Minerva Endocrinologica
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Title: Novel strategies in the management of polycystic ovary syndrome
Paper code: Minerva Endocrinol-2338
Submission Date: 2015-03-10 19:16:41
Article Type: Review Article

Files:
1): Manuscript
    Version: 2
    Description: MA
    File format: application/msword

2): Tables 1
    Version: 1
    Description: TABLE I
    File format: application/msword

3): Figures 1
    Version: 1
    Description: FIG1
    File format: image/tiff

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    Version: 1
    Description: FIG3
    File format: image/tiff

TITLE

Novel strategies in the management of polycystic ovary syndrome

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NOTES
Dates of any congress where the paper has already been presented. Mention of any funding, research contracts or conflict of interest. Acknowledgements..

Congresses:NO
Funding:NO
Conflicts of interest:NO
Acknowledgements:NO

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ABSTRACT

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S is a common endocrinopathy affecting reproductive-aged women. PCOS has been recognized as a syndrome combining reproductive and metabolic abnormalities with lifelong health implications. Cardiometabolic alterations require regular screening and effective and targeted lifestyle advice to lose weight as well as to prevent weight gain. Pharmacological therapy includes insulin-sensitizer drugs and agents that act directly on metabolic comorbidities, such as statins and anti-obesity drugs. Bariatric surgery may be an option for severely obese women with PCOS Regarding reproductive aspects, ovulation induction with anti-estrogens such as clomiphene citrate or letrozole is the first-line medical treatment. Exogenous gonadotropins and in vitro fertilization are recommended as second line treatment for anovulatory infertility. Laparoscopic ovarian diathermy may be used in special cases and metformin is no longer recommended for ovulation induction. Combined oral contraceptives (OCs) are the first-line treatment for the management of menstrual irregularities in women not seeking pregnancy, also providing endometrial protection and contraception. Progestin-only pills or cyclical progestins are recommended for those with contraindications to OCs. Metformin is also considered a second-line choice for improving menstrual cycles in women presenting insulin-resistance and dysglicemia. Hirsutism requires cosmetic procedures and medical treatment with OCs. More severe cases may need anti-androgen drugs added to the OCs. In conclusion, strategies regarding the management of reproductive issues in PCOS encompass a tailored approach to individual needs of each patient.

Key words:

Key words: insulin resistance; menstrual irregularity; hyperandrogenism; ovulation induction; combined oral contraceptives,Advanced Glycated End Products

TEXT

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Insert the text here. INTRODUCTION

The Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting 6,8% of reproductive-aged women [1]. PCOS has been recognized as a syndrome combining reproductive and metabolic abnormalities with lifelong health implications. Anovulation and androgen excess are the hallmark clinical features of the syndrome, while insulin resistance is a significant contributor to the pathogenesis of PCOS. Insulin resistance participates in the reproductive as well as metabolic abnormalities associated with PCOS [2]. Increasingly appreciated are the metabolic and cardiovascular sequelae of the syndrome. The expanding knowledge in the pathophysiology and clinical spectrum of PCOS has modified therapeutic management of affected women. The research focus has been placed in the discovery of novel strategies for the global, multi-level therapeutic management of this

syndrome. A pathophysiologically rationalized therapeutic approach should take into account the fact that reproductive and cardiometabolic abnormalities coexist and interact with each other in the context of PCOS.

PATHOPHYSIOLOGY OF PCOS

The pathophysiology of PCOS is complex involving multiple components of the reproductive and metabolic functions. The major pathophysiologic mechanisms of PCOS include androgen overproduction due to intrinsic theca cell defects, impaired function of the GnRH axis and insulin resistance.

The ovary is located at the pathophysiologic core of PCOS. The ovarian disarray involves various processes inside and outside the ovary. Theca cells propagated from women with PCOS display an intrinsic steroidogenic defect which leads to a constitutive increase of androgen production .

In turn, ovarian androgen excess can exert local/ paracrine as well as neuroendocrine effects on the hypothalamic –pituitary –ovarian (HPO) axis. In the ovary, androgens modulate gonadotropin-induced steroidogenesis in granulosa cells and folliculogenesis [3]. Intraovarian androgen excess could impair folliculogenesis in a dual fashion, by stimulating the growth of small follicles and by hindering follicular maturation towards the dominant stage [3].

Available literature suggests that androgens contribute to the control of follicular fate, acting in a developmental stage-specific manner and in co-operation with the intrafollicular hormonal microenvironment .

Additionally, androgens may disturb the normal feedback control of the hypothalamic GnRH pulse generator [4]. In humans sustained androgen exposure during critical windows of human neuroendocrine maturation may dysregulate the HPO feedback

loop. However, in a proportion of individuals, progesterone feedback is preserved despite the presence of androgen excess and the mechanisms of this varied susceptibility may partly reflect genetic differences .

In particular, PCOS is associated with an increased frequency of pulsatile GnRH release, which results in a selectively increased frequency of pulsatile LH secretion while simultaneously suppressing FSH release [4]. LH stimulates increased androgen production by the theca cells of the ovarian follicle [5]. Because of the relative deficiency of FSH, follicular growth is arrested resulting in a lack of granulosa cell maturation [3].

Overall, it seems that the central neuroendocrine alterations associated with PCOS are not primary but rather secondary to the events that take place within the ovary [5]. Androgen excess contributes to reproductive aberrations including impaired function of the ovary and the HPO axis [3, 5]. In fact recent studies in experimental androgenized animals have provided evidence that androgens interfere with the intraovarian antioxidative system by decreasing the activity of glyoxalase -1,leading to accumulation of detrimental oxidative molecules like AGEs [6].

Another major pathophysiologic component of PCOS is insulin resistance accompanied with hyperinsulinemia. These interdependent factors contribute to the ovarian disorder as well as the metabolic derangement in PCOS. The resultant metabolic phenotype displays a variable clustering of features typical of the Metabolic Syndrome [7]. Obesity, a common characteristic of PCOS women, aggravates insulin resistance and its reproductive and metabolic sequelae [8].

Insulin resistance in PCOS is tissue specific and pathway selective involving various molecules of insulin signaling. The PCOS ovary remains sensitive to the steroidogenic and mitogenic actions of insulin, despite metabolic insulin resistance [9]. Insulin plays a central part in ovarian function, since insulin receptors are present in both ovarian theca and

granulosa cells. By binding to its own receptor, insulin retains its classic metabolic effects but also modulates specific pathways of steroidogenesis and folliculogenesis in ovarian cells . Thereby, both theca and granulosa cells are capable of responding to prevailing hyperinsulinemia, which overdrives steroidogenic and mitogenic pathways [9]. Hyperinsulinemia acts as a co-gonadotropin to increase LH-induced androgen synthesis in theca cells. Additionally, insulin excess in PCOS may trigger premature LH receptor expression leading prematurely to terminal differentiation of granulosa cells in small follicles. The latter phenomenon called premature luteinization and leads to the arrest of follicular growth and linked to failure of ovulation [10, 11]. The signaling events that mediate intraovarian insulin action, as well as the pathophysiologic importance of insulin in ovarian function and dysfunction are currently actively investigated. Moreover, inflammation and oxidative stress may play an intriguing in the pathophysiology of PCOS, [12]. Dietary triggers such as glucose and glycotoxins in PCOS rat models are capable of modifying the expression of scavenger receptors and are reinducing oxidative stress and inflammatory responses independent of obesity [13]. The inflammatory response may aggravate insulin resistance and pro-inflammatory stimuli may upregulate androgen production in ovarian theca [12]. Furthermore, accumulating data suggest that a class of oxidative molecules, known as Advanced Glycated End products (AGEs), may be increased in PCOS women, independently of insulin resistance and obesity [14, 15]. AGEs are produced endogenously as well as consumed by diet and may affect various processes of reproduction, metabolism and cardiovascular function [6, 16, 17].

Overall, insulin resistance and androgen excess appear to be the major pathophysiologic mechanisms in PCOS. Oxidative stress, in the form of AGEs, may act independently and participate in the pathophysiologic pathways of PCOS. It remains

unclear which one of the above mechanisms precedes the other and how they interact with each other in the developmental course of PCOS.

CARDIOMETABOLIC ASPECTS

It is well known that PCOS is a general health pathology involved not only in infertility and menstrual alterations but also in metabolic disturbances . Among these metabolic disturbances, cardiometabolic aspects, including higher risk of insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipidemia, hypertension, subclinical atherosclerosis, endothelial dysfunctions and other risk factors for cardiovascular disease (CVD), are highly prevalent in women with PCOS [18]. In addition, PCOS patients show increased prevalence of sleep apnea, altered secretion of adipokines and adipose tissue-derived pro-inflammatory factors, which influence the metabolism, insulin sensitivity and energy homeostasis [19, 20]. Thus, the management of cardiometabolic alterations is an important issue in women with PCOS and comprises metabolic and cardiovascular risk aspects (Figure 1).

Lifestyle changes

Although the recommended first line of treatment of PCOS is lifestyle management (physical exercise and an appropriate diet), the optimal dietary composition remains unknown. Regarding anthropometric, reproductive, metabolic and psychological outcomes in women with PCOS, it has been found that a monounsaturated fat-enriched diet is more effective in weight loss and that low-glycemic diet reverses menstrual irregularities, improves insulin sensitivity and quality of life, and decreases total fibrinogen and HDL-cholesterol [21]. In addition, it has been reported that a high-carbohydrate diet increases the free androgen index, that a high-protein diet improves depression and self-esteem, and that a

low-carbohydrate diet decreases insulin resistance, total fibrinogen levels and HDL-cholesterol [21].

In the treatment of PCOS patients, it is important to consider the role of vitamins as supplements. In fact, in PCOS patients vitamin D deficiency is related to insulin resistance and obesity [22] and the regulation of vitamin D receptor is associated with glucose and lipid metabolism and blood pressure regulation [23]. In addition, it has been established that administration of vitamin B12 is associated with increased insulin sensitivity, and decreased obesity and homocystein levels .

Finally, both the diet and the cooking methods (precooked fast-food meals heated at high temperatures) dramatically increase advanced glycated end products (AGEs), thus, increasing the atherosclerosis risk in women with PCOS and/or metabolic syndrome [14]. These findings together with the fact that serum AGEs levels and testosterone and anti-mullerian hormone levels are positively associated in PCOS women [15, 24] allow to suggest that low AGEs dietary content changes during lifestyle changes in women with PCOS [25].

Endothelial dysfunction markers are surrogate markers of CVD risk, which is high in PCOS patients . Physical exercise improves endothelial function in PCOS patients thus reducing CVD risk factors [26]. It has been reported that after a 16-week exercise program, brachial artery endothelial function is improved, independently of changes in body weight or composition [27], and that dietary management and exercise, either alone or in combination, modulate serum anti-mullerian hormone and improve insulin sensitivity in overweight/obese women with PCOS [28]. Lifestyle intervention restores menstrual cycles, prevents androgen excess and CVD and improves intima media thickness [29].

Pharmacological treatments

Combined Oral contraceptives

Combined oral contraceptives (OCs) have been the main therapy for PCOS patients. However, the effects of OCs on cardiometabolic aspects are controversial. When comparing with other therapies, such as insulin sensitizers and insulin-lowering agents, OCs are more effective in improving menstrual cycles and reducing serum androgen levels [19, 30]. However, OCs containing antiandrogenic progestins increase the risk of cardiovascular and thromboembolic events . In addition, OCs have limited effect on carbohydrate metabolism and the dyslipidemic effect has been linked to the progestogen component of OCs . The effects of OCs on lipid alterations are also controversial. Some reports have indicated that OCs increase LDL-cholesterol and total cholesterol and decrease HDL-cholesterol [31], whereas others have shown that OCs increase [32] or have no effect on triglycerides . As a way to neutralize some of the negative effects of OCs, some authors have proposed the combination with lifestyle modifications [33]. In summary, as OCs may have a negative effect on metabolic aspects of women with PCOS, their administration should be based on the PCOS phenotype, and the metabolic state and clinical history of the patient.

Insulin sensitizers

There is a general consensus that insulin resistance, in particular hyperinsulinemia, leads to hyperandrogenemia and is associated with risk for CVD. Then, insulin sensitizers, mainly metformin and thiazolidinediones (TZDs) ameliorate the metabolic aberrations of PCOS patients.

Although the way in which metformin prevents these aberrations is not yet established, it is known that the molecular mechanism is complex and tissue-specific [34-36]. Metformin suppresses gluconeogenesis and hepatic glucose output in the liver, enhances peripheral insulin action in skeletal muscle and reduces glucose absorption from the digestive tract, but has a controversial effect on adipose tissue lipolysis [37]. Metformin has

additional benefits on weight loss in the combined treatment with lifestyle changes (via diet or exercise) . This combined treatment also results in a significantly greater decrease in hyperandrogenism and insulin resistance . Metformin also ameliorates cardiometabolic parameters by enhancing insulin sensitivity and lowering blood glucose and androgen levels [38] and contributes to fewer atherothrombotic events by reducing the circulating levels of plasminogen activator inhibitor-1 (PAI-1) [38]. Several studies support that metformin has a beneficial effect on lipid profile but no effect on normolipidemic patients [39]. In fact, it has been reported that metformin is least effective in women who have a body mass index greater than 35kg/m^2 .

Regarding insulin-sensitizing drugs versus combined OCs in PCOS patients, it has been reported that metformin is more effective than OCs in reducing fasting insulin and triglycerides [40]and Advanced Glycated End products [30], but there is insufficient evidence on their effects on fasting glucose and cholesterol levels [40].

Metformin also interacts with the peroxisome proliferator-activated receptor gamma (PPARγ) pathway, which binds TZDs [34]. In summary, metformin has multiple favorable actions on cardiometabolic aberrations of PCOS patients and together with lifestyle changes, it appears to be a good option of treatment.

TZDs (pioglitazone and rosiglitazone) are synthetic ligands of PPARγ. The activation of PPARγ by TZDs increases insulin sensitivity and stimulates differentiation of adipose cells, increases HDL-cholesterol levels, reduces triglycerides, improves hepatic insulin signaling and reduces overproduction of hepatic lipoprotein . However, rosiglitazone treatment has been suspended due to its association with increased cardiovascular mortality . On the other hand, as ligands of PPARα, fibrates have a major impact on triglyceride metabolism and on atherogenic dyslipidemia by increasing HDL-cholesterol and decreasing LDL-cholesterol .

Antiobesity agents

Orlistat, a pancreatic lipase inhibitor, reduces the absorption of dietary fat, body weight, insulin resistance and total testosterone levels in PCOS patients and a long-term orlistat treatment reduces increased AGE levels independently of the BMI [41]. It has been recently reported that orlistat is as effective as metformin in improving the lipid profile and pregnancy rates in obese PCOS patients. However, orlistat has minimal side-effects and is better tolerated than metformin . On the other hand, a recent study has shown that metformin and sibutramine, but not orlistat, reduce PAI-1 levels, which are increased in insulin-resistant and obese women with PCOS [42]. In combination with lifestyle changes, orlistat induces substantial weight loss in women with PCOS, resulting in improvements in insulin sensitivity, hyperandrogenemia and cardiovascular risk factors [43].

Sibutramine, a selective serotonin and adrenergic reuptake inhibitor, also has a positive effect on metabolic abnormalities in obese PCOS patients [44]. In obese women with PCOS, sibutramine reduces the waist-hip ratio, serum triglyceride levels [8] and PAI-1 levels [42]. However, as sibutramine can cause a rise in blood pressure and can increase cardiovascular risk, it has been withdrawn from the market in both the United States and Europe.

Statins

Atorvastatin and simvastatin improve the cardiometabolic aspects, including lipid metabolism of PCOS patients . However, the effect of simvastatin remains controversial. Some authors have reported that simvastatin has a lower impact on the atherogenic lipoprotein phenotype with a moderate beneficial effect [45] whereas others have reported a reduction in total cholesterol, triglycerides and LDL-cholesterol . In a multicenter, open-

labeled, randomized trial, Park et al (2010) found that rosuvastatin was more effective than atorvastatin on lipid and glycemic profile in patients with metabolic syndrome.

Bariatric surgery

In the recent consensus statement of the Androgen Excess and Polycystic Ovary Society [46], it has been recommended that bariatric surgery should be performed only after standard weight loss strategies have failed in PCOS patients with a BMI greater than 40 kg/m^2 or greater than 35 kg/m^2 with a high-risk obesity-related condition according to the 1992 NIH Consensus Development Conference Statement (1992).

In conclusion, based on all the above-described data and considering the long-term health, cardiometabolic alterations present in PCOS patients require more regular screening for such risks as well as effective and targeted lifestyle advice to prevent weight gain (Table 1). The diagnosis and subsequent management of women with PCOS are continuously in discussion. Although most PCOS patients are overweight, there is a significant number of lean women with PCOS who have cardiometabolic abnormalities. The most common pharmaceutical products deal with obesity, hypertension, dyslipidemia, diabetes, inflammation and atherogenic risks. However, further research should focus on these issues in patients with PCOS.

REPRODUCTIVE ASPECTS

The management of reproductive aspects in women with PCOS should focus on the treatment of infertility in women seeking pregnancy or the improvement of menstrual abnormalities and clinical hyperandrogenism as well as endometrial protection in women not seeking pregnancy.

Management of Infertility

Infertility in women with PCOS is associated not only to dysovulation but also to low oocyte quality and disturbed endometrial receptivity. In addition, these reproductive disturbances are worsened in the presence of obesity and/or insulin resistance [18]. Therefore, the first non-pharmacological approach for overweight or obese women with PCOS is lifestyle changes and weight loss. Modest decreases in body weight have been associated with improvement in ovulation and pregnancy rates as well as on requirements for ovulation induction drugs [18].

Clomiphene citrate

The first-line pharmacological treatment for infertility secondary to anovulation in PCOS is ovulation induction. Classically, clomiphene citrate (CC) is the most frequent choice because of their known effects on hypothalamus, competing with estradiol by the estrogen receptor and blocking its negative feedback on the gonadotropin secretion. In consequence to higher gonadotropin levels, ovaries are stimulated leading to follicular development (Figure 2). Effectiveness of CC is around 23% of live birth rate [47, 48]. In turn, the risk for ovarian hyperstimulation syndrome (OHSS) is rare and the risk for multiple gestations is around 6%, being almost limited to twin pregnancies [47].

Metformin

Metformin was first proposed for inducing ovulation in women with PCOS, based on the high prevalence of obesity, insulin resistance and compensatory hyperinsulinemia in

these patients. Insulin is known to act as a co-gonadotropin in the ovary, activating the cytochrome P-450 enzyme complex, leading to increased androgen production. Therefore, as metformin improves insulin action and, in consequence, decreases insulin levels the final effect might be a decrease on ovarian androgen secretion (Figure 2). Metformin may also exert a direct ovarian effect improving the follicular microenvironment . However, evidence indicates that metformin alone or associated to CC does not improve live births rates in PCOS [47, 49]. Therefore, currently, metformin is no longer considered as first-line drug to induce ovulation. In contrast, specific cases such as those presenting impaired glucose tolerance or BMI>35 kg/m^2 associated to CC resistance might benefit with this drug associated to lifestyle changes or other ovulation inducing agents, as described later. In addition, metformin may also be used as an adjuvant therapy in women with PCOS undergoing *in vitro* fertilization in order to prevent ovarian hyperstimulation syndrome (OHSS) [50].

Aromatase inhibitors

More recently, accumulating evidence suggests aromatase inhibitors, such as letrozole, may be effective for ovulation induction in women with PCOS. Letrozole acts by inhibiting androgen conversion to estrogen, leading to a lower feedback effect of endogenous estrogen on the hypothalamus and pituitary (Figure 2) [51]. Aromatase inhibitors seem to exert an adequate endometrial stimulus and a more physiological follicle recruitment [48]. In fact, in a recent randomized clinical trial comparing letrozole with CC in 750 PCOS women, Legro et al [48] found a higher cumulative live birth in the letrozole group (27.5%) than in the CC group (19.1%, p=0.007) (Figure 3). In addition, the study showed no differences on the rates of miscarriage, multiple pregnancies, or congenital malformations between the groups, suggesting letrozole might be superior to CC for treating infertility in PCOS. Moreover, a recent meta-analysis, including other nine studies and totalizing 1,783

women also showed that letrozole is superior to CC in the treatment of infertile women with PCOS (OR 1.64, CI 1.32-2.04), although the quality of the evidence was low [51]. However, concerns with letrozole are related to its potential fetal teratogenicity, as reported previously, although not confirmed in the study of Legro et al [48].

Exogenous gonadotropins

A second-line therapy for ovulation induction in women with PCOS is the use of exogenous gonadotropins, mainly low-dose FSH (Figure 2). Both the step-up protocol, in which the dose of gonadotropin is gradually increased according to follicular development at ultrasound and the step-down protocol, that begins with higher doses and advances with lesser doses may be used . Using low-dose FSH the risk for multifetal pregnancies and cancellations rate due to multifollicular recruitment has been reported to be less pronounced than in the past with conventional doses [52, 53]. In addition, one meta-analysis reported a possible beneficial effect of metformin, added to low-dose FSH treatment on live birth and pregnancy rates in patients with PCOS, although the quality of the evidence was low [54] indicating that further randomized clinical trials are needed to confirm these data.

In vitro fertilization

In vitro fertilization (IVF) is also recommended to women with PCOS who are not-responsive to ovulation induction. While classically regarded as a third choice for treating infertility in women with PCOS, after low dose FSH, IVF may be a better approach than FSH for older women with PCOS. IVF presents a specific benefit of limiting multiple pregnancies - but not the risk of OHSS, by employing single embryo transfer (Figure 2) [55]. In addition, there is inconclusive evidence regarding any influence of metformin before or

during IVF or intracytoplasmic sperm injection (ICSI) on live birth rates but metformin added to women with PCOS undergoing IVF was associated with a decrease in the risk of OHSS [55]. Obesity exerts a negative impact on live birth rate with IVF treatment [56], supporting the common sense that obese women with PCOS should lose weight before IVF procedures. *In vitro* maturation (IVM) of oocytes obtained from women with ovaries minimally stimulated has been proposed as an alternative to IVF because of the potential lower risk of OHSS. However, up to now there is no convincing evidence, which could allow deciding the more effective and safe procedure, IVM versus IVF or ICSI [57].

Laparoscopic ovarian diathermy

Laparoscopic ovarian diathermy is an option to CC-resistant women with PCOS, particularly for those who cannot follow the intensive monitoring required for low-dose FSH . The procedure, using either electrocautery or laser, includes the insertion of a laparoscopic needle into the ovarian stroma promoting a thermal injury (Figure 2) . Around 50% of women undergoing laparoscopic ovarian diathermy have an improvement on menstrual cycles and ovulation. Live births rates are similar to low-dose FSH [57]. Concerns related to this procedure are the possibility of adhesion formation and the potential reduction of ovarian reserve [58].

Management of menstrual abnormalities, endometrial protection and hirsutism in women not seeking pregnancy

Menstrual disturbances

Menstrual disturbances are a very frequent clinical feature in women with PCOS, varying from menstrual irregularity to oligo/amenorrhea and signalize the occurrence of

anovulatory cycles. While weight loss in overweight and obese patients may improve menstrual cyclicity and restore ovulation in some cases, most of patients will need a medical treatment for this complaint. Effective treatment will additionally protect endometrium against unopposed estrogen stimulation and the recognized higher risk for endometrial hyperplasia and cancer .

Combined oral contraceptives

Combined oral contraceptives (OCs) are the first-line pharmacological treatment for the management of menstrual irregularities in PCOS, providing endometrial protection and contraception. The estrogen component increases SHBG, reducing bioavailable androgen levels and the progestin component suppresses circulating luteinizing hormone, thereby decreasing ovarian androgen secretion. Currently, OCs contain low doses of estrogens and synthetic progestins, equivalent to ≤ 35 µg ethinyl estradiol and between 0.1 and 3 mg of different progestins. There is a consensual idea that no evidence exists until now showing any difference in the effectiveness of distinct OCs in the treatment of PCOS [50, 59].

While the benefits of OCs in the long-term treatment of PCOS outweigh the risks, concerns emerge regarding the relative risk of venous thrombosis as well as the potential metabolic adverse effects of these drugs [18, 60]. A meta-analysis including 35 studies found OCs in PCOS were not associated with alterations in fasting glucose or laboratorial markers of insulin resistance [61]. Overall, screening for contraindications to OCs is recommended before prescription in women with PCOS [18, 50, 59].

Progestin-only hormonal contraceptive pills and cyclical progestins

Medical alternatives for treating menstrual irregularities, providing endometrial

protection and guaranteeing contraception to women with contraindications to OCs are progestin-only hormonal contraceptive pills [62] or intrauterine devices, although these methods may be associated with spotting or intermenstrual bleeding. Metformin is also considered a second-line choice for improving menstrual cycles in women presenting insulin-resistance and dysglicemia . In turn, cyclical progestins, such as micronized progesterone, dydrogesterone or medroxyprogesterone acetate for 10–14 days/month are plausible options for those women who do not need contraception [18].

Clinical hyperandrogenism

Non-pharmacological and topical treatment

Clinical manifestations of hyperandrogenism, such as hirsutism, acne and androgenetic alopecia are also common in women with PCOS and are a source of anxiety and stress to these patients. The most frequent feature of clinical hyperandrogenism is hirsutism and non-pharmacological management includes cosmetic procedures such as shaving, waxing and bleaching. In addition, more efficient for long-term hair removal is laser therapy (photoepilation) [50]. Another choice for mild or moderate facial hirsutism, is the topical application of eflornithine , an irreversible inhibitor of the enzyme ornithine decarboxylase, related to cellular growth and proliferation .

Combined oral contraceptives

In women with moderate or severe hirsutism pharmacological therapy is recommended in addition to cosmetic procedures. The aims of the treatment are to suppress ovarian androgen excess and inhibit androgen action on hair follicle. OCs are the first-line choice to treat hirsutism, acting on suppressing LH secretion, leading to a decrease on

ovarian androgen production. OCs also increase SHBG hepatic secretion, thus reducing circulating free testosterone levels [18, 50, 63]. At long-term OCs may decrease the binding of dihydrotestosterone to the androgen receptor [64].

Anti-androgen drugs

Anti-androgen therapy is recommended in addition to OCs for more severe hirsutism [65] or if the response is not complete after 6 months of treatment with OC pills [18, 50]. Both cyproterone acetate (CPA) and spironolactone are effective for treating hirsutism. CPA is a progestin with anti-androgenic properties that reduces the androgen action by competing with endogenous androgens for binding to androgen receptor. In addition, due to its progestogenic activity, CPA also suppresses gonadotropin secretion and reduces androgen production [66], and may be administered in a cyclical way. Spironolactone, an antagonist of the mineralocorticoid receptor, presents anti-androgenic properties, having a structure that is very close to the testosterone and also binds competitively to the androgen receptor . The reduction of hirsutism starts to be evident after around 6 months of treatment with CPA or spironolactone [66, 67]. It is important to point out the need to guarantee contraception during anti-androgen therapy, because of the teratogenic effects of these drugs and their effects on fetal sexual differentiation.

Among other anti-androgens that have been proposed for the treatment of hirsutism, flutamide, a nonsteroidal molecule, is effective in reducing androgen action, although it presents a dose-dependent hepatic toxicity [68, 69]. For this reason, it is not recommended as first-line option to treat hirsutism. Another anti-androgen drug is finasteride that acts by inhibiting the activity of the enzyme of 5α-reductase, and in consequence reduces the conversion of testosterone to its more potent metabolite DHT in the hair follicle. Although

finasteride is not extensively used it may present the same effects as spironolactone or flutamide in the treatment of hirsutism [70]. However, no definitive evidence emerges from literature regarding the effectiveness and safety of finasteride in comparison with other anti-androgens [71, 72].

In conclusion, management strategies for women with PCOS desiring pregnancy should focus on weight loss for overweight and obese women. Ovulation induction with anti-estrogens such as clomiphene citrate or letrozole is the first-line medical treatment. Exogenous gonadotropins and in vitro fertilization are recommended as second line treatment for anovulatory infertility. Laparoscopic ovarian diathermy may be used in special cases and metformin is no longer recommended for ovulation induction because evidence has shown that it does not increase live birth rates. However, metformin might be administered during IVF cycles to prevent ovarian hyperstimulation syndrome. Combined oral contraceptives (OCs) are the first-line treatment for the management of menstrual irregularities in women not seeking pregnancy, restoring menstrual cycles and providing endometrial protection and contraception. Progestin-only pills or cyclical progestins are recommended for those with contraindications to OCs. Metformin is also considered a second-line choice for improving menstrual cycles in women presenting insulin-resistance and dysglicemia. In the presence of mild hirsutism cosmetic procedures are recommended, while moderate hirsutism requires medical treatment with OCs. Management of more severe cases of hirsutism or cases with incomplete response to OCs involves anti-androgen drugs, mainly ciproterone acetate or spironolactone. In conclusion, strategies regarding the management of reproductive issues in PCOS encompass a tailored approach to individual needs of each patient.

NOVEL STRATEGIES IN ADOLESCENTS

Polycystic ovary syndrome (PCOS) is a common disorder among reproductive- age women. This syndrome is increasingly recognized in adolescent girls and is one of the most frequent causes of androgen excess in this age group [73]. Although the clinical and metabolic features are similar to those found in young adult women with PCOS, the diagnosis may be overlooked during adolescence, as irregular menses with anovulatory cycles, polycystic ovarian morphology, obesity, and acne are frequent in teenagers without this syndrome [74, 75]. Therefore, strict diagnostic criteria have been proposed to limit premature and overdiagnosis of PCOS in adolescents .

Management of the adolescent with PCOS is complex and requires a multidisciplinary team approach, including endocrinologists, gynecologists, dermatologists, psychologists, and nutritionists, who should have a deep knowledgment of the disease for optimal results. Due to the fact that PCOS is a lifelong condition, patients should be carefully monitored during adolescence and thereafter in adulthood. Early treatment of menstrual irregularity and hirsutism may improve an adolescent´s self-image and quality of life. Moreover early intervention for PCOS-associated morbidities such as insulin resistance, obesity, and dyslipidemia may modify the progression of these chronic conditions later in life [76].

In general treatment of PCOS in adolescents is symptomatic and preventive. Lifestyle changes are the first-line intervention in women with PCOS, who are overweight. Management of menstrual abnormalities, endometrial protection and cutaneous manifestations of hyperandrogenism is similar to those employed in young PCOS women who do not desire pregnancy. Insulin resistance can be managed by diet and exercise, and with appropriate weight control. Metformin improves insulin sensitivity and glucose metabolism [77], and ameliorates hyperandrogenism and irregular menses in adolescents [78, 79].

Metformin is also beneficial in normalizing the lipid profile [78]. However, questions about how long treatment should be continued and regarding the long-term safety are controversial. Actually the major debate in the management of PCOS is the long-term treatment with insulin sensitizers starting in adolescence.

Lifestyle changes

Early lifestyle changes may prove to be the most effective approach as younger adolescents with PCOS and obesity are more prone to adopt healthy lifestyle changes than older adolescents [29]. It has been demonstrated that a reduction of 5-10% in body weight in obese women with PCOS can, for example improve hirsutism in 40-55% within 6 months of weight reduction [80] and restore regular menstrual cycles. Similar findings have been observed in adolescents with PCOS . Nevertheless, there is limited data regarding the most effective dietary intervention, exercise regimen, or behavior modification program for obese adolescents with PCOS [81]. Caloric reduction will lead to weight loss, however it is not clear if low carbohydrate or low fat diets are preferred for achieving and maintaining long-term weight loss [82].. In a multidisciplinary clinic approach for adolescents with PCOS, nearly 70% of patients succeeded in short-term weight stabilization, with 57% demonstrating weight loss. Interactions with the health psychologist and dietitian appeared to play a key role in successful weight control, supporting the importance of psychology and nutrition expertise in the management of this disorder [83].

Reproductive Abnormalities

Menstrual irregularities such as persistent oligomenorrhea, primary or secondary amenorrhea and menorrhagia are the most frequent cause of consultation of PCOS adolescent. As previously mentioned, lifestyle changes are the first line of treatment in these girls.

The use of cyclic progestins or OCs constitutes the second line of treatment. Progestin regulates menstrual cycles and may protect against endometrial hyperplasia, which is secondary to chronic anovulation. Treatment with cyclic progestin is useful in girls with PCOS who are not candidate for OCs or have not initiated their sexual activity. Nevertheless they must be advised that cyclic progestin will not treat androgenic symptoms and is not a contraceptive. In adolescents requiring contraception OCs or a progestin intrauterine device could be the option.

OCs and anti-androgens are also useful tools for the treatment of the clinical manifestations of hyperandrogenism. Nevertheless, concerns exist about the risk of venous thromboembolism (VTE), insulin resistance and dyslipidemia caused by OCs in adolescents with PCOS. PCOS may represent an independent risk factor for VTE in young women with PCOS and OCs may further increase the relative risk of VTE in these women . Concerns regarding the risk of VTE with OCP containing drosperinone have emerged. Nevertheless, observational trials have not considered other factors such as prolonged immobility, obesity, smoking history, and family history of VTE [84]. Increased risk for IR caused by OCs in adolescents with PCOS has been suggested by a number of clinical trials [85, 86]. A 6- months study with drosperinone/ethinilestradiol (EE) showed no effect on insulin sensitivity or in insulin secretion measured by hyperinsulinemic-euglycemic clamp [87]. On the contrary the combination of desogestrel/EE and cyproterone acetate/EE showed an increase in insulin resistance estimated by HOMA-IR [88]. In addition, OCs increase LDL and HDL cholesterol,

leading to unchanged total cholesterol-to-HDL ratio [87, 88]. However, the long-term impact of the use of OCs in adolescents on cardiovascular and diabetes risk is not known; further studies remain to be conducted.

For cosmetic improvement of acne and hirsutism, low dose antiandrogen drugs used alone or in combination with OCs had beneficial effects on hiperandrogenism or hirsutism in adolescents [89, 90]. Nevertheless, the use of antiandrogens in late adolescence requires concurrent use of an effective contracepcion to prevent the risk of feminization of a male fetus if they get pregnant. Spironolactone at a dose100 mg/day has been shown to be more effective than placebo in reducing hirsutism in women with PCOS [70]. The addition of spironolactone (100 mg/day) to an OCs containing drosperinone did not lead to elevated potassium levels in small trials but the safety of this combination has not been evaluated in larger trials . More recently, it has been shown that the combination of low-dose spironolactone (50 mg/d) and metformin improved insulin sensitivity to a magnitude superior to either drug alone [91]. Regarding flutamide, an androgen receptor antagonist, the group of Ibanez et al, published a series of clinical trials using combination therapy with low dose flutamide and insulin –sensitizers in adolescents showing improvement of clinical manifestations as well as cardiovascular risk factors [92, 93].

Metabolic derangement

In the last years there is a growing concern about the increase in dyslipidemia, impaired glucose tolerance, and hypertension in adolescents with PCOS, especially in obese girls. Therefore, management of PCOS with insulin sensitizers like metformin [37] and thiazolidinediones [94], has generated significant interest.

Metformin, an oral biguanide, is well established for the treatment of diabetes and it is now considered the first –line drug in the management of women with PCOS and insulin resistance. In addition to its insulin sensitizing properties, metformin may also have a direct action on human theca cells, reducing androgen synthesis, through an insulin- independent mechanism [95]. A recent survey indicated that 30% of pediatric endocrinologists consider metformin appropriate treatment for adolescents with PCOS, and 68% for obese adolescents with PCOS .

Many studies has demonstrated the efficacy of metformin in improving menstrual cyclicity, anovulation, inflammation, endothelial dysfunction, and various metabolic parameters. Low dose metformin alone or in combination with flutamide has been used in lean adolescents with PCOS and insulin resistance by Ibañez et al [96] showing an improvement in the lipid profile. Few studies that compare OCs and metformin in adolescents have been published, making difficult to draw conclusions . Studies that have evaluated the effectiveness of metformin therapy alone or in conjunction with lifestyle modifications suggest that metformin decreases serum androgens and clinical hyperandrogenism and improve lipid profile and chronic anovulation [76].

In summary, studies indicate that the degree to which metformin therapy is effective in improving the androgenic and metabolic profile in adolescents with PCOS may be related to (i) the dose used, particularly when metformin is used as monotherapy, necessitating higher doses [77]; (ii) the agent with which metformin is combined, estrogen-progestin combination pills or anti-androgenic agents such as flutamide, spironolactone, and cyproterone acetate [97]; and (iii) the characteristics of the PCOS patient being treated, whether obese or lean, hyperinsulinemic, or normoinsulinemic [77, 79]. All these aspects have to be considered before initiating metformin therapy in these girls.

Thiazolidinediones (TZDs) are a family of insulin-sensitizer drugs that act through the nuclear receptor PPAR-γ that when stimulated, are able to mediate the genetic transcription and regulate the glucose metabolism, inflammatory response and the differentiation of adipocytes. These drugs have also shown very similar effects to the ones obtained with metformin, improving hyperandrogenism, anovulation, and insulin resistance in adult women with PCOS . In addition they show a favorable effect on visceral adipose tissue which was also observed in young PCOS women [94]. Nevertheless, despite its proven efficacy in adult women with PCOS these medications have not been rigorously studied in adolescents, in either traditional states of IR or in late adolescent girls with PCOS. Therefore, it is not recommended in this age group. As previously mentioned, metformin is recommended as first line insulin sensitizer given the larger evidence in the beneficial use of this drug in the clinical practice.

Other treatment alternatives

Recently the employment of electroacupunture and the use of berberine have emerged as new therapeutic options. Electroacupunture and Chinese kidney-nourishing medicine in obese Chinese women with PCOS improve obesity-related indexes, insulin sensitivity and adiponectin levels . This favorable effect was not demonstrated in a previous study using electroacupuncture and exercise in Caucasian PCOS women [98].

Berberine, the major active component of rhizomacoptidis, exists in a number of medicinal plants and displays a broad array of pharmacological effects. In Chinese medicine, Berberine has long been used for its anti-diabetic effects. Recently it has been shown to have

positive effects on insulin resistance, lipid metabolism, nitric oxide production, and metabolic syndrome .

The mechanisms of berberine in treating PCOS are partially known. Berberine acts through the activation of AMP-activated protein kinase (AMPK), improving insulin resistance in theca cells and granulosa cells in a way similar to metformin [99].

Risk Factors and prevention

Risk factors such as premature pubarche , ethnicity [100], and a positive family history [101-103] should alert the clinician about the possibility of PCOS in adolescent girls. Moreover, in recent years a relationship between early puberty [104], low and high birth weight have been described [105] and the events that may occur during pregnancy are becoming very relevant in the ontogeny of this syndrome. Understanding how perturbations of the maternal-fetal environment influence the developmental origins of PCOS will allow the set up of preventive strategies.

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TITLES OF TABLES

Table I. Management of cardiometabolic aspects of adult patients with PCOS

TITLES OF FIGURES

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Legend of Figures

Figure 1. Strategies to be considered in adult patients with PCOS.

Figure 2. Mechanisms of action of induction of ovulation and IVF treatments.

Clomiphene citrate acts on the hypothalamus-pituitary axis, competing with estradiol for estrogen receptor binding and blocking its negative feedback on gonadotropin secretion. In consequence to higher gonadotropin levels, ovaries are stimulated leading to follicular development (➔); aromatase inhibitors (letrozole) act by inhibiting androgen conversion to estrogen, leading to a weaker feedback effect of endogenous estrogen on the hypothalamus and pituitary, thereby enhancing follicle recruitment (➔); exogenous gonadotropin (low-dose FSH) directly stimulates follicular development (➔); in IVF GnRH analogs promote suppression of the hypothalamus-pituitary axis and gonadotropins stimulate multiple follicular development (➔); Laparoscopic ovarian diathermy promotes a thermal injury by the insertion of laparoscopic needle into the ovarian stroma (➔);metformin improves insulin action and decreases ovarian androgen secretion and may exert a direct ovarian effect improving the follicular microenvironment; however it does not improve live births rates and it is no longer considered as first-line drug to induce ovulation in PCOS (➔).

Figure 3. Cumulative live birth rates in Letrozole versus Clomiphene treatments.

Data from Ref 74. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P *et al*. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med 2014;371(2):119-29.

Table I. Management of cardiometabolic aspects of adult patients with PCOS

Treatment	**Positive and negative effects on cardiometabolic aspects**
Lifestyle changes (Physical exercise and an appropriate diet)	- Induce weight loss - Improve insulin sensitivity - Decrease total fibrinogen - Regularize blood pressure - Improve endothelial functions - Restore menstrual cycle
Combined oral contraceptives (OCs)	-Controversial evidence - OCs are more effective in reducing serum androgen levels than affecting cardiometabolic aspects - Some OCs may increase thromboembolic events - Flutamide improves lipid profiles and adipokine levels, decreases visceral fat content and improves insulin sensitivity. Presents a dose-dependent hepatic toxicity
Insulin sensitizers	Metformin - Enhances peripheral insulin action and reduces glucose absorption from the digestive tract - In combination with lifestyle changes results in a significantly greater decrease in insulin resistance and hyperandrogenism - Decreases plasminogen activator inhibitor-1, thus reducing atherothrombotic events - Improves lipid profile in dyslipidemic patients Thiazolidinediones - Increase insulin sensitivity and stimulate differentiation of adipose cells, increase HDL-cholesterol, reduce triglycerides, improve hepatic insulin signaling and reduce overproduction of hepatic lipoprotein. May promote weight gain - Rosiglitazone treatment has been suspended due to its association with increased cardiovascular mortality. Fibrates

	- Improves triglyceride metabolism (decreases triglycerides, LDL- and total -cholesterol and increases HDL-cholesterol)
Antiobesity agents	Orlistat - Reduces the absorption of fat, body weight, insulin resistance and total testosterone - A long-term orlistat treatment reduces advanced glycated end products - Improves lipid profile - In combination with lifestyle changes, orlistat induces substantial weight loss reducing cardiovascular risk Sibutramine - Reduces plasminogen activator inhibitor-1 - Reduces the waist-hip ratio, triglyceride levels and plasminogen activator inhibitor-1 - As adverse effects: sibutramine raises blood pressure and cardiovascular risk thus, sibutramine has been withdrawn from market in United States and Europe
Statins	Atorvastatin improves cardiometabolic aspects including lipid metabolism The effect of simvastatin remains controversial (low impact on the atherogenic lipoprotein phenotype and high effect in reducing total cholesterol, triglycerides and LDL-cholesterol) Rosuvastatin is more effective than atorvastatin on lipid and glycemic parameters in patients with metabolic syndrome
Bariatric surgery	Recommended only after standard weight loss strategies have failed in PCOS patients with body mass index greater than 40 kg/m^2