Obesity and Polycystic Ovary Syndrome

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Key Words

Polycystic ovary syndrome · Obesity · Diabetes mellitus

Summary

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women of fertile age. Obesity is encountered in 30–70% of PCOS-affected women, and its presence significantly modifies both clinical and laboratory expression of the syndrome. Obesity increases the risk of co-morbidities associated with PCOS, such as impaired glucose tolerance and type 2 diabetes mellitus, hyperlipidemia and arterial hypertension. The etio-pathogenesis of obesity in PCOS has not yet been exactly clarified. There clearly is a vicious circle of abdominal obesity, insulin resistance, and hyperandrogenemia. Differences in ghrelin and neuropeptide Y levels between PCOS patients and those with simple obesity were also described. Weight loss is the first choice recommendation for the treatment of clinical manifestations of PCOS, such as menstrual cycle irregularities, infertility or hirsutism. However, the best treatment approach in obese PCOS patients remains to be defined. Studies concerning different weight loss regimens, antiobesity drugs, bariatric surgery, insulin sensitizers, and hormonal therapy are reviewed.

Definition and Diagnosis of Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women of fertile age and affects up to 6–7% of this population [1–3]. It is a heterogeneous disorder the principal features of which are androgen excess, ovulatory dysfunction, and polycystic ovaries. The first clinical description of the syndrome dates back to 1935 [4]. However, its pathogenesis has still not yet been fully explained [5]. The study of PCOS has been hampered by the lack of clear diagnostic criteria. It is necessary to emphasize that PCOS is still a ‘syndrome’, and no single test is diagnostic. The first attempt to define PCOS was undertaken in 1990 by the consensual conference sponsored by the National Institutes of Health (NIH) [6]. Ovulatory dysfunction together with clinical or biochemical hyperandrogenism was defined as necessary for the diagnosis of PCOS, after the exclusion of other specific disorders such as nonclassic adrenal hyperplasia, hyperprolactinemia, hypercortisolism or thyroid dysfunction, which can also lead to similar clinical manifestation. The presence of a morphological picture of polycystic ovaries (PCO) was not required for the establishment of the diagnosis. However, most of European gynecological endocrinologists still stressed the presence of PCO as an important diagnostic feature. Since 1990, it has been also recognized that the syndrome encompasses a broader spectrum of signs and symptoms than those defined in the original NIH diagnostic criteria. Thus, a transatlantic consensual conference was held in Rotterdam in 2003 under the auspices of both prestigious professional gynecological societies, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine. The experts stated that PCOS could be diagnosed when any two features out of the following are present: ovulatory dysfunction, clinical or bio-

Table 1. Comparison of different diagnostic criteria for PCOS

Criteria	Ovarian dysfunction	Ovarian morphology	Hyperandrogenism	Exclusion
NIH	oligo-ovulation (less than 6 menses per year)	not considered	clinical or biochemical (not specified)	other known disorders
ESHRE	oligo-anovulation (nonspecified)	PCO (>12 follicles 2–9 mm, or ovarian volume >10 ml)	clinical (hirsutism) or biochemical (free testosterone or free testosterone index)	disorders with similar clinical presentation
AES	oligo-anovulation and/or PCO		clinical (hirsutism) or biochemical (free testosterone)	other androgen excess and related disorders

Table 2. The prevalence of overweight and obesity in different cohorts of women with PCOS

Reference	Country of setting	Number of evaluated subjects	BMI > 25 kg/m ² , %
Franks 1989 [16]	UK	300	35
Azziz et al., 2004 [14]	USA	873	80
Glintborg et al., 2004 [17]	Denmark	125	66
Hahn et al., 2007 [18]	Germany	411	66
Cupisti et al., 2008 [15]	Germany	184	60

chemical hyperandrogenism, and PCO [7]. The Rotterdam criteria define, besides two phenotypes which agree with NIH diagnosis, two additional phenotypes (PCO+ ovulatory dysfunction without hyperandrogenism and PCO+ hyperandrogenism without ovulatory dysfunction). Thus, these criteria do not replace but extend the NIH diagnostic criteria. However, a significant controversy about the universal acceptance of the ESHRE criteria evolved [8, 9]. It is known that many patients with specific disorders as stated above could have ovulatory dysfunction without hyperandrogenemia or PCO morphology on ultrasound. It cannot be excluded that these subjects could be falsely diagnosed using the Rotterdam ESHRE criteria as having PCOS when an appropriate differential diagnostic evaluation is not performed. Besides this, PCO morphology is seen in up to 20–30% of otherwise healthy females [10] in whom, when not accompanied by any clinical or laboratory feature of hyperandrogenism, the diagnosis of PCOS is not fulfilled. The presence of metabolic features associated with PCOS in different phenotypic categories according to the Rotterdam criteria is another area of discrepancy. There are to date only few data concerning women with PCOS who fulfilled the ESHRE but not the NIH criteria. Recently it was shown that normoandrogenemic oligomenorrheic women with PCO are metabolically indistinguishable from control women and have significantly fewer metabolic features than PCOS women who are also hyperandrogenemic [11]. Similarly, there was no significant difference in the prevalence of metabolic syndrome between PCOS women manifesting ovulatory dysfunction with PCO and control subjects, even in obese women [12]. It would seem that the above-mentioned new ESHRE phenotypes are not as tightly associated with metabolic disorders as ‘classical’ PCOS phenotypes.

The most recent modification of the diagnostic criteria of PCOS was suggested by the position statement of the Androgen Excess Society (AES) [13]. AES is an internationally recognized organization dedicated to promote knowledge and research in all aspects of androgen excess disorders. The panel of experts charged by AES has determined that it is metabolic risk, especially insulin resistance, that is the feature which accompanies PCOS, and they have evaluated all large studies concerning PCOS phenotype which have been published with this in mind. Resulting from this approach, the AES position statement confirmed the presence of hyperandrogenism, either clinical or biochemical, as a necessary prerequisite for PCOS diagnosis (table 1).

Pathogenetic Links between Obesity and Polycystic Ovary Syndrome

Obesity is common in PCOS and affects between 30–70% of women depending on the setting of the study and the ethnic background of the subjects [14–18] (table 2). On the other hand, PCOS was found in nearly 30% of morbidly obese women, compared with only 5% of the lean population [19]. However, as not all morbidly obese women develop PCOS, some primary abnormality in androgen production is supposed as necessary for the development of the syndrome [20]. On the other hand, there is much evidence suggesting that hyperandrogenemia could aggravate visceral obesity in women, in contrast to men where beneficial effects of testosterone were recognized [21, 22]. Androgen promoted central fat deposition in female-to-male transsexuals [23]. Testosterone increased lipogenesis in visceral fat deposits in women [24]. Premeno-

pausal women with central obesity had higher testosterone production rates than those with peripheral obesity [25]. Antiandrogen therapy decreased adiposity in females with hyperandrogenism [26, 27]. Furthermore, the association of hyperandrogenemia and insulin resistance in women is supported by the finding of partial improvement in insulin sensitivity after antiandrogen treatment [28, 29].

The pathogenetic importance of obesity in the development of PCOS is stressed by the results of a prospective study determining the relationship between body size and self-reported PCOS symptoms. Both abdominal obesity and weight gain after adolescence were predictive for the development of PCOS. An increased risk of self-reported PCOS symptoms was observed among 30-year-old overweight or abdominally obese women who had either normal weight in adolescence or who were overweight or obese at both adolescence and adult age. Furthermore, to stress the role of obesity, about 30–40% of symptomatic cases of PCOS could have been prevented if these women had normal body weight [30].

PCOS has a strong heritable component. Recently, the Dutch twin study demonstrated that the concordance in monozygotic twin sisters for PCOS was about twice higher than in dizygotic twin and other sisters (correlation 0.71 vs. 0.38) [31], which suggested an oligogenic genetic component. Nearly 70 genes have been evaluated till now using candidate gene approach in genetic studies conducted in different populations of women affected with PCOS. Unfortunately, these studies yielded very disparate results, obviously due to small sample sizes and complex PCOS phenotype. Studies concerning functional candidate genes for human obesity, such as pro-opiomelanocortin, leptin and leptin receptor, uncoupling proteins 2 and 3, melanocortin 4 receptor and adiponectin, gave mostly unconvincing or negative results as was reviewed by Urbanek [32].

Recently, fat mass and obesity associated gene (FTO) has been identified as an obesity-related gene using a genome-wide association study approach by two independent research groups [33, 34]. The cluster of common SNPs in intron 1 was strongly associated with type 2 diabetes mellitus (T2DM); however, this association was abolished after BMI adjustment, suggesting that the association was mediated by adiposity. The influence of FTO on BMI is modest but consistent in Caucasians. Each risk allele increases BMI by 0.4–0.6 kg/m². The conflicting reports whether the FTO variants influence features of metabolic syndrome were recently addressed in a meta-analysis comprising of about 17,000 subjects [35]. The authors concluded that FTO variant in intron 1 was associated with metabolic traits to an extent entirely consistent with BMI effect. However, an independent association between glucose intolerance and SNP rs1421085 in intron 1 was described in a smaller Caucasian cohort of PCOS-affected women [36]. The exact mechanism how the FTO product could affect energy balance has not been clarified till now [37]. FTO is abundantly expressed in the hypothalamus [33]. However, its peripheral effects on fat lipolysis were also reported [38].

In 2008, a strong association was found between FTO variant rs9939609 in intron 1 and PCOS status. This association was weakened but not eradicated after BMI adjustment. However, it was also much weaker when restricted to leaner PCOS subgroups. The authors suggested that the effect of FTO on PCOS susceptibility was mediated through its effect on fat mass and that the association seen after BMI adjustment was due to sampling error [39].

One of the theories on the pathogenesis of PCOS suggests as the primary defect the exaggerated ovarian androgen production. There is clear evidence supporting an increased transcription of genes encoding specific steroidogenic enzymes, and this leads to the increased production of progestins and androgens [40]. The steroidogenic abnormalities associated with PCOS in long-term theca cells culture are characterized by an increase in 3 β -hydroxysteroid dehydrogenase type II (3 β -HSD), 17 α -hydroxylase/17,20-lyase (P450c17) and 20 α -hydroxysteroid dehydrogenase (20 α -HSD) enzyme activities and an increased mRNA accumulation for P450-side chain cleavage enzyme (P450scc), 3 β -HSD, P450c17 and 20 α -HSD. On the other hand, similar mRNA levels of steroidogenic acute regulatory protein (StAR) and 17 β -hydroxysteroid dehydrogenase type V (17 β -HSDV) between PCOS and healthy women were found. Furthermore, some of above stated defects could be manifested by the hyperinsulinism and insulin resistance [41].

Obesity could aggravate all of the clinical manifestations of PCOS [42]. Obese PCOS patients are more hirsute and have higher androgen levels than their lean counterparts as reviewed recently by Hoeger [43]. Moreover, obesity alone is associated with an increased risk of infertility [44]. Many features of PCOS are completely resolved by the weight loss following bariatric surgery [19].

It is still not clear if there are consistent differences in the levels or in the effects of appetite-regulating hormones as is ghrelin, neuropeptide Y (NPY) or cholecystokinin in PCOS. Fasting ghrelin was found to be reduced in most [45–49], but not all studies [50, 51]. A blunted suppression of ghrelin after test meals and significantly greater hunger and lower satiety scores on visual analogue scales were described in a small cohort of obese PCOS women even after weight reduction [47] and recently confirmed in another study comprising of both lean and obese PCOS patients and weight-matched controls [52]. No difference in fasting or postprandial levels of peptide YY and cholecystokinin before or after weight loss was seen in obese PCOS patients [53]. Discrepant data about plasma NPY levels in PCOS still exist. Baranowska and colleagues [54] observed lower basal NPY concentrations in obese PCOS women compared to the weight-matched controls. In contrast, Gennarelli et al. [55] reported similar NPY levels at rest in PCOS and normo-ovulatory women, but an impaired NPY response to hypoglycemia in PCOS women.

To conclude, abdominal obesity is considered an important factor contributing to ovarian and possibly adrenal hyper-

androgenism. However, androgen excess itself might also contribute to abdominal fat deposition in hyperandrogenic women. The exact clarification of an interplay between fat tissue, ovarian and adrenal steroid production and insulin sensitivity, similarly as of the role of genetic factors in PCOS and obesity pathophysiology, still remains a hot topic for future research.

Cardiovascular Risk Factors in Polycystic Ovary Syndrome – Is Obesity the Culprit?

PCOS is a lifelong lasting disease. It has been recognized that PCOS is associated with metabolic abnormalities such as insulin resistance, dyslipidemia, chronic low-grade inflammation, and arterial hypertension [56, 57]. However, all of these abnormalities are also more common in obese subjects, and thus the specific influence of PCOS is often difficult to establish.

The prevalence of both impaired glucose tolerance (IGT) and T2DM is increased in PCOS women even early in their fertile age [58–62], and obesity further increases the risk for IGT/T2DM. Moreover, obese PCOS women had 7- to 10-fold increase in the conversion rate from normal glucose tolerance to IGT or T2DM in comparison with normal weight subjects [63]. Evidence regarding the risk of IGT in lean PCOS women however is limited [64, 65]. Therefore, the minority report of the recent position statement concerning screening for IGT and T2DM in PCOS [66] suggested using oral glucose tolerance test (OGTT) only in obese patients or, alternatively, screening lean patients only if they have at least one additional risk factor for T2DM such as advanced age, family history of T2DM or a personal history of gestational diabetes.

Obesity also influences the association of PCOS with metabolic syndrome. In a relatively lean (BMI 24 ± 4.8 kg/m²) Czech PCOS cohort, overt metabolic syndrome according to ATP III criteria was not more common than in healthy controls [67]. Similarly, in Brazilian PCOS patients the prevalence of metabolic syndrome increased from 3.2% in lean to 52.3% in obese women [68]. On the contrary, metabolic syndrome was diagnosed in 46% of white American women with PCOS [69]. Recently, a similar study in the US population has confirmed these data [70]; the authors described that the prevalence of metabolic syndrome in PCOS women was twice as high as that found in the general population data [70]. The observed discrepancies could be explained by the fact that the US women were significantly more obese (85% with a waist circumference of over 88 cm in [69] or BMI between 31.7 and 42 kg/m²).

Arterial hypertension is another important risk factor for coronary heart disease. There are, to date, only a few studies concerning blood pressure in PCOS, as reviewed by Wild [71]. Recently, obesity was found as the major determinant of blood pressure abnormalities during 24-hour monitoring [72].

Dyslipidemia characteristic for metabolic syndrome with a decrease in HDL cholesterol, increase in triglycerides, and increase in small dense LDL is found in women with PCOS [73, 74]. Obesity aggravates this pattern [75]. Non-classical risk factors of coronary heart disease, as markers of chronic inflammation, were found to be more strongly associated with obesity than with PCOS per se in some studies [76, 77]. Similarly, a recent study found impaired microcirculatory function after insulin infusion only in obese, but not in lean PCOS [78].

It is thus possible to conclude that the relative independent contribution of obesity and PCOS to cardiovascular risk factors is still not fully clarified and that data concerning separate clinical endpoints for lean and obese PCOS patients are lacking.

Depression, Health-Related Quality of Life and Polycystic Ovary Syndrome

A significantly increased prevalence of depression and anxiety in women with PCOS was described using validated questionnaires [79–81] and verified using structured clinical assessment [82, 83]. Significantly impaired health-related quality of life (QoL) in PCOS was also described repeatedly as reviewed recently by Jones et al. [84].

There are to date only sparse and discrepant data about possible pathogenetical links between PCOS and depression. Some [85, 86], but not all [81] studies found an association between hyperandrogenemia and symptoms of depression. Insulin resistance could be another factor connected with both depression and PCOS [87, 88]. The risk of depression was independent of present obesity, even when depressed women in this study had higher BMI than non-depressed women [81]. Similarly, the relationship between BMI and health-related QoL is complex. The lack of a relationship between BMI and QoL indicate that all women with PCOS, regardless of their BMI measurement, have weight concerns and that PCOS women with a normal BMI struggle to maintain their weight at this level [84].

Treatment Approaches (Table 3)

Therapeutical options specifically targeted to influence hyperandrogenic symptoms are combined oral contraceptives (COC) and antiandrogens. Obesity influenced markedly the effect of both of these treatment modes on androgen levels and androgenic symptoms. A recently published meta-analysis has shown the reduced efficacy of antiandrogens for the treatment of hirsutism in obese PCOS patients [89]. Similarly, the positive effect of COC treatment on androgen production, serum androgen binding capacity, and clinical androgenic symptoms was diminished in obese subjects [90].

Table 3. Symptomatic therapy in women with PCOS

Symptom	Therapy
Hirsutism/acne	combined oral contraceptives antiandrogens laser therapy weight reduction
Irregular menstrual cycle	combined oral contraceptives weight reduction metformin
Infertility	weight reduction clomiphene citrate gonadotropins aromatase inhibitors metformin in vitro fertilization

The effect of COC on insulin sensitivity and glucose tolerance in PCOS was inconsistent, as was reviewed by Nader and Diamanti-Kandarakis [91]. Insulin sensitivity may decrease in PCOS, and the effect could be again modified primarily by the degree of obesity, with a decrease in obese women only [92, 93]. It is possible that the composition of COC could also play a role as only the higher-, but not the low-dose estrogen COC increased insulin resistance by 25% in an obese cohort of PCOS [94]. The studies comparing different COC products are however sparse, and therefore it is not possible to conclude whether some combinations are superior to others. It should be emphasized that all available studies are limited in the duration of hormone use, and long-term effects are not known [95]. Based on the observation of lower effectiveness of both COC and antiandrogens in obese PCOS women, lifestyle modification is important in a complex treatment approach.

In the general population, COC treatment is not free of serious side effects. Second-generation COC were associated with a 1.85 and 2.54 times increased risk of myocardial infarction and ischemic stroke events, respectively, and third-generation COC were connected with a 2.0 times increased risk for ischemic stroke outcome [96]. Similar data specific for PCOS women are unfortunately lacking. However, as obese women with PCOS exhibit many of the risk factors of coronary heart disease, the possible exacerbation of adverse long-term outcomes of PCOS by COC may be taken into account when deciding about therapy.

Insulin sensitizers were shown to normalize menstrual irregularity [97]. However, they were not as effective as antiandrogens in the improvement of hirsutism [98, 99]. In the UKPDS study [100], metformin significantly reduced stroke, diabetes-related endpoints and all-cause mortality compared with intensive treatment with insulin or sulphonylurea, despite similar glycemic control in T2DM. However, a meta-analysis of studies in T2DM patients did not find a significant treatment effect of metformin on blood pressure, HDL cholesterol, and triglycerides [101]. The hypothesis that insulin sensitizers

could be superior for metabolic aspects of PCOS in comparison with COC was tested in few short-term randomized trials [102–104] which are summarized recently in a meta-analysis [105]. Fasting insulin and triglycerides decreased after metformin, however they did not change after COC treatment. Fasting glucose or total cholesterol did not change after any of the treatment modes. COC, in contrast to metformin, decreased markedly serum testosterone and improved menstrual cycle pattern. However, all of the studies included in the meta-analysis were relatively small and short-term lasting. Thus, it is not possible to definitively conclude if any of these treatment modes is superior over the others.

Thiazolidinediones as another class of insulin sensitizers were also used in clinical trials in PCOS. They decreased both fasting and post load glucose and insulin values [106, 107] and improved hyperandrogenism and ovulation rates [106, 107], thereby providing both metabolic and reproductive benefits. However, some of the effects of glitazones are not common for all of these drugs. For example, both drugs affect lipid metabolism differently. Rosiglitazone increased both triglycerides and LDL particle concentration, and pioglitazone led to significant improvements in triglycerides, HDL cholesterol, LDL particle concentration and LDL particle size [108]. Recently, the results of a trial randomly assigning obese PCOS women to rosiglitazone or COC treatment were published. Rosiglitazone reduced insulin resistance but had limited effect on lipids, androgens, and hirsutism. COC did not modify insulin resistance but increased high-density lipoprotein cholesterol and triglycerides and decreased androgens and hirsutism [109]. As far as is known to us, no trial combining COC and pioglitazone has been published.

Glitazones are not free of side effects. They led to an increase in weight in some trials in PCOS [106, 107, 110]. Another point of concern is the negative influence of rosiglitazone on cardiovascular mortality [111]. Both pioglitazone and rosiglitazone are pregnancy category C drugs as they caused increased fetal loss and retarded fetal growth even if they appeared unlikely to increase the risk of congenital malformations in animal studies. There have been no controlled studies in women, and there are no published studies on their use during human pregnancy. Their use in women of fertile age is thus limited.

Weight reduction is the first-line intervention in obese PCOS women. It was shown that as little as a 5% decrease in body weight restored ovulation in anovulatory obese PCOS patients [112, 113], and weight loss of about 10% was associated with a 50% chance of returning ovulation [114]. Moreover, a weight reduction as little as 5% has been shown to reduce insulin resistance and testosterone levels [47, 112, 113, 115–119]. These results are similar to the data from the general population, showing that a weight loss of 5–7% exerted significant benefit in cardiovascular risk factors and in the reduction of incidence of T2DM [120].

Concerning infertility, weight loss was shown to increase ovulatory rates as stated previously. A trial of complex lifestyle

improvement lasting at least 6 months is recommended as the first-line approach before any specific infertility treatment is started [121]. Clomiphene citrate (CC) still remains the first-choice medication for the induction of ovulation even if it is not possible to discern if metformin could be more effective [122]. Another promising drug group are aromatase inhibitors which are free of the unwanted effects of CC on endometrium. However, their place in the treatment is not fully defined till now [123].

Not only caloric density reduction, but also macronutrient content of diet could be of concern in the complex management of PCOS. There are to date few and discrepant data about the acute and short-term effects of dietary composition in PCOS. Recently, a small study ($n = 15$) including women with very large range of BMI showed surprisingly that testosterone remained below pre-meal values significantly longer after the ingestion of high-fat meal than after a low-fat, high-fiber meal. In this study, no effect of meal composition on postprandial DHEAS, cortisol, and SHBG levels was observed [124]. On the contrary, oral glucose ingestion led to an increase in plasma cortisol and adrenal androgens and to reactive hypoglycemia in comparison with whey protein ingestion in overweight/obese PCOS [125]. High-protein or a high-carbohydrate diet induced similar weight loss and a similar degree of improvement in circulating androgens, measures of glucose metabolism, and leptin in a small pilot study lasting 4 weeks [126]. Another short-term study compared eucaloric diets either enriched with monounsaturated fatty acids or low in carbohydrates with a standard diet among women with PCOS and described lower fasting insulin and lower acute insulin response to glucose after low-carbohydrate diet [127]. An increased intake of polyunsaturated fatty acids led to a reduction in plasma free fatty acids and to an increase in fasting glucose but exerted no changes in insulin and steroid hormones [128]. Recently, high-protein, low-carbohydrate diet, but not low-protein, high-carbohydrate diet was associated with significant improvement in ratings of depression and self-esteem despite the fact that both regimens led to a similar decrease in body weight [129]. A 6-month trial comparing moderate fat or carbohydrate restriction has shown that both are equally effective in maintaining weight reduction and improving reproductive and metabolic variables [130]. Relatively little attention was paid to diets with different glycemic index in PCOS [130]. This point could be of concern, as diets with low glycemic index generally improved insulin resistance, influenced blood lipid concentrations and inflammation [131], and reduced the risk of endometrial cancer [132].

Most of the above cited trials were relatively small and short-term. Further studies concerning both acute effects of different macronutrients and different dietary composition for longer periods on both hormonal and metabolic environment and psychological aspects in PCOS are thus highly warranted. Metformin decreased BMI significantly in the pioneering observational study of Velazquez et al. [133]. Recently, a

meta-analysis of 14 trials including 649 women and comparing metformin and placebo with or without lifestyle modification showed a statistically significant decrease in BMI after treatment (weighted mean difference, -0.68 ; 95% CI -1.13 to -0.24) [134]. There was some indication that a high dose of metformin ($>1,500$ mg/day) and longer duration of therapy may have greater effect. However, only 3 out of 14 trials used intention-to-treat analysis, and most of them were designed for a different primary outcome. The authors concluded that adequately powered randomized trials are required to confirm the findings and to assess whether the addition of high-dose metformin therapy to a structured lifestyle modification program might contribute to a more profound weight loss.

All of the drugs recommended for use as antiobesity agents were used in PCOS, and all of them led to similar weight decrease as was described in studies conducted in the general population [135].

Orlistat treatment in obese PCOS patients led to a weight loss, reduced testosterone levels [136–139], and improved insulin sensitivity in some [137, 139], but not all studies [138]. However, all the studies presented were relatively short-term (lasting between 3 and 6 months) and were not aimed to evaluate changes in menstrual cyclicity or in clinical signs of hyperandrogenism.

Sibutramine was added to the hypocaloric diet in an open-label randomized study lasting 6 months. Sibutramine caused greater weight loss (15 vs. 11%), together with greater decrease in AUC for glucose during OGTT than diet only. Free androgen index also declined more profoundly in the sibutramine arm [140]. Similarly, in a placebo-controlled 6-month trial, sibutramine led to a more profound weight loss than lifestyle modification (9 vs. 1.7%) as well as to a greater increase in SHBG and a greater improvement in triglycerides and apoB levels [141]. Both sibutramine and weight reduction ‘only’ improved menstrual cycle frequency significantly but had no effect on insulin sensitivity, blood pressure or on androgen levels [141]. A small study comparing sibutramine, COC and their combination administered together with hypocaloric diet described similar decrease of BMI in all groups. Sibutramine in monotherapy was superior in the improvement of insulin sensitivity and triglycerides; however, this positive effect was not apparent in the combined treatment group. Androgen levels and hirsutism improved similarly in all groups [142].

Recently, rimonabant was used in a randomized trial with metformin in 20 women with PCOS. Body weight, insulin resistance, and testosterone levels decreased after rimonabant, but not after metformin [143]. However, one of the unwanted side effects of cannabinoid receptor blockers is depression, which was reported in 26% of subjects given 20 mg of rimonabant [144].

During postmarketing surveillance, it was recognized that there was approximately doubling of the risk of psychiatric disorders in patients taking rimonabant (Acomplia®, Sanofi-

Aventis, Berlin, Germany) compared with placebo. Moreover, patients at an elevated risk of developing psychiatric disorders could not be identified in advance. Resulting from these facts European Medical Agency (EMA) has recommended the suspension of marketing authorization for this formulation [145]. Antidepressants could be effective in weight reduction [146]. However, as far as we know, there have been no trials with these drugs in PCOS.

Bariatric surgery is currently viewed as the most effective approach for the treatment of morbid obesity [147]. Several studies have shown improvement in fertility in women of reproductive age after surgery-induced weight loss [148]. Two small studies on the effects of bariatric surgery in morbidly obese PCOS women have been published up to now. A retrospective study evaluated 30 women with PCOS who underwent laparoscopic Roux-en-Y gastric bypass. All of them had complete resolution of their menstrual irregularity, 75% of them had marked improvement in hirsutism score, and all who wished to be pregnant were able to conceive spontaneously. Moreover, all subjects with T2DM were normoglycemic at the follow-up, normal blood pressure without antihypertensive treatment was restored in 78% of the formerly hyperten-

sive subjects, and 92% of the formerly dyslipidemic subjects no longer required hypolipidemic drugs [149]. These results were confirmed in a prospective study evaluating 17 women with PCOS. All but one subject demonstrated marked improvement in clinical and biochemical hyperandrogenism and in insulin resistance [19].

In conclusion, obesity is often encountered in PCOS and modifies significantly both hormonal and metabolic phenotypes of these women. In addition, obese PCOS women have worse therapeutical response to some treatment modalities than their lean counterparts, and the best therapeutical regimen for them remains to be defined.

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