHBG), leading to an increase in free testosterone levels.

Moreover, hyperandrogenemia favors excess abdominal fat deposition, exacerbating insulin resistance and hyperinsulinemia for women with PCOS, further enhancing the secretion of ovarian androgens [4]. The etiology for the increased insulin resistance and, consequently, the hyperinsulinism in PCOS remains unclear. A post-binding defect in receptor signaling that selectively affects metabolic, but not mitogenic, pathways in classic insulin target tissues (e.g., adipose tissue, muscle, and possibly the ovaries) has been described. These defects seem to affect glucose transporter-4 (GLUT4) expressions. Additionally, epigenetic dysfunction may play a role in the insulin resistance of PCOS [3].

The presence of obesity worsens insulin resistance, the degree of hyperinsulinemia, the severity of ovulatory and menstrual dysfunction, and pregnancy outcome in PCOS women. Adding, it is associated with an increasing prevalence of metabolic syndrome, glucose intolerance, CVD risk factors, and sleep apnea [9]. Although the risk of PCOS increases modestly with the degree of obesity and that the metabolic features of PCOS are worsened by the concomitant presence of obesity, it is still unclear whether obesity itself is causative [6,8]. While hyperinsulinism is associated with hyperandrogenism in PCOS, insulin resistance alone is not sufficient for the development of PCOS, suggesting that a genetic predisposition to hyperandrogenism must also be present. Variants of several genes involved in the regulation of androgen biosynthesis or action have been described in PCOS [10].

Hyperandrogenism, either clinical or biochemical, is required for the diagnosis of PCOS. Although obesity, LH elevations, and insulin resistance are common among PCOS, these are not required for diagnosis [11]. Chronic anovulation is suggested by oligomenorrhea, with nine or fewer menstrual cycles annually, although amenorrhea with absent ovulation is present in 20% of PCOS patients. Transvaginal ultrasound is considered the best imaging modality, with polycystic ovaries defined as having either ≥12 follicles 2-9 mm in diameter or ovarian volume >10 cm^3 in at least one ovary in the absence of ovarian lesions [2]. It is important to appreciate that polycystic ovaries morphology is not specific to PCOS and can be found in 20-30% of the general population of women 20-25 years of age therefor, isolated polycystic ovaries should not be considered an indication of the syndrome in the absence of menstrual irregularities, infertility or complaints of hirsutism [5,7].

PCOS is a common chronic condition with implications for morbidities, both in short-term (e.g., subfertility and pregnancy-related complications) and long-term risks (e.g., T2DB, CVD, depression, poor quality of life, and overall mortality). A prompt diagnosis allows opportunities for early institution of preventive strategies for the prevention of squeals. However, diagnosing PCOS can be challenging, as the symptoms do overlap with many disorders requiring specific treatment. No single symptom, examination finding, or laboratory data is diagnostic of this disorder. Rather, arriving at a diagnosis requires a systematic approach aimed at excluding the differential diagnoses that could account for the patient's presentation [12]. Etiologies that must be excluded include pregnancy, ovarian or adrenal androgen-secreting tumors thyroid dysfunction, hyperprolactinemia, nonclassical congenital adrenal hyperplasia, ovarian insufficiency, androgen-secreting neoplasm, hypothalamic amenorrhea, and Cushing syndrome [13].

Management of polycystic ovary syndrome

Treatment goals address a variety of symptoms from reproductive function to hirsutism and acne, as well as commonly associated issues such as insulin resistance. First-line pharmacological treatment for menstrual irregularity and hyperandrogenism is oral contraceptive pills, with metformin recommended for management of metabolic features [3]. In addition to symptom management, treatment goals include the prevention of long-term complications associated with PCOS, such as DM and CVD. Treatment protocols for PCOS are complex, and include more than 160 recommendations and practice guidelines. However, treatment outcomes are dependent on adherence to treatment regimens [3,14].

Treatments for PCOS usually require a multi-component plan that necessitates substantial patient engagement. While the literature is replete with studies examining the outcomes associated with various treatments for PCOS, it is critical to understand the role of patient adherence to the treatments to evaluate the value of the treatments for patients in the real world. This is especially important given that the World Health Organization (WHO) reports that in developed countries only 50% of patients with chronic diseases adhere to treatment recommendations [3,14]. Treatment regimens are of no use if a patient does not take the medication or engage in the recommended behavior (e.g., physical activity). Treatment plans for PCOS often include medications that are known to have side effects that may impact adherence. Many PCOS patients are also asked to include lifestyle management interventions in the treatment regimen. Although noting that adherence to diet and physical activity treatment recommendations can be challenging for patients [3].

Dietary management and lifestyle changes of polycystic ovary syndrome

Most women with PCOS, regardless of weight, have a form of insulin resistance that is intrinsic to the syndrome. For this reason, lifestyle changes that improve insulin sensitivity should be the first line of treatment for women with PCOS, particularly for those who are overweight (Figure 2). Lifestyle interventions should also accompany pharmacological treatment [3,15]. While the dietary management of PCOS should focus on weight reduction for those who are overweight, consideration also needs to be given to the role of varying dietary composition in increasing insulin sensitivity [8,9].

Obesity and weight loss in polycystic ovary syndrome

Women with PCOS may need to restrict energy intake significantly to maintain a normal weight. Women with PCOS, with or without insulin resistance, had a significantly lower basal metabolic rate (BMR) compared to non-PCOS women. Levels of ghrelin and cholecystokinin (CCK), hormones that play an important role in appetite regulation, are impaired for women with PCOS [16].

Lifestyle changes effective for women with polycystic ovary syndrome

Lifestyle modifications, including diet, exercise, and weight loss; are effective for women with PCOS, with a reduction in weight of as little as 5% of total body weight having been shown to reduce insulin levels, improve menstrual function, reduce testosterone levels, improve symptoms of hirsutism and acne and increase ovulation and fertility [15]. Furthermore, research suggests that diet and lifestyle changes may be more effective for women with PCOS than the insulin-lowering medication metformin [3,17]. Similarly, no benefits on insulin sensitivity or glucose metabolism were found with the addition of metformin to lifestyle changes, although the combination did result in a greater weight loss and reduction in androgen levels compared to lifestyle changes or metformin alone. Lifestyle interventions for women with PCOS show improvements in weight, hyperandrogenism, and insulin resistance [17].

Dietary management of polycystic ovary syndrome - more than just weight loss

In most of the dietary studies on women with PCOS, improvements in metabolic and reproductive outcomes have been closely related to amelioration of insulin sensitivity, suggesting that dietary modifications designed to improve insulin resistance may produce benefits greater than those achieved by energy restriction alone [17].

Exercise in the treatment of polycystic ovary syndrome

Exercise can play an important role in the prevention and treatment of PCOS, not only through the management of body weight, but also through its effects on the metabolic and hormonal environment associated with PCOS [18].

Exercise and weight loss

Although the metabolic benefits of weight loss are clear, there is still little information regarding the effects of weight loss through exercises for women with PCOS. Further research is required to examine both the negative and the positive effects of exercises in reproductive improvements of PCOS, in addition to the amount and duration of exercises required to modify different aspects of the syndrome.

Potential benefits of exercises in polycystic ovary syndrome patients

It is clear that the major impact of exercises in the treatment of PCOS is through effects on insulin sensitivity and weight loss however, exercises can have many other potential benefits that can help in the treatment of the disease. Regular exercises have been shown to significantly lower plasma homocysteine concentrations in young overweight or obese women with PCOS [14,18].

Medical treatment

Recommendations for the pharmacological treatment of PCOS include the use of the combined oral contraceptive pill (COCP) and/or metformin in those with a clear diagnosis or adolescents deemed at risk of PCOS for the management of symptoms. The following practice points should apply to all medications used in PCOS when considering or recommending pharmacotherapy [20]:

- An individual's characteristics, preferences and values are of importance when recommending pharmacotherapy.
- The benefits, adverse effects, and contraindications in PCOS and general populations should be considered.
- The fact that COCPs, metformin, and other pharmacological treatments are generally off-label for the treatment of PCOS should be discussed to consider the evidence and potential side effects for each option.

Important considerations before medical treatment

Role of insulin resistance in polycystic ovary syndrome

PCOS is associated with the long-term consequences of insulin resistance syndrome. It has been recognized for 20 years that most women with PCOS are indeed insulin resistant. Numerous studies have shown that treatments improving insulin resistance in lean and obese women with PCOS reduce androgen levels, improve ovulatory function and decrease the exaggerated androgenic response to LH and adrenocorticotropic hormone (ACTH) (as shown in Table 1) [3,8]. Hyperandrogenemia is also improved in hyperinsulinemic PCOS women after interventions that only decrease insulin levels [8,14]. However, only a minority of women with insulin resistance, such as most of those who are obese, develop PCOS. Although insulin action seems to play an important role in PCOS pathogenesis, metabolic insulin resistance, and compensatory hyperinsulinemia are not necessary to develop PCOS [3,8,14].

Insulin sensitization significantly decreases testosterone levels and improves ovulation frequencies in PCOS women. Metformin reduces insulin and improves hyperandrogenemia in part by decreasing insulin levels. Peroxisome proliferator-activated recep-

Lifestyle modification: may help attenuate all symptoms of PCOS and reduce the long-term risk of infertility, cardiovascular diseases (CVD) and tpy 2 diabetes mellitus (T2DM).	This is the first line of PCOS management. Increased exercise, improved diet, and weight loss can help to reduce the metabolic abnormalities associated with PCOS. Weight loss of as little as 5-10% has been shown to correct oligoanovulation and improve the gestation of women with PCOS.
Estrogen and progestin oral contraceptive pills (OCPs) therapy: treatment of acne, hirsutism and irregular menstrual cycles.	OCPs therapy can be used to normalize androgen levels, attenuate the signs of hyperandrogenism, and to regulate menstrual cycles. It also helps to reduce the risk of heavy and irregular menstrual bleeding associated with the loss of normal estrogen and progestrone levels.
Anti-androgens (e.g., spironolactone, finasteride, flutamide): treatment of acne and hirsutism.	Spironolactone and flutamide competitively inhibits dihydrotestosterone (DHT) and testosterone by binding to their receptors in peripheral cells (e.g., hair follicles). Finasteride is a 5a-reductase inhibitor that inhibits conversion of testosterone to the more potent DHT in peripheral cells. Anti-androgens can be used synergistically with OCPs, which centrally suppress androgen release. Anti-androgens are contraindicated in pregnancies because they are teratogens.
Metformin: treatment of glucose intolerance, hyperinsulinemia, and anovulation. Reducing circulating insulin levels may secondarily reduce ovarian androgen synthesis.	Metformin reduces glucose intolerance and hyperinsulinemia by increasing insulin sensitivity and decreasing hepatic gluconeogenesis and lipogenesis; therefore can be used for preventing and treating T2DM, thus inducing ovulation. Combined treatment with metformin and clomiphene citrate (CC) has been shown to be more effective than either agent alone for inducing ovulation.
Clomiphene citrate (CC): for inducing ovulation.	CC is a selective estrogen receptor modulator (SERM), which induces ovulation by interfering with estrogen feedback to the brain and thus increasing FSH release. CC treatment is associated with increased risk of multigestational pregnancy because of the large number of antral follicles in polycystic ovaries. Although most women will ovulate on CC only 50% of them will actually conceive, due to the anti -estrogenic effects of clomiphene, which results in thinning of the endometrium. Moreover, CC treatment should be limited to 12 cycles, since longer-term treatment is associated with increased risk of ovarian cancer due to ovarian hyperstimulation.
Gonadotropin therapy: recombinant follicle-stimulating hormone (FSH) and human chorionicgonadotropin (hCG) can be used to induce ovulation in case of unsuccess-ful treatment with clomiphene citrate and metformin.	Exogenous gonadoptropins can be administered to mimic physiological mechanisms of follicle development. FSH is given to promote growth of a dominant follicle to a particular size, and then human chorionic gonadotropin is used to induce ovulation. This therapy must be closely monitored with imaging and laboratory studies to minimize the risks of multigestational pregnancy and ovarian hyperstimulation.
Laparoscopic ovarian drilling (LOD): a surgical procedure that may be used to treat clomiphene citrate-resistant anovulation.	LOD involves the creation of ~10 perforations in the ovary using either cautery or laser. The ablation of some of the ovarian theca is thought to induce ovulation by decreasing androgen production. This procedure may have similar efficacy to hCG therapy, but surgical complications such as adhesion formation remain a concern. This procedure is especially useful in patients with other existing indications for laparoscopy.
In-Vitro Fertilization (IVF): used for the treatment of infertility in women who have not responded to other therapies to induce ovulation.	IVF involves the retrieval of oocytes from the ovaries and *in vitro* combination with sperm to produce embryos, then viable embryos are transferred into the uterus. Women with PCOS have similar success and live birth rates compared to women without PCOS. Risks of the procedure include multigestational pregnancy because of the transfer of multiple embryos and ovarian hyperstimulation as a consequence of gonadotropin therapy, which is used prior to oocyte retrieval to promote follicular development.

Table 1: Various treatment protocols of Polycystic Ovary Syndrome (PCOS) [3].

tor (PPAR) agonists increase metabolic insulin actions in adipose, muscle, and hepatic tissues, without changing insulin sensitivity and levels for women with normal insulin sensitivity. PPAR agonists improves hyperandrogenemia without decreasing insulin in lean PCOS women, by directly restoring normal androgen production in these women [21].

Polycystic ovary syndrome: a syndrome of androgenic insulin hypersensitivity

The foregoing studies suggest that women develop PCOS in part because of selective androgenic insulin hypersensitivity (Figure 2). In some women, this defect may be sufficiently severe to cause typical PCOS, in the absence of insulin resistance and hyperinsulinemia. PCOS consequences in these women will improve by reducing insulin levels (i.e., acarbose, diazoxide, and metformin) or improving specifically androgenic insulin hypersensitivity gamma peroxisome proliferator activator receptors (PPAR γ-agonists). However, in most women with PCOS, the development of compensatory hyperinsulinemia is probably necessary for the expression of the syndrome. In these women, interventions that improve insulin resistance and compensatory hyperinsulinemia (weight loss, insulin-sensitizing drugs), decrease directly insulin levels (acarbose, diazoxide), or improve specifically androgenic insulin hypersensitivity, PPAR γ-agonists would improve their PCOS manifestations [22].

Oral contraceptive pills

When lifestyle intervention fails to control PCOS symptoms or long-term cardiometabolic risk factors, or if symptoms require rapid intervention, pharmacologic treatment needs to be considered. For years, the only treatment of PCOS was oral contraceptive pills (OCPs), when fertility is not an issue. They remain the mainstay for the treatment of PCOS because they effectively regulate menstrual cycles, decrease the risk of endometrial cancer and improve acne and hirsutism, while assuring a reliable reversible contraceptive method. However, OCPs have well-known increased risks of thromboembolism, hypertension, and hypertriglyceridemia [23]. Moreover, OCPs decrease insulin sensitivity and glucose tolerance in the short term therefore, may increase the long-term risk of T2DM [21].

Finally, OCPs may potentially increase CVD risks in these women. Therefore, for women with PCOS, especially those who do not need contraception, OCPs may not be the optimal treatment, since they are already at higher risks for T2DM and CVD than the general population and they will have to use OCPs for long periods [24].

Insulin-sensitizing drugs

Since insulin action plays a key role in the pathophysiology of PCOS, growing interest was given in the past years to the use of insulin sensitizers as a metabolically suited alternative for PCOS management however, none of them have received approval for specific use in PCOS by governmental regulatory agencies [3,8].

Metformin

Metformin is a biguanide approved for DM control, whose primary mechanism of action is the reduction of hepatic gluconeogenesis, via activation of the liver kinase B1 (LKB1) - adenosine monophosphate-activated protein kinase (AMPK) pathway, along with other systemic insulin-sensitizing effects. Metformin is not a pure insulin sensitizer because it will reduce gluconeogenesis and insulin levels in all individuals, even those without insulin resistance and hyperinsulinemia. Importantly, metformin does not cause hypoglycemia. The regular formulation of metformin was beneficial at dosages between 1275 and 2550 mg/day for ovulation for women with PCOS and hyperandrogenism. Furthermore, it was shown that a higher dose of metformin (2.5 g/day) is more effective on waist circumference and weight loss than a lower dose (1.5 g/day) [25].

It is probably advisable to prescribe initially the highest dosage in obese patients (1000 mg twice daily) and use a lower dosage in non-obese ones (875 mg twice daily), to minimize side effects. The most serious risk with the use of metformin is lactic acidosis, which has been reported rarely and almost exclusively in populations at high risk, such as individuals with renal insufficiency (creatinine clearance <30 mL/min), liver disease, or congestive heart failure (left ventricular ejection fraction <30%). The most common side effects are gastrointestinal disturbance [26]. When prescribing the regular formulation of metformin, it is important to increase the dose progressively to minimize side effects. Another way to reduce side effects is by splitting the dose to three or four times a day. Metformin is classified as a Category B drug in pregnancy [17].

Thiazolidinediones

Thiazolidinediones (TZDs) are a class of insulin-sensitizing drugs approved for the treatment of T2DM, by enhancing glucose

uptake in adipose and muscle tissues and decreasing hepatic glucose output. TZDs activates PPAR γ-receptors, which make them true insuline sensitizers, without altering insulin levels in individuals with normal insulin sensitivity or causing hypoglycemia. Pioglitazone, approved in USA since 2001, is administered at dosages of 15, 30, or 45 mg/day. Due to the mechanism of action, the TZDs' actions increase progressively with maximal effects peaking only after 6-8 weeks of treatment. However, there is much less experience with these drugs for women with PCOS, as well as in T2DM, as compared to metformin but, side effects with the use of TZDs for women with PCOS are rarely reported. That is, the most common side-effects in diabetics include edema, which is increased with the concurrent use of insulin or insulin secretagogues, and weight gain. Moreover, pioglitazone treatment was followed by decreased lumbar and hip bone mineral density (BMD) and decreased measures of bone turnover even for women with PCOS. TZDs are classified as Category C drugs in pregnancy because they have been shown to cause decreased fetal maturation in animal models. Therefore, these drugs should be used with an effective contraceptive method and should be avoided for women seeking fertility [3,8].

Clinical benefits for women with polycystic ovary syndrome

Improving menstrual cyclicality and fertility with metformin

Interestingly, ovulation and pregnancy rates increased progressively with the use of metformin, since it is not a non-specific ovulation inducer. It will improve ovulation in PCOS women only after reducing insulin resistance and levels [27]. Therefore, in the absence of the expected metabolic improvements with metformin, it is not a surprise that fertility parameters did not improve. Thus, due to unexpected minimal metabolic and ovulatory effects of the formulation of metformin used in the PCOS studies, it should not be probably considered the definitive study for the choice of the best pharmacologic first-line therapy in PCOS anovulatory women. For women with PCOS who became pregnant, metformin intake during pregnancy resulted in a higher live birth and lower miscarriage, preterm labor, gestational hypertension, preeclampsia, gestational diabetes, and intrauterine growth retardation [28].

Indeed, it has been shown that a polymorphism of LKB1 was associated with ovulatory response to metformin treatment of pregnancy in PCOS. Furthermore, the use of metformin during pregnancy has been shown to reduce first-trimester pregnancy loss, which can be as high as 30-50% for women with PCOS. In fact, serum levels of glycodelin and insulin-like growth factor-binding protein-1 (IGFPB-1), two important proteins for embryo implantation, have been shown to be low in PCOS women during the first trimester of pregnancy, which were corrected with metformin. Finally, metformin induces normal ovulation, such that the risk of multiple gestations is no more than the general population [3,8].

Improving menstrual cyclicality and fertility with thiazolidinediones

TZDs appear effective drugs to restore normal menstrual frequency and ovulation for women with PCOS, similar to metformin or even better therefore, they are potential drugs for treating oligomenorrhea. Inositol resulted in higher *in vitro* fertilization (IVF) rates of assisted reproduction [29]. Combined therapy of inositol, antioxidants, and vitamins may be a successful approach for the management of PCOS. Adding that, pioglitazone and inositol improve the menstrual frequency in ovulation induction (OI) [30].

Benefits of clinical hyperandrogenism hirsutism

Metformin could be considered as first-line therapy for mild-to-moderate hirsutism in some women. However, severe hirsutism needs to be treated with anti-androgen drugs, supplemented with an appropriate contraceptive method. But for women who do not require hormonal contraception, the combination of metformin with an anti-androgen may be considered [2,17].

Management of long-term risks of type-2 diabetes and cardiovascular diseases

Since PCOS is associated with significant long-term risks of T2DM and probably CVD, its chronic management should not exacerbate and ideally reduce them. In this context, treatment regimens of insulin-sensitizing agents for women with PCOS have been shown to increase glucose tolerance; improve endothelial function and markers of established atherosclerosis; and reduce CVD risk factors (e.g., serum triglycerides, high-density lipoproteins cholesterol, blood pressure, c-reactive protein, and endothelin-1 concentrations) [3,8].

Concerns for pharmacological management

For women with PCOS, the first-line agent for improving fertility should be chosen by the physician after considering and discussing available data and according to the patient's will. The decision should put safety, healthy pregnancy, and rapidity issues in perspective to make a choice. If achieving rapid pregnancy is

required by the couple, because of age or longstanding infertility, clomiphene citrate (CC) should probably be preferred as first-line therapy, along with lifestyle modifications. CC could be used in combination with metformin to maximize fertility. However, when the couple is willing to wait, metformin should probably be the first treatment because it will favor the return of normal ovulation, which carries the same risk of multiple pregnancies as the general population and may decrease the risk of early pregnancy loss. Even more importantly, metformin acts more slowly and tends to reduce appetite, which allows for lifestyle changes and weight loss before pregnancy. Better weight control during pregnancy is essential to prevent adverse maternal and offspring outcomes [3,8].

When contraception is desired, the benefits of OCPs probably outweigh any potential risks in most women with PCOS. However, if a PCOS woman has impaired glucose tolerance (IGT) or T2DM or has developed a metabolic complication following the use of OCPs, she should be probably recommended another contraceptive method and prescribed an insulin sensitizer. If the OCPs cannot be stopped, insulin sensitizers should be prescribed to use in combination, since insulin sensitizers will effectively counteract the deleterious effects of OCPs. The preferred insulin-sensitizing drug should be metformin, which is associated with a significant weight loss in most women while TZDs can cause weight gain [30].

When fertility is not an issue and oral contraception is not required, the first-line therapy can consist of either OCPs use or an insulin sensitizer. Fortunately, insulin-sensitizing drugs are new therapies for women to whom OCPs are contra-indicated or not tolerated. Otherwise, because of long-term metabolic risks, insulin sensitizers should probably be preferred for women with PCOS, who:

- Have excess body weight [body mass index (BMI) > 25 kg/m^2] or central adiposity (waist circumference >88cm);
- Display the metabolic syndrome;
- Have another clinical evidence of insulin resistance, such as acanthosis nigricans, high insulin levels [during fasting or an oral glucose tolerance test (OGTT)] or sex hormone-binding globin (SHBG); or
- Have genetic predisposition to T2DM or CVD, (e.g., a positive first-degree family history of T2DM or early CVD or strong second-degree family history).

Of note, insulin-sensitizing agents have been shown to improve hyperandrogenemia, anovulation, and acne in all PCOS women, regardless of pre-treatment degree of obesity or insulin resistance. Thus, both alternatives should be discussed with the patient to help her choose best-individualized therapy, even in non-obese women with PCOS [6,8].

Monitoring of clinical outcomes

All women should be screened with a complete lipid profile and OGTT, keeping in mind that fasting glucose is not appropriate for screening women with PCOS for abnormal glucose tolerance. Women seeking fertility should be screenied for IGT or DM, since any degree of abnormal glucose tolerance before pregnancy would translate into gestational diabetes once pregnancy occurs and should be managed as such. After its initial management is provided to the patient, it is essential to offer an appropriate follow-up to ensure adherence to lifestyle modifications and medications, to verify weight changes, and to assess responses to therapy and side effects [21].

Women treated with metformin alone for fertility should be followed-up every 3-6 months, depending on the desired rapidity of the intervention. In general, the addition of CC should be discussed after 6 months, if the woman is not yet pregnant, because maximal effects of the drug by itself are probably achieved at that time, although progressive weight loss would provide subsequent improvement of fertility. Women with PCOS not seeking fertility, who are on a long term treatment with insulin sensitizers, should be followed-up at least every 6 months. An initial telephone availability or 3-month visit is required to discuss the side effects and if metformin is not tolerated, a slow-release formulation or a TZD should be considered. Since metformin and TZDs have favorable effects on insulin sensitivity and glucose control in type 2 diabetics, it could be envisaged to combine these medications if symptoms are not improved by metformin alone. Besides, weight monitoring (and waist circumference in overweight women), blood pressure, and lipids should be assessed at every visit [3,8].

Therapy should aim for non-deterioration and ideally the improvement of these parameters. Furthermore, it is recommended that patients with normal glucose tolerance should be rescreened with an OGTT at least once every 2 years, or more frequently if additional risk factors emerge. Weight loss and exercise are effective means for restoring normal ovulatory menstrual cycles and andro-

gen levels. It is also the best method for DM prevention. With adequate follow-up, it is possible to achieve clinically significant and sustainable weight loss for women with PCOS, particularly with the combination of metformin. Therefore, insulin sensitizers could be stopped if clinical outcomes, androgen levels, and metabolic parameters are well controlled, and the woman lost at least 10% of her initial body weight. This degree of weight loss is normally associated with a significant proportion of subjects displaying cessation of symptoms and metabolic anomalies. If the prospect of stopping the drug is explained to the patient, providing she has lost such amount of weight, this may increase her motivation to embrace lifestyle modifications with a clear and realistic objective [21].

Ovulation induction in polycystic ovary syndrome

Patient characteristics, rather than treatment protocols, may determine the success and/or complication rates of OI. About 80% of the anovulatory patients can be classified as normogonadotropic normoestrogenic, where patients with PCOS are within the World Health Organization class 2 (WHO2). Before treatment initiation, preconception counseling should address any potential lifestyle modifications (i.e., overweight, smoking, and alcohol consumption). The most effective first-line treatment in WHO2 anovulation is CC, tradionally followed by FSH in case of conceiving failure, where a cumulative single live birth rate of 71% after 2 years follow-up is achived. Like FSH, laparoscopic ovarian drilling (LOD) maybe as effective as second-line OI treatment in CC-resistant anovulation, yet both strategies have their advantages and disadvantages. The use of metformin in OI should be restricted until suitable patient groups can be identified. There is insufficient evidence to apply aromatase inhibitors for OI. Thus, patient-tailored treatment protocols, based on initial patient characteristics, should be developed to improve outcomes and decrease complications [31].

Many treatments are proposed by different guidelines for infertility with PCOS and include CC, letrozole, and gonadotrophins. However, there is a lack of clarity around the relative efficacy of these different treatments. Despite the agreement between most guidelines of the importance and priority of lifestyle modifications in PCOS and weight loss, when women are overweight or obese, there are still limited studies that compare lifestyle modifications and pharmacological treatments for reproductive outcomes [32]. With regards to only pharmacological treatments, CC is recommended as the first-line treatment for OI in infertile women with POCS, with the alternative treatment letrozole, which has encouraging results in many recent trials [33]. Although the insulin sensitizer metformin has been recently recommended as a first-line treatment, its role and specific indication are controversial [17].

The second-line treatment is usually recommended as gonadotrophins or LOD. Additional issues relating to the treatment of reproductive outcomes which are still somewhat controversial include the best time to use *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) for women who failed to become pregnant after pharmacological treatment and the potential benefit of modern techniques like *in vitro* maturation (IVM) [2].

In unselected women with PCOS, letrozole was associated with a higher live birth rate than CC while, CC was better than metformin or placebo. For women with CC-resistant PCOS, GnRH were associated with a higher live birth rate than CC plus metformin, which was better than LOD, known to be associated with lower multiple pregnancy rates than other medical treatments. For women with PCOS undergoing IVF/ICSI, the addition of metformin to GnRH resulted in less ovarian hyperstimulation syndrome (OHSS), and higher pregnancy and live birth rates than GnRH alone, as shown in the sceheme of Figure 2. GnRH antagonist was associated with less OHSS, gonadotrophin units, and shorter stimulation length than GnRH agonist. Letrozole appears to be a good first-line treatment and GnRH, as a second-line treatment, for anovulatory women with PCOS. LOD results in lower multiple pregnancy rates, however due to the heterogeneous nature of the included populations of women with PCOS, further larger-scale trials are needed with a more precise assessment of treatments according to heterogeneous variants of PCOS [32].

Clomiphene citrate

Meta-analyses reports showed that CC had statistically higher ovulation and pregnancy as compared to placebo in overall women with PCOS. Early follicular CC had higher pregnancy than late luteal CC with less mature follicles [34]. Higher ovulation, pregnancy, and live birth happened after CC mainly for women with BMI ≥30 kg/m^2, while metformin resulted in higher pregnancy for women with BMI <30 kg/m^2. Treatment with CC plus metformin was far more efficient than CC or metformin alone, with regards to ovulation, pregnancy, and live birth; yet causing unpleasant gastrointestinal side effects [17,30].

GnRH treatment resulted in higher pregnancy and live birth as compared to CC treatment for 10 days and for 5 days, respectively. For women with CC-resistant PCOS, GnRH resulted in a statistically higher ovulation, pregnancy, and live birth than CC plus metformin, which in turn resulted in a higher live birth than LOD. In the same population of women, the addition of dexamethasone, N-acetyl cysteine (NAC), or contraceptive pills to CC resulted in higher ovulation, pregnancy, and live birth than CC alone. Furthermore, the addition of metformin to CC resulted in more favorable outcomes compared with the addition of NAC, regarding ovulation and pregnancy. However, the cost of treatment with GnRH followed by LOD then CC plus metformin is higher [34].

Letrozole

For women with CC-resistance, letrozole with or without metformin resulted in higher live births as compared to CC with metformin besides, letrozole resulted in higher ovulation and pregnancy than anastrozole and higher ovulation than LOD. Long-term letrozole (10 days) resulted in higher pregnancy than short-term letrozole (5 days) [30,33].

Gonadotrophins

Meta-analyses reports showed that, GnRH treatment resulted in statistically higher multiple pregnancies, live births, and costs of short- and long-term treatments in comparison with LOD for women with CC-resistant PCOS [35]. It resulted also in higher ovulation, pregnancy, and live birth as compared to CC with and without metformin [34], but lower pregnancy in comparison with letrozole [33]. GnRH coadministration with metformin resulted in higher pregnancy and live birth in OI [36], higher OHSS, number of oocytes retrieved, implantation rate, live birth, and lower miscarriages, in IVF [29]. Recombinant FSH resulted in a lower dose and stimulation duration than other urinary gonadotrophins in OI [31].

In Vitro fertilization in polycystic ovary syndrome

Coadministration of metformin has beneficial effects on clinical outcomes and biochemical markers of hyperinsulinemia in IVF cycles [37]. In afct, metformin treatment was found to decreases the total number of follicles for patients on the day of human chorionic gonadotropin (hCG) treatment, with no change in follicles 14 mm in diameter or the mean number of oocytes retrieved. However, the mean number of mature oocytes, oocytes fertilized, and cleaving embryos (4-cell or greater by 72 h) was higher after metformin treatment [36]. Fertilization rates (64% vs. 43%) and clinical pregnancy rates (70% vs. 30%) were also increased after pretreatment with metformin.

Metformin is coadministered also to women with PCOS undergoing IVF cycles, who require coasting to allow their oestradiol (E2) levels to fall before hCG administration. The maximum E2 concentrations and number of days of coasting were all found low in the metformin-treated women with increased clinical pregnancy rates (71 vs. 30%, P < 0.05). In contrast, Kjøtrød., *et al*. [38], conducted a randomized controlled trial to assess the impact of pretreatment with metformin on the outcome of IVF/ICSI in 72 oligomenorrhoeic women with PCOS. They reported no differences in the primary end-points to the duration of FSH stimulation of E2 on the day of hCG injection in the metformin and placebo groups, respectively. The secondary end-point number of oocytes, fertilization rates, embryo quality, pregnancy rates, and clinical pregnancy rates were equal. For women with normal BMI (<28 kg/m^2), pregnancy rates following IVF were 71% vs. 23% in the metformin and placebo groups, respectively (P = 0.04). The overall clinical pregnancy rates were 51% vs. 44% in the metformin and placebo groups, respectively. However, in the normal weight subgroup, clinical pregnancy rates were 67% and 33%, respectively (P = 0.06).

The biochemical environment of PCOS, namely the elevation of LH and hyperandrogenism are both independent risk factors for the development of OHSS [29,32,36]. The exact mechanism for ovarian responsiveness remains unknown in PCOS, yet it may be mediated via insulin-like growth factor (IGF) driven production of vascular endothelial growth factor (VEGF) in the ovarian stroma, leading to increased delivery of ovarian stimulatory drugs to the ovary by improving overall blood flow [39].

The mainstay of the ovarian stimulation agent in modern practice is the choice of a GnRH preparation, which lies between the urinary derived or recombinant FSH [29,36]. Daya [40] had shown in a meta-analysis of 18 randomized controlled trials that there is no difference in the oocyte yield or risk of OHSS for women with either product. This contradicts the meta-analysis of the Cochrane database by Hughes., *et al*. [41], who showed a reduction in the risk of OHSS for women with CC-resistant PCOS, when using purified forms of FSH compared to urinary FSH. Rather than the type of FSH used, it is the polycystic ovary's sensitivity to FSH that remains the most significant factor with a higher peak E2 level attained with

low doses of FSH or human menopausal gonadotropin (hMG) and with a steeper slope of increment during stimulation [37,38]. Thus, stimulation regimes for women with PCOS have employed much lower doses of FSH with a stepwise increase if the response was inadequate (low-dose step-up protocol) with close ultrasound and serum E2 monitoring to ensure early identification of over response. With this approach, the incidence of OHSS and multiple pregnancies have been significantly reduced [32,36].

In general, women with PCOS have a higher yield of oocytes in response to OI compared to other groups of infertile women [38]. However, the quality of oocytes for women with PCOS seems to be less good with a lower overall fertilization rate and poorer embryo quality. The etiology behind this remains unclear but may be reflective of the abnormal biochemical environment in which the oocytes develop in PCOS. As a result of the lower fertilization rate, most women with PCOS will undergo ICSI, rather than conventional IVF in an attempt to improve fertilization rates [29,38].

The standard long protocol with the use of GnRH agonist starting in the preceding cycle to down-regulate the hypothalamic-pituitary axis is a well-established regime, because it leads to improved cycle control, higher pregnancy rates, lower cycle cancellation rates, and improved yield of mature oocytes. However, there is usually a higher requirement for GnRH with this approach, since GnRH agonist tends to suppress the ovarian response. In the context of PCOS, the GnRH agonist-mediated suppression of ovarian response should theoretically be a positive phenomenon, as it would dampen the otherwise high sensitivity of the polycystic ovary for GnRH, with the added benefit of a reduction in cases of OHSS [41].

However, several authors have reported that this expected reduction has not been seen in practice, and since the introduction of GnRH agonists into IVF cycles, there has been a six-fold increase in the incidence of OHSS in GnRH agonist cycles compared to non-GnRH agonist cycles. In cycles using GnRH agonists for women with PCOS, there remains a higher yield of oocytes and higher peak E2 level. This paradoxical effect on oocyte yield and OHSS rates with GnRH agonists may be due to the abolition of the spontaneous LH surge that would otherwise occur and would in turn cause spontaneous luteinization and prevent excessive follicular growth [36]. This abolition of the LH surge would also explain the finding of an increased risk of OHSS for women with PCOS using GnRH agonist in a short protocol regime [29,35]. Similar effects on oocyte yield and the risk of OHSS have also been found for women with PCOS using GnRH antagonists during ovarian stimulation.

In a systematic review and meta-analysis of five randomized trials, Al-Inany [42] showed that the use of antagonists does not confer a statistically significant reduction in the risk of developing OHSS. However, in practice most IVF centers would continue to use GnRH agonists in the management of cycles for women with PCOS, not least to prevent premature ovulation but also due to the improved outcomes concerning pregnancy. GnRH antagonists do however offer the potential option of triggering oocyte maturation with GnRH agonists rather than hCG, a strategy which may reduce the risk of developing OHSS [41].

The surgical management of polycystic ovarian syndrome

The surgical management of PCOS has evolved with the introduction of new laparoscopic and minimally invasive techniques. There is good evidence from randomized studies to support the use of LOD for women with PCOS, especially those who are resistant to CC treatment. The benefits of LOD include increased ovarian sensitivity as well as reduced circulating androgens and follicular phase LH levels, which result in more regular menstruation and ovulation and increased fertility. There is some evidence showing a reduction in miscarriage rates along with a reduced risk of OHSS following IVF treatment. This approach allows for a complete inspection of the female pelvis along with the treatment of other conditions such as endometriosis, uterine fibroids, and pelvic adhesions [35].

Meta-analyses reports showed that LOD resulted in lower live births than treatment with CC plus metformin and GnRH, respectively; higher pregnancy than metformin alone; lower ovulation than letrozole; higher costs than CC plus metformin, but lower than GnRh; and lower multiple pregnancies than other medical treatments. Ovulation and pregnancy were higher for lean women (BMI <25 kg/m^2) with CC-resistant PCOS than for overweight and obese women (BMI ≥ 25 kg/m^2) undergoing LOD [32].

The technique of ovarian diathermy was described in a small study involving 21 nulliparous women with PCOS, oligomenorrhoea, and infertility; which introduced four 40 W diathermy burns to a depth of 4 mm to each ovary for 4 seconds. Regular menstrual cycles and regular ovulation ensued in 81% of women, and 52% of women conceived spontaneously. It was concluded that LOD was a useful option for women with PCOS [32,35]. It has been also sug-

gested that the benefits of LOD can be achieved when ovarian diathermy is performed on just one of the ovaries. Women with PCOS were randomized to either unilateral or bilateral LOD as part of treatment in CC-resistant PCOS. The results showed that both unilateral and bilateral LOD resulted in ovulation from both ovaries. The mechanism of action of LOD is believed to be via a correction of disturbed ovarian-pituitary feedback. Unilateral LOD was believed to be as effective as bilateral ovarian diathermy in the resumption of menstruation and pregnancy rates. The risk of adhesion formation, bleeding and infection is extremely small following LOD, although women should be counseled about these risks before undergoing surgery [32].

A new technique of transvaginal hydrolaparoscopy can be performed under local anesthesia in an outpatient setting. LOD by transvaginal fertiloscopy with bipolar electrosurgery appears to be an effective minimally invasive procedure in CC-resistant women with PCOS [32,35]. It also allows for aqua assessment of the pelvis, fallopian tubes, and ovaries. Subtle para-ovarian and peri-tubular adhesions are more readily seen and can be treated [43]. Therefore, LOD in the form of hysteroscopy and endometrial curettage should be performed at the same time for women with anovulatory PCOS. To prevent the long-term complications of unopposed estrogen stimulation of the endometrium, regular menstruation should be induced with cyclical progestogens (e.g., provera for 1 week every 3 months). This however may not be necessary if regular menstruation resumes following LOD. There is evidence that LOD has long-term benefits for women with anovulation secondary to PCOS. In a long-term follow-up study, 6-10 years after a randomized controlled study comparing LOD with gonadotrophin therapy, the LOD group of women had an increased number of ongoing spontaneous menstrual cycles and 79% had delivered live infants. Unilateral LOD seems to be a suitable replacement for conventional bilateral LOD for CC-resistant PCOS [44].

A large meta-analysis of nine studies compared the outcomes of CC-resistant women with PCOS undergoing LOD or gonadotrophin stimulation [32,35]. It examined primary outcomes as ovulatory, pregnancy, and live birth rates and secondary outcomes as miscarriage, multiple pregnancies, and OHSS rates. Whilst all the primary outcomes were similar, the LOD group had lower multiple pregnancies and ovarian OHSS rates compared to gonadotrophin treatment, but similar pregnancy rates. There was no clear outcome data on the long-term effects of LOD on ovarian function. It is believed that LOD may be beneficial in decreasing the risk of OHSS and improving the ongoing clinical pregnancy rate for women with PCOS undergoing IVF. Ovarian diathermy did not appear to have a deleterious effect on IVF outcomes, in terms of the number of oocytes retrieved or embryos resulting [45].

Mechanisms by which laparoscopic ovarian drilling induces ovulation

The mechanism by which ovarian diathermy induces ovulation remains unclear, but many theories have been suggested. Disruption of the ovarian cortex is thought to affect local paracrine factors leading to a reduction in androgen production. A prospective study examined the effects of LOD on 50 women with PCOS, where pre- and post-operative mean levels of inhibin B were measured. There was an inverse correlation between BMI and inhibin B serum levels. The study failed to show any significant changes in inhibin B following LOD, which makes it unlikely that this hormone has any direct role in the effects of LOD [35].

Another mechanism of action has been shown from the decrease in ovarian stromal blood flow velocity following LOD. In a study where colour Doppler blood flow within the ovarian stroma was recorded and serum concentrations of FSH, LH, and testosterone were measured for 52 women with PCOS before and after LOD, there was a significant correlation between hormonal and ovarian stromal blood-flow changes. The changes in the Doppler indices were significantly higher for women who ovulated. The measurement of ovarian stromal blood flow correlated to changes in androgen markers of PCOS [32]. LOD significantly reduced ovarian reserve parameters [i.e., AMH, ovarian volume (OV), and antral follicle count (AFC)] and ovarian stromal blood flow indices [i.e., vascularization index (VI), flow index (FI), and vascularization flow index (VFI)], with no observed correlation between AMH levels and Doppler indices [46].

Intrauterine insemination, *in vitro* fertilization, intracytoplasmic sperm injection-related interventions

Along with the general considerations for optimizing maternal health pre-conception, such as cessation of smoking, taking folic acid, and reduction in alcohol intake; there are several specific factors to be addressed for women with PCOS. One of the most important factors to be considered is weight reduction in obese or overweight patients. Excess body fat, and especially central obe-

sity, with a concomitant increased BMI, are associated with insulin resistance, hyperinsulinemia, and hyperandrogenaemia. Actually, up to 80% of women with PCOS will have evidence of biochemical insulin resistance. Insulin has a trophic action on ovarian steroidogenesis and LH secretion and will cause a reduction in sex hormone-binding globulin secretion. Furthermore, there is a direct correlation between the patient's weight, cycle disturbance, and risk of infertility with even moderate obesity (i.e., BMI >27), being associated with an increased risk of anovulation. Therefore, obese women (i.e., BMI >30) should be encouraged to lose weight before the commencement of any fertility treatment [15,37].

Obese women are also likely to respond less well to ovarian stimulation with a higher requirement for GnRH, a greater risk of response, and a lower pregnancy rate with a higher miscarriage rate. Furthermore, the risk to both mother and baby from obstetric complications is also considerable. Therefore, weight loss should be the first-line treatment in obese women. Indeed, a loss of 5-10% of total body weight in obese women with PCOS has been shown to restore spontaneous reproductive function in 55-100% of women within 6 months of weight reduction. Weight loss will cause an improvement of insulin sensitivity and a concomitant correction of hyperinsulinemia and nearly every other biochemical abnormality seen within this group of women [15,17,21].

Meta-analyses repors showed statistically significant lower values of progesterone, LH, and premature luteinization rate during intrauterine insemination (IUI) after GnRH antagonist and lesser dose, duration of gonadotrophins, and OHSS rate after GnRH antagonist during IVF/ICSI. Metformin compared to placebo in IVF resulted in higher live births, pregnancy, lower miscarriage, lower OHSS, and lower E2, gonadotropin dose, and higher implantation rate; however disadvantages included more, yet mild, gastrointestinal side effects [32]. Compared to placebo, inositol resulted in higher pregnancy with better results after myoinositol than D-Chiro inositol, while mannitol resulted in lower OHSS [41]. IVM used for women with PCOS had higher implantation but lower mature oocytes, lower canceled cycles, and higher pregnancy than IVM for non-PCOS patients [37,38].

Other interventions

Bariatric surgery improved menstrual frequency for women with PCOS. Statins did not improve menstrual frequency of ovulation for women with PCOS not trying to conceive. Reports on endocrine and metabolic outcomes between fluoxetine with sibutramine found no significant difference between both drugs. Orlistat versus other anti-obesity drugs was assessed and found no difference in reproductive outcomes. Finally, a review assessed the use of antidepressants for women with PCOS [47-50].

Conclusions

Treatment of anovulation in PCOS should start with lifestyle modification before commencing pharmacological agents, especially in obese women with BMI >30 kg/m^2. The firstline pharmacological agent is usually CC and some guidelines propose letrozole as an alternative. Overall, letrozole resulted in higher live birth and clinical pregnancy rates than other OI drugs, especially CC, for women with PCOS (with or without CC resistance), although letrozole is an off-label drug in OI. Nevertheless, the issue of safety in pregnancy for both CC and letrozole has not been completely resolved. Most large retrospective studies found no evidence of any difference between these drugs [32]. Metformin is recommended in many guidelines as an adjunctive treatment with CC for women with glucose intolerance and obese women, while the National Institute for Health and Clinical Excellence Guidance (NICE) recommended metformin alone or with CC as a first-line treatment. For women with PCOS, treatment with CC plus metformin also resulted in better reproductive outcomes than CC or metformin alone [26,27,33].

The Australian National Health and Medical Research Council evidence-based guidelines suggested that it is acceptable to use GnRH as a first-line treatment. Generally, the use of gonadotrophins resulted in a higher live birth and clinical pregnancy rates than CC for women with PCOS. As recommended by many guidelines, CC is usually used for six months, after which period women are considered to be CC resistant and necessitates a further second-line treatment [34].

Most fertility guidelines recommend low dose gonadotrophins or LOD as a second-line treatment. Treatment with CC plus metformin was also recommended by some guidelines, if not already used as a first-line treatment. GnRH have the disadvantage of cost and increased rates of multiple pregnancies, while LOD has a risk with anesthesia, decreased ovarian reserve, and the need to use adjuvant drugs for OI after surgery. For women with CC resistant PCOS, GnRH resulted in better reproductive outcomes than many

OI drugs, with the disadvantages of increased multiple pregnancies and increased cost. Women who used GnRH had higher live birth than those who were prescribed CC plus metformin or LOD, respectively, and higher clinical pregnancy and ovulation rates than CC plus metformin. CC plus metformin resulted in a higher live birth rate and lower cost than LOD. GnRH are more expensive than LOD, which has the advantage of lower rates of multiple pregnancies compared to other interventions, such as GnRH for CC-resistant PCOS. LOD for lean women seems to have better reproductive outcomes than for overweight and obese women [32].

There is a lack of data on the use of IVM in PCOS, yet current recommendations state that IVF should be used in case of CC failure, which is defined by the failure of conception after 6-9 months. Current scientific evidences suggest the use of GnRH antagonists and the addition of metformin to GnRH agonist to decrease OHSS. Reports shwed akso higher pregnancy and implantation rates with lower cancellation rates for women with PCOS undergoing IVM compared to IVM in non PCOS women [37,38].

Despite the large number of reviews and randomaized controlled studies that have been conducted assessing different treatments for the management of reproductive outcomes for women with PCOS, there are still a considerable number of research gaps. Recently, the international evidence-based guideline for the assessment and management of PCOS has issued new recommendations for the management of PCOS. These guidelines state that letrozole should be considered a first-line pharmacological treatment for OI for women with PCOS, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy, and live birth rates. They also stated that inositol should currently be considered an experimental therapy in PCOS, with emerging evidence on efficacy highlighting the need for further research [30].

Furthermore, research on the possible reasons for CC resistance and failure utilizing unified definitions is needed. This is particularly relevant, given some recent reviews revealed that the antiestrogenic effect of CC, specifically on endometrial tissue; is not enough rationale for resistance and failure [32]. Also, a recent crossover randomized control study found that there is no difference in clinical pregnancy and live birth rates between CC and letrozole, when used as a second-line treatment for women who failed to ovulate or conceive with CC or letrozole as a first-line of treatment [33].

It is also important to note that a thorough study of the cost-effectiveness of any of these treatments has not been performed, particularly in low-income countries. Further investigation of metformin with regards to its cost-effectiveness, safety, and effectiveness for non-obese women is also needed. There is also a lack of data relating to the comparison between the use of LOD and medical treatment as a first-line treatment, and the minimum efficient dose of LOD to induce ovulation without affecting ovarian reserve [37,38].

In agreement with most recent international guidelines on the management of PCOS, letrozole was superior to other OI agents as a first-line pharmacological treatment with gonadotrophins a second-line pharmacological treatment for anovulatory women with PCOS [32].

Competing Interests

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