Chapter 4

Lifestyle Changes and Weight Loss: Effects in PCOS

Cringu Antoniu Ionescu, Ina Popescu,
Mihail Banacu and Mihai Dimitriu

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Abstract

Even though controversies surrounding the polycystic ovary syndrome are not yet close to be solved, its clinical manifestations are well known—insulin resistance and obesity, hirsutism, irregular and anovulatory menstrual cycles. The treatment of polycystic ovarian syndrome (PCOS) is mainly symptomatic as its etiology is not yet clear. Lifestyle changes are the primary therapy in overweight and obese women with PCOS. According to majority of the studies, lifestyle changes are the most effective form of treatment not only for weight loss but also for the improvement of insulin sensitivity, decreasing incidence of metabolic syndrome and type 2 diabetes. Studies also show that weight loss has fertility benefits by restoring ovulatory cycles. Although initial studies researching pharmacologic treatment were showing excellent results concerning the weight loss, maintenance of weight loss and reduction of cardiovascular risks, some of these drugs were in the end, has proven to actually increase the risk for cardiovascular events and were removed from the market. Bariatric surgery has been demonstrated to improve or even cure type 2 diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea. More so, there are studies that reported complete resolution of all features of PCOS, even hirsutism, hyperandrogenism, anovulation, and menstrual irregularity.

Keywords: polycystic ovarian syndrome (PCOS), obesity, hyperandrogenism, anovulation, hirsutism, metabolic syndrome, weight loss

1. Introduction

Polycystic ovary syndrome (PCOS) is considered to be the most common endocrinopathy affecting women with an incidence ranging from 5 to 13% [1], depending on the diagnostic criteria applied.

Polycystic ovary syndrome—in spite of many years of research—is still a controversial topic. We have come to know in detail its clinical manifestations such as metabolic disorders, menstrual and ovulatory dysfunctions, and clinical hyperandrogenism. However, not knowing its etiology, most of the treatments suggested to patients with PCOS are symptomatic, not addressing to the underlying cause, but rather each symptom in part.

Following numerous studies and research on PCOS and despite that the exact mechanism is not completely understood, the conclusions of most researchers are the same; lifestyle change and weight loss have beneficial effects on the entire panel of symptoms associated with this syndrome.

2. Which are the main goals when treating PCOS?

2.1. Management of underlying metabolic disorders, reduction of risk factors for type 2 diabetes and cardiovascular disease

2.1.1. Obesity

Under the metabolic disorders, which are commonly encountered in patients with PCOS, it is worth mentioning: obesity, insulin resistance, metabolic syndrome, dyslipidemia, and type 2 diabetes mellitus.

Some researchers state that the obesity rate in the case of the women with PCOS is even up to 70%, but most agree that at least half of the women with PCOS suffer from obesity (body mass index (BMI) = 19–25 kg/m^2) [2] and in most cases, it is of a central distribution (waist circumference > 88 cm) [3]. Of the nonobese patients, one-third has increased intra-abdominal fat [4]. There is no specific data on why the prevalence of obesity is much higher in women with PCOS, but most researchers attribute it to the hyperinsulinemia resulting from the insulin resistance, an important factor of adipogenesis, lipogenesis, and lipolysis inhibition [5].

2.1.2. Increased insulin resistance

Insulin resistance and reactive hyperinsulinemia are definitely implicated in the physiopathological mechanism of PCOS. With respect to insulin resistance, some authors consider it to be uncorrelated to the degree of the obesity [6], while others argue that the obesity, especially the central one, seems to increase the metabolic and clinical features of insulin resistance [7]. Although obese patients seem to be more affected by insulin resistance, this also occurs in the cases of nonobese patients with PCOS [8].

2.1.3. Metabolic syndrome

The metabolic syndrome is commonly associated with PCOS, with a prevalence ranging between 33 and 47% [9]. Both PCOS and the metabolic syndrome have features that generate an increased risk of cardiovascular diseases–if this risk is independent of PCOS or it is caused

by its association with the metabolic syndrome, it is still a topic of debate [10]. Studies demonstrate that in patients with PCOS, even if the criteria for the metabolic syndrome are not fully met, there is at least one component of the metabolic syndrome [11].

The research in the field demonstrates the presence of the risk factors for the metabolic syndrome in women with PCOS. Of these, the following appear to be important: the level of fasting insulin (which in these patients is doubled [12]) and obesity (an independent risk factor for the metabolic syndrome).

2.1.4. Impaired glucose tolerance or type 2 diabetes mellitus

Impaired glucose tolerance (IGT) or even type 2 diabetes mellitus (T2DM) are common in patients with PCOS with a prevalence rate of 30–40% for impaired glucose tolerance and 7.5–10% for type 2 diabetes mellitus [13, 14]. The risk of patients with PCOS to develop these pathologies is considerably higher than in healthy patients. In these cases as well obesity appears to play an important role–impaired glucose tolerance and diabetes mellitus have an increased prevalence in obese patients (31.3% IGT and 7.5% T2DM) in comparison to non-obese patients (10.3% IGT and 1.5% T2DM) suffering from PCOS.

2.1.5. Cardiovascular disease

It is not known exactly to what extent PCOS would be an independent risk factor for cardiovascular diseases but, unquestionably, through associated pathologies (obesity, increased resistance to insulin, IGT, T2DM, and/or dyslipidemia), it contributes to an increased risk [15].

2.2. Improvement of hyperandrogenic symptoms (hirsutism, acne, scalp hair loss)

Most experts consider that hyperandrogenism is the main characteristic of PCOS [16], whether is biochemically or clinically identified. Alteration in insulin action as well as enzymatic defaults has been discussed as possible pathogenic theories.

Studies suggest that the androgenic hyper-responsiveness that characterizes women with PCOS is probably due to the factors controlled by insulin sensitization rather than luteinizing hormone (LH), adrenocorticotropin hormone (ACTH), or ovarian steroids *per se* [16]. Multiple molecular and cellular pathways seem to be involved in the production of androgenic hormones, most of them involving ovarian theca cells, insulin receptors, Cytochrome P450 17α-monooxygenase (P450c17) activity as well as components of mitogen-activated protein kinase (MAPK) insulin pathway.

The clinical correspondence of this intricate biochemical processes have incredible impact on patients' quality of life and psychological status. Virilising signs and symptoms, acne and hirsutism are most often the first elements to lead to the clinical suspicion of PCOS.

Obesity is a key metabolic entity in some PCOS patients. Because of its undeniable influence on insulin resistance, it has become a target to treat when identified. PCOS women, who are obese tend to have higher hirsutism and acne scores than their lean counterparts [16]. The consequent importance of weight loss is therefore essential to be taken into account. It is

certified in medical literature that a weight loss of 5–10% can reduce hyperandrogenism and insulin levels [17]. Lifestyle modifications reside once again as the first step therapeutical management in patients with PCOS.

2.3. Prevention of endometrial hyperplasia

The modified metabolic background associated with PCOS is basically characterized by unbalanced estrogen serum levels due to lack of progesterone production. Left untreated, the main effects of this modified environment leads to atypical endometrial hyperplasia, and endometrial dysfunction-induced infertility [18].

Even though progesterone-based oral contraceptive therapy is often efficacious [19], approximately 30% of women with PCOS fail to respond to such treatment [20] and progress to the development of atypical hyperplasia and further transformation to endometrial cancer [21].

The mechanism of progesterone resistance is determined at molecular level and based on the imbalance of two progesterone receptor (PR) isoforms PRA and PRB. Patients with PCOS have a modified ratio of PRA to PRB receptors present on stromal and epithelial cells of endometrium [21].

Progesterone resistance is associated with insulin resistance [20] and this way, a new perspective in the prevention of endometrial hyperplasia can be contoured: targeted therapy on reducing insulin resistance may benefit both endometrial tissue and serum hyperinsulinemia.

2.4. Voluntary contraception for patients

Although most of PCOS-diagnosed patients complain about the inability to pursue a pregnancy, it is important to have in mind the situation when women diagnosed and treated for PCOS do not want to obtain a pregnancy.

A recent study states that in women aged 28–33 years old, women with PCOS were less likely to be using contraception (61 versus 79%, $P < 0.001$) and more likely to be trying to conceive (56 versus 45%, $P < 0.001$), compared with women not reporting PCOS [22]. However, the same study mentions that fewer women with PCOS (61%) were using contraception than women without PCOS (79%) ($P = 0.001$) [22].

Because women with oligomenorrhea ovulate intermittently and rarely use contraception-unwanted pregnancy may occur.

2.5. Induced ovulation for patients pursuing pregnancy

As part of the PCOS, infertility secondary to anovulation is usually the main complaint of patients diagnosed with this metabolic disorder.

Pathological basis of infertility in this particular medical situation resides in the low Follicle-stimulating hormone (FSH) serum level, which is responsible for the impossibility of ovarian follicles to reach maturity due to their persistence in final growth stages.

Aiming to treat this frequent cause of anovulation, there are two ways to ensure the wellbeing of the patient based on each woman's choice: evaluating the options for further contraception or starting a therapeutical plan for inducing ovulation.

With respect to the latter, inducing ovulation still remains a medical challenge in some patients with PCOS. There are a few known therapeutical approaches for achieving this: medical treatment with clomiphene citrate, tamoxifen, aromatase inhibitors, metformin, glucocorticoids, or gonadotropins or surgically management by laparoscopic ovarian drilling [23]; in vitro fertilization is also taken into consideration when all the other options failed to induce pregnancy.

3. Why are lifestyle changes and weight loss important in women with PCOS?

Taking into account the morpho-clinical picture of the patients with PCOS and common sense, lifestyle changes and weight loss would, at first glance, be effective. It seems simple that by adopting a healthy lifestyle and weight loss, as with the patients who do not suffer from this pathology, it would improve the metabolic profile, reduce the risk of diabetes mellitus, cardiovascular disease or endometrial hyperplasia. Moreover, there are studies that discuss the complete or at least partial disappearance of the symptoms [24] and PCOS phenotype after weight loss.

Studies with various degrees of evidence have been conducted in an attempt to quantify their effect in patients with PCOS. While some parameters are certainly improved, there are still others involved in a series of controversies.

3.1. Metabolic profile

An improved lifestyle will undoubtedly improve the distribution of the adipose tissue and will in most cases lead to weight loss. A weight loss of between 5 and 10% will ameliorate IGT and will decrease the prevalence of the metabolic syndrome and diabetes mellitus [25].

Research suggests that these interventions are associated with lower fasting insulin levels and insulin resistance [26], and consequently a decreased risk for metabolic syndrome, cardiovascular disease, and diabetes mellitus [27].

It has been shown that improvement of the lipid profile resulting from weight loss and lifestyle changes is nonuniform. Thus, in the case of some patients, a significant decrease in cholesterol levels will be observed while in others the change will be insignificant [24]. However, in all cases there will be a significant increase of high density lipoprotein (HDL)–cholesterol levels (thus reducing the risk of cardiovascular disease) and a decrease of triglyceride levels [24].

3.2. Hormonal profile

During the treatment, we also seek to improve the hormonal profile since PCOS being a pathology with deep hormonal implications. Unanimously, studies describe a decrease in the

total testosterone level [28] and in androstenedione [29] as a result of lifestyle changes and weight loss. There is, however, controversy in terms of improving the level of SHBG and free androgen index (FAI) [29]. However, in all cases, an improvement in hirsutism will result when using the Ferriman-Gallwey (FG) score as an objective measuring method.

While the level of FSH increases as a result of lifestyle changes and weight loss, more by means of physical exercise than a result of diet [29], the level of LH does not seem to be improved by following a hygienic-dietary diet.

3.3. Reproductive potential

In PCOS treatment, we aim to restore both normal menstrual function and fertility. In some cases, there may also be a decrease in ovarian volume and a reduction in the number of follicles [30] following weight loss and lifestyle changes. Ovulatory menstrual cycles can be obtained for obese women with PCOS, even when the weight loss is relatively low [31], thus increasing considerably the chances of getting pregnant. However, not all patients equally respond to these measures even if their weight loss is similar [24]. Hollmann et al. describe an 80% improvement in ovulation rate and 29% in the pregnancy rate in the case of a 10% weight loss [32].

4. What lifestyle changes should be adopted for women with PCOS?

Although the last decades have been revolutionary in terms of understanding this pathology, its etiology is not elucidated, hence we cannot talk about the existence of a curative treatment, but rather of symptomatic treatments. The spectacular evolution in this field also refers to the many symptomatic treatments, whose efficiency, although relatively high, address each symptom in part and not the pathology as a whole. The change in lifestyle, with all the developments in the last decades, still seems the most approachable and most effective treatment method, at the same time covering a broad spectrum of symptoms.

When we talk about lifestyle changes, we refer to a healthy lifestyle that involves exercise and weight loss. Although in many cases, patients are able to lose weight and lead a healthy lifestyle for a while, the difficulty they encounter is to maintain this lifestyle and their weight in the long run.

A solution to this problem is the behavioral treatment by "Burtyn and co." designed specifically to help with this–a complex program that not only helps patients to lose weight efficiently but also to maintain their weight in the long term or even continue to lose more over time. Patients undergo this program for a period of 4–6 months under the supervision of a group of specialists: nutritionists and psychologists [33]. Patients learn how to choose healthy foods, how to ration their portions and how to get social support. After setting objective targets in terms of daily caloric intake, time spent on physical exercise and other behavioral changes, patients share in weekly or bi-weekly group sessions the obtained results. Specialists recommend patients to expect a weight loss of 0.5–1 kg per week, mentioning that the final target is a 10% decrease in weight relative to their initial weight [33]. They argue that by a comprehensive behavioral approach, patients manage to decrease 8–10 kilograms in weight

and that about 80% of patients starting this program manage to complete it [34]. However, specialists mention that in the absence of weight maintenance therapy, regaining weight will be inevitable.

The National Institute of Health also recommends psychotherapeutic and social support for these patients in order to manage to maintain their weight in the long run or even to further lose weight.

4.1. What diets do we choose in order to lose weight?

Regarding the type of diet, there are no clinically relevant data to prove the efficacy of any of them in the case of patients suffering from PCOS. However, based on food principles and taking into account that a decrease in carbohydrate intake would lead to a decrease in hyperinsulinemia, which in turn would lower insulin resistance, low-carbohydrate diets would be favored. Nevertheless, a comparative study between a high protein/low carbohydrate diet (40% carbohydrate, 30% protein, and 30% fat) and a low protein/high carbohydrate diet (55% carbohydrate, 15% protein, and 30% fat) proved the same efficacy in both cases [26] in terms of weight loss, waist circumference decrease and effects on insulin sensitivity. The same study emphasizes the importance of a calorific deficit in PCOS treatment, noting that the differences in dietary compounds are relatively insignificant when comparing their effect on metabolic and reproductive improvements [26]. A meta-analysis of 48 clinical trials involving a total of 2886 patients concludes that regardless of the type of diet and macronutrient on which they are based, there will be a relatively comparative weight loss–the same thing happening with maintaining weights at follow-up for 6 months and 12 months [35]. The impact of the type of macronutrients used in the diet is still debated. What is certain is that less energy intake than energy consumption will result in a weight loss. Thus, high-level metabolic studies conclude that a caloric intake of less than 1000 kcal/day will show results in all cases, with no exception.

New diet hypothesis have emerged over the last few years, and here we want to mention the fast-paced ones, which are still under investigation and seem to be ground-breaking. Researchers believe that patients with PCOS might have significant benefits in terms of PCOS symptoms but also complications in the medium to long term if approaching this type of diets. The data we currently have on intermittent fasting diet obtained on rodent models are promising in terms of results. Thus, intermittent fasting diets, as compared to diets based on energy restriction of continued iso-energetic type, improve insulin sensitivity [36], provide protection for the cardiovascular system [37], and increase the lifespan of the rodent in the model. [38] Moreover, 3 days or more of the fasting will result in at least a 30% decrease in circulating insulin levels, glucose levels, and insulin-like growth factor 1 (IGF-1), which plays a key role in the metabolic homeostasis and changes associated with aging [39]. Current theories take into account the possibility that this type of diet can improve the symptoms of hyperandrogenism, based on the argument that improving insulin resistance would reduce compensatory hyperinsulinemia and ultimately the excess of androgen involved in the PCOS symptomatology.

Finally, we want to emphasize the importance of weight loss, pointing out the uselessness of this fact if the patients fail to maintain their long-term weight.

4.2. What is the importance of physical exercise?

Physical exercise is definitely a part of the lifestyle changes. Studies show that the type, frequency or duration of the exercise do not influence the results that patients get from it. It has been shown that regular, aerobic exercise of moderate intensity does not only contribute to weight loss and improved insulin resistance, but also improves reproductive outcomes, including ovulation and regulation of menstrual cycles. The recommendation for patients with PCOS in view of the improve reproductive and cardio metabolic outcomes is – aerobic physical activity of moderate intensity for 90 minutes per week [40].

5. What methods do we choose in order to obtain weight loss?

5.1. Pharmacological treatment for obesity

In a relatively recent past, following multiple clinical trials, medical journals supported the benefit of adding anti-obesity drugs to lifestyle changes–both in terms of maintaining weight in the long-term and reducing associated co-morbidities. Drugs such as sibutramine, orlistat, and rimonabant have been shown to be effective in improving the lipid profile, lowering blood pressure, glycosylated hemoglobin (in diabetics), and pro-inflammatory cytokine levels, thus reducing cardiovascular risk [41]. Meanwhile, it has been shown that the majority of these drugs instead of lowering cardiovascular risk have the opposite effect, which has led to their removal from the market [42].

Currently, drugs used in the treatment of obesity are–orlistat, lorcaserin, phentermine-topiramate, bupropion naltrexone, liraglutide and noradrenergic sympathomimetic drugs but there are no specific studies with patients suffering from PCOS. A list of medication used to treat obesity is shown in **Table 1**.

5.1.1. Drugs that alter fat digestion

Orlistat, being an inhibitor of pancreatic and gastric lipases, inhibits the hydrolysis of triglycerides from the diet by up to 30%, thus reducing total caloric intake [41]. Hence, weight loss is not significant using this medication only and requires a calorie-restricted regimen. The X-PERT study establishes a 3-month weight loss that exceeds 5% of the initial weight as an accurate predictor of long-term weight loss. A 12-month meta-analysis concludes that patients undergoing lifestyle changes that also associate orlistat as an adjuvant medication will lose an average of 8–10 kg over 12 months as opposed to those who associate lifestyle change with a placebo who will lose an average of 3–6 kg [43]. In addition to weight loss, it has positive effects in reducing cardiovascular risk factors due to its effects on triglyceride and LDL cholesterol [41]. Moreover, in Orlistat treatment, a better glycemic control with decreasing fasting glucose and glycosylated hemoglobin is noticed [44]. This is considered to be a relatively safe drug, with adverse effects mainly upon the intestinal tract such as increased defecation, fatty stools, and fecal urgency.

Drugs that alter fat digestion	Orlistat
Serotonin agonists	Lorcaserin
Sympathomimetic drugs	Phentermine
	Diethylpropion
	Benzphetamine
	Phendimetrazine
Antidepressants and antiepileptic drugs	Bupropion
	Venlafaxine
	Desvenlafaxine
	Topiramate
	Zonisamide
	Lamotrigine
	Ziprasidone
Diabetes drugs	Metformine
	Pramlintidine
	Exenatide
	Liraglutide
Combination drugs	Phentermine-topiramate
	Bupropion-naltrexone

Table 1. Medications used in the treatment of obesity and their classification.

5.1.2. Serotonin agonists

Lorcaserin is believed to activate serotonin 5-HT2c receptors stimulating pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. Thus, it increases alpha-melanocortin stimulating hormone resulting in satiety and consequently in a decreased food intake [45]. Lorcaserin is indicated for the treatment of obesity when it is associated with at least one comorbidity such as type 2 diabetes mellitus, high blood pressure, high cholesterol or sleep apnea [46]. This is an alternative to orlistat, with similar efficacy but fewer side effects. In addition to weight loss, studies show that it lowers: blood pressure, heart rate, total cholesterol, LDL cholesterol, fasting glucose, and insulin levels.

5.1.3. Sympathomimetic drugs

Noradrenergic sympathomimetics, of which we currently find phentermine, diethylpropion, benzphetamine, and phendimetrazine, cause early satiety and reduce food cravings. Although they have increased effectiveness and their use is widespread, they are indicated for a treatment of a maximum of 12 weeks and have large potential for abuse. We must mention that all sympathomimetic drugs have side effects such as tachycardia, increased blood pressure, cause insomnia, constipation, nervousness, and dry mouth. In fact, their side effects on the

cardiovascular system were those that caused the withdrawal of some drugs of this class from the market, such as sibutramine (removed from the market in 2010 [47] after it was shown to increase the risk of myocardial infarction and stroke [48]) or phenylpropanolamine (removed from the market due to association with increased risk of hemorrhagic stroke in women [49]).

5.1.4. Antidepressants and antiepileptic drugs

Antidepressants and antiepileptics can affect weight in different ways, while some lead to weight gain, others to loss. Among the drugs that lead to weight loss, we mention: bupropion, venlafaxine, desvenlafaxine, topiramate, zonisamide, lamotrigine, and ziprasidone [45].

Bupropion is an antidepressant commonly used in cases of smoking cessation, to prevent weight gain [50]. It can also be used in combination with naltrexone, although there are currently no data on an augmenting the effect of bupropion by naltrexone.

Topiramate is an antiepileptic agent that blocks neuronal voltage-dependent sodium channels, enhances gamma-aminobutyric acid (GABA) A activity and inhibits carbonic anhydrase, generating appetite suppression and satiety enhancement. Amongs its adverse effects, we mention paresthesia, somnolence, and metabolic acidosis. Studies recommend its use in combinations with other substances and not as a sole agent in the treatment of obesity.

Zonisamide is another antiepileptic with serotoninergic and dopaminergic activity, which has effect on weight loss. Randomized trials in obese patients demonstrate that zonisamide at high doses is superior to placebo, while at low doses has effects similar to placebo [51].

5.1.5. Diabetes drugs

Metformin is an anti-hyperglycemic biguanide, used in the treatment of type 2 diabetes mellitus. It reduces liver production and intestinal absorption of glucose and therefore insulin secretion. By its anti-lipolytic effect, free fatty acid concentrations and gluconeogenesis decrease [52, 53]. Numerous studies have been performed on obese patients with PCOS, who received metformin. While the first studies seemed to demonstrate its effects in terms of weight loss, decreased serum androgen levels (and implicitly hirsutism), restoration of menstrual cycles, and induction of ovulation [54], further studies concluded its ineffectiveness in treating hirsutism or increasing live birth rates, even if it is effective in increasing the ovulatory rates and pregnancy rates. Metformin is no longer used as a first-line treatment for oligomenorrhea or weight loss.

Pramlintide is a synthetic analog of human amylin whose effect in terms of weight loss is relatively modest, due to its slowing effect on gastric emptying and the reduction in postprandial blood glucose concentration it causes.

Exenatide is a long-acting synthetic peptide (GLP-1 -glucagon-like polypeptide-1-agonist receptor), the effect of which is the increased secretion of dose-dependent and glucose-dependent insulin. Its' use is avoided because of the relatively low weight loss effect in conjunction with its mode of administration by subcutaneous injection [45].

Liraglutide, like exenatide, is a GLP-1 analog with significant weight-reducing effects. Studies in obese, non-diabetic patients have shown better efficacy against placebo at normal doses and

even orlistat when administered in high doses [55]. Among its adverse effects when administered at high doses are included nausea and vomiting, which may in part contribute to the weight-loss effect [55]. This drug is quite often avoided due to its route of administration (subcutaneous injection) but also due to its potential adverse effects, that although rare, they are severe (pancreatitis, renal impairment and gallbladder disease). Further, we consider important to mention that rodent studies have demonstrated the association of this drug with the increased frequency of thyroid C-cell tumors (benign and malignant), which is why it is not recommended in the case of the patients with personal or family history of medullary thyroid cancers [56].

5.1.6. Combination drugs

The combination of phentermine and topiramate is another two drug combination with good effect in terms of weight loss, being pharmacologically included in the sympathomimetic anorexia class. Being a two drug combination, it has a complex mechanism of action. Thus, phentermine, which is a sympathomimetic amine, like amphetamines, will reduce the appetite after the stimulation of the hypothalamus and the release of the norepinephrine. Topiramate also has appetite suppressing effects and causes rapid satiety. Studies show that after a 1-year administration, the effect of this combination drug on weight loss decreases, but nevertheless it seems to contribute in maintaining the weight obtained up to that point [57, 58]. Side effects of this drug include dry mouth, constipation, paresthesia, psychiatric and cognitive impairment. It is also contraindicated during pregnancy, having teratogenic effects [59].

The bupropion-naltrexone combination, though effective in weight loss, seems to have cardiovascular side effects, such as high blood pressure or tachycardia, so if it would be administered it would fail in addressing the underlying reason for initiating this therapy.

5.2. Surgical treatment of obesity–bariatric surgery

Bariatric surgery is indicated in cases of morbid obesity (BMI = 40 kg/m^2 or BMI greater than or equal to 35 kg/m^2 associated with different comorbidities). A study that enrolled obese patients who underwent bariatric surgery divided the treated patients into 3 groups; obese with PCOS, obese with hyperandrogenemia characteristics but with regular menstrual cycles and a third group with obese patients without hyperandrogenic traits. After applying the exclusion criteria, the group of patients with PCOS was studied in detail and the results were surprising. Within 12 +/− 5 months, the weight loss was of 41 +/− 9 kg, associated with the improvement of clinical and biochemical markers of hyperandrogenism. It was noted that an improvement in hirsutism had been observed and from a biochemical point of view markers such as: free testosterone, total testosterone, androstenedione and dehydroepiandrostenedione sulfate have been normalized while the level of SHBG increased. From a metabolic point of view, the improved insulin sensitivity was proved by the decrease in fasting insulin levels. With regard to the reproductive system, the restoration of regular menstrual cycles and ovulation were noticed [60].

A newer study, conducted in 2012, concludes that weight loss after bariatric surgery is not associated with significant changes in the menstrual cycle, the luteal phase length or the amount of blood lost during menstruation. A relatively modest improvement was found with respect to biochemical hyperandrogenism but without effects on the clinical markers

of hyperandrogenism. Instead, an 8–9 day follicular phase shortening associated with decreased fertility, was observed. What was new in this study was the finding that patients undergoing bariatric surgery after weight loss improve their sex life [61].

6. Conclusion

We consider to be of major importance the adoption of a healthy lifestyle, composed of a hypo caloric diet and physical exercise that will generate weight loss. Unlike any other treatment, weight loss without adjuvant medication (which brings various side effects) in many cases leads to at least partial resolution of PCOS symptoms. Although in this chapter by enlarge we have approached the subject of slimming medications, we consider it important to use them only in carefully selected cases, lifestyle changes continue to be the first-line treatment.

Conflict of interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this chapter.

Author details

Cringu Antoniu Ionescu[1,2]*, Ina Popescu[1,2], Mihail Banacu[1,2] and Mihai Dimitriu[1,2]

*Address all correspondence to: antoniuginec@yahoo.com

1 University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

2 Clinical Emergency Hospital St. Pantelimon, Bucharest, Romania

References

[1] Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: A systematic review and meta-analysis. Human Reproduction. 2016 Dec;**31**(12):2841-2855

[2] Ehrmann DA. Polycystic ovary syndrome. The New England Journal of Medicine. 2005;**352**(12):1223

[3] Rebuffe-Scrive M et al. Anthropometric variables and metabolism in polycystic ovarian disease. Hormone and Metabolic Research. 1989;**21**:391-397

[4] Dumesic DA, Akopians AL, Madrigal VK, Ramirez E, Margolis DJ, Sarma MK, Thomas AM, Grogan TR, Haykal R, Schooler TA, Okeya BL, Abbott DH, Chazenbalk GD. Hyperandrogenism accompanies increased intra-abdominal fat storage in normal weight polycystic ovary syndrome women. The Journal of Clinical Endocrinology and Metabolism. 2016;**101**(11):4178 Epub 2016 Aug 29

[5] Corbould A, Dunaif A. The adipose cell lineage is not intrinsically insulin resistant in polycystic ovary syndrome. Metabolism. 2007;**56**(5):716

[6] Rosenfield RL. Clinical review: Adolescent anovulation: Maturational mechanisms and implications. The Journal of Clinical Endocrinology and Metabolism. 2013 Sep;**98**(9):3572-3583 Epub 2013 Aug 2

[7] Abate N et al. Relationships of generalized and regional adiposity to insulin sensitivity in men. The Journal of Clinical Investigation. 1995;**96**:88-98

[8] Dunaif A. Insulin resistance and the polycystic ovary syndrome: Mechanism and implications for pathogenesis. Endocrine Reviews. 1997;**18**:774-800

[9] Essah PA, Wickham EP, Nestler JE. The metabolic syndrome in polycystic ovary syndrome. Clinical Obstetrics and Gynecology. 2007 Mar;**50**(1):205-225

[10] Cattrall FR, Healy DL. Long-term metabolic, cardiovascular and neoplastic risks with polycystic ovary syndrome. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2004;**18**:803-812

[11] Apridonidze T, Essah PA, Iuorno MJ, et al. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**:1929-1935

[12] Ehrmann DA, Liljenquist DR, Kasza K, et al. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. The Journal of Clinical Endocrinology and Metabolism. 2006;**91**:48-53

[13] Ehrmann DA et al. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care. 1999;**22**:141-146

[14] Legro RS et al. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: A prospective, controlled study in 254 affected women. The Journal of Clinical Endocrinology and Metabolism. 1999;**84**:165-169

[15] Lo JC, Feigenbaum SL, Yang J, Pressman AR, Selby JV, Go AS. Epidemiology and adverse cardiovascular risk profile of diagnosed polycystic ovary syndrome. The Journal of Clinical Endocrinology and Metabolism. 2006;**91**(4):1357

[16] Baptiste C, Battista M, Trottier A, et al. Insulin and hyperandrogenism in women with polycystic ovary syndrome. The Journal of Steroid Biochemistry and Molecular Biology. 2010 Oct;**122**(0). DOI: 10.1016/j.jsbmb.2009.12.010

[17] Moran L, Norman RJ. Understanding and managing disturbances in insulin metabolism and body weight in women with polycystic ovary syndrome. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2004;**18**(5):719-736

[18] Hardiman P, Pillay OC, Atiomo W. Polycystic ovary syndrome and endometrial carcinoma. Lancet. 2003;**361**:1810-1812

[19] Vrbikova J, Cibula D. Combined oral contraceptives in the treatment of polycystic ovary syndrome. Human Reproduction Update. 2005;**11**:277-291

[20] Aghajanova L, Velarde MC, Giudice LC. Altered gene expression profiling in endometrium: Evidence for progesterone resistance. Seminars in Reproductive Medicine. 2010;**28**: 51-58

[21] Li X, Feng Y, Lin J, et al. Endometrial progesterone resistance and PCOS. Journal of Biomedical Science. 2014;**21**(1):2

[22] Joham AE, Boyle JA, Ranasinha S, et al. Contraception use and pregnancy outcomes in women with polycystic ovary syndrome: Data from the Australian longitudinal study on women's health. Human Reproduction. 2014 Apr;**29**(4):802-808

[23] Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. International Journal of Women's Health. 2011;**3**:25-35

[24] Pasquali R, Gambineri A, Cavazza C, Ibarra Gasparini D, Ciampaglia W, Cognigni GE, Pagotto U. Heterogeneity in the responsiveness to long-term lifestyle intervention and predictability in obese women with polycystic ovary syndrome. European Journal of Endocrinology. 2011 Jan;**164**(1):53-60. DOI: 10.1530/EJE-10-0692. Epub 2010 Oct 18

[25] Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. The New England Journal of Medicine. 2002 Feb 7;**346**(6):393-403

[26] Moran LJ, Noakes M, Clifton PM, Tomlinson L, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. The Journal of Clinical Endocrinology and Metabolism. 2003;**88**:812-819

[27] Reaven GM. The insulin resistance syndrome: Definition and dietary approaches to treatment. Annual Review of Nutrition. 2005;**25**:391-406

[28] Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome (review). Cochrane Gynaecology and Fertility Group. 2011 July;**6**(7). DOI: 10.1002/14651858.CD007506.pub3

[29] Haqq L, McFarlane J, Dieberg G, Smart N. Effect of lifestyle intervention on the reproductive endocrine profile in women with polycystic ovarian syndrome: A systematic review and meta-analysis. Endocr Connect. 2014 Mar 1;**3**(1):36-46

[30] Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A, Ragni G. Overweight and obese anovulatory patients with polycystic ovaries: Parallel improvements in

anthropometric indices, ovarian physiology and fertility rate induced by diet. Human Reproduction. 2003;**18**(9):1928

[31] Restoration of Reproductive Potential by Lifestyle Modification in Obese Polycystic Ovary Syndrome: Role of Insulin Sensitivity and Luteinizing Hormone* Huber-Buchholz M-M, Carey DGP, Norman RJ. Reproductive Medicine Unit, University of Adelaide, Queen Elizabeth Hospital, Woodville, South Australia 5011; and the Department of Diabetes and Endocrinology, Princess Alexandra Hospital, Brisbane, Queensland 4102, Australia

[32] Hollmann M, Runnebaum B, Gerhard I. Effects of weight loss on the hormonal profile in obese, infertile women. Human Reproduction. 1996 Sep;**11**(9):1884-91

[33] Butryn ML, Webb V, Wadden TA. Behavioral treatment of obesity. The Psychiatric Clinics of North America. 2011 Dec;**34**(4):841-859

[34] Wadden TA, Butryn ML, Wilson C. Lifestyle modification for the management of obesity. Gastroenterology. 2007 May;**132**(6):2226-2238

[35] Johnston BC, Kanters S, Bandayrel K, Wu P, Naji F, Siemieniuk RA, Ball GD, Busse JW, Thorlund K, Guyatt G, Jansen JP, Mills EJ. Comparison of weight loss among named diet programs in overweight and obese adults: A meta-analysis. Journal of the American Medical Association. 2014 Sep;**312**(9):923-933

[36] Anson RM, Guo Z, de Cabo R, Iyun T, Rios M, Hagepanos A, Ingram DK, Lane MA, Mattson MP. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proceedings of the National Academy of Sciences. 2003;**100**:6216-6220

[37] Mattson MP, Wan R. Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems. The Journal of Nutritional Biochemistry. 2005;**16**:129-137

[38] Sogawa H, Kubo C. Influence of short-term repeated fasting on the longevity of female (NZB x NZW)F1 mice. Mechanisms of Ageing and Development. 2000;**115**:61-71

[39] Thankamony A, Capalbo D, Marcovecchio ML, Sleigh A, Jørgensen SW, Hill NR, Mooslehner K, Yeo GSH, Bluck L, Juul A, Vaag A, Dunger DB. Low circulating levels of IGF-1 in healthy adults are associated with reduced β-cell function, increased Intramyocellular lipid, and enhanced fat utilization during fasting. The Journal of Clinical Endocrinology and Metabolism. 2014;**99**:2198-2207

[40] AU Harrison CL, Lombard CB, Moran LJ, Teede HJ. Exercise therapy in polycystic ovary syndrome: A systematic review. Human Reproduction Update. 2011 Mar;**17**(2):171-183 Epub 2010 Sep 10

[41] Rubio MA, Gargallo M, Isabel Millan A, Moreno B. Drugs in the treatment of obesity: Sibutramine, orlistat and rimonabant. Public Health Nutrition. 2007;**10**:1200-1205

[42] Legro RS. Obesity and PCOS: Implications for diagnosis and treatment. Seminars in Reproductive Medicine. 2012 Dec;**30**(6):496-506. DOI: 10.1055/s-0032-1328878

[43] Leblanc ES, O'Connor E, Whitlock EP, Patnode CD, Kapka T. Effectiveness of primary care-relevant treatments for obesity in adults: A systematic evidence review for the U.S. preventive services task force. Annals of Internal Medicine. 2011;**155**(7):434

[44] Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Kim C, et al. Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: A meta-analysis. Archives of Internal Medicine. 2004;**164**:1395-1404

[45] George A, Bray MD. Obesity in Adults: Drug Therapy. https://www.uptodate.com/contents/obesity-in-adults-drug-therapy?source=search_result&search=obesity%20in%20adults&selectedTitle=3~150. (Accessed: September 1, 2017)

[46] FDA Highlights of Prescribing Information: BELVIQ (Lorchttps://www.uptodate.com/contents/obesity-in-adults-drug-therapy?source=search_result&search=obesity%20in%20adults&selectedTitle=3~150aserinhydrochloride) tablets, for oral use. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022529lbl.pdf (Accessed: September 17, 2017)

[47] European Medicines Agency. European Medicines Agency Recommends Suspension of Marketing Authorisation for Sibutramine http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/01/news_detail_000985.sjsp&jsenabled=true (Accessed: October 1, 2017)

[48] James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, Torp-Pedersen C, Sharma AM, Shepherd GM, Rode RA, Renz CL, SCOUT Investigators. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. The New England Journal of Medicine. 2010;**363**(10):905

[49] Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, Morgenstern LB, Wilterdink JL, Horwitz RI. Phenylpropanolamine and the risk of hemorrhagic stroke. The New England Journal of Medicine. 2000;**343**(25):1826

[50] Gadde KM, Parker CB, Maner LG, Wagner HR 2nd, Logue EJ, Drezner MK, Krishnan KR. Bupropion for weight loss: An investigation of efficacy and tolerability in overweight and obese women. Obesity Research. 2001;**9**(9):544

[51] Gadde KM, Kopping MF, Wagner HR 2nd, Yonish GM, Allison DB, Bray GA. Zonisamide for weight reduction in obese adults: A 1-year randomized controlled trial. Archives of Internal Medicine. 2012;**172**(20):1557

[52] Ferrannini E. The target of metformin in type 2 diabetes. The New England Journal of Medicine. 2014;**371**(16):1547

[53] Madiraju AK, Erion DM, Rahimi Y, Zhang XM, Braddock DT, Albright RA, Prigaro BJ, Wood JL, Bhanot S, MacDonald MJ, Jurczak MJ, Camporez JP, Lee HY, Cline GW, Samuel VT, Kibbey RG, Shulman GI. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature. 2014 Jun;**510**(7506):542-546 Epub 2014 May 21

[54] Singh-Franco D, Perez A, Harrington C. The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: A systematic review and meta-analysis. Diabetes, Obesity & Metabolism. 2011;**13**(2):169

[55] Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, Madsen J, Rasmussen MF, Lean ME, NN8022-1807 Study Group. Effects of liraglutide in the treatment of obesity: A randomised, double-blind, placebo-controlled study. Lancet. 2009; **374**(9701):1606. Epub 2009 Oct 23

[56] FDA News Release. FDA Approves Weight–Management Drug Saxenda; Released 23 December 2014 – Web Address: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427913.htm (Accessed: September 15, 2017)

[57] Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, Day WW, Bowden CH. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): A randomized, placebo-controlled, phase 3 extension study. The American Journal of Clinical Nutrition. 2012 Feb;**95**(2):297-308 Epub 2011 Dec 7

[58] Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, Tam PY, Troupin B, Day WW. Controlled-release phentermine/topiramate in severely obese adults: A randomized controlled trial (EQUIP). Obesity (Silver Spring). 2012 Feb;**20**(2):330-342 Epub 2011 Nov 03

[59] Héctor F. Escobar-Morreale, José I. Botella-Carretero, Francisco Á lvarez-Blasco, José Sancho, and José L. San Millán. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. The Journal of Clinical Endocrinology and Metabolism. 2005 Dec;**90**(12):6364-6369. Epub 2005 Sep 27

[60] Legro RS, Dodson WC, Gnatuk CL, Estes SJ, Kunselman AR, Meadows JW, Kesner JS, Krieg EF Jr, Rogers AM, Haluck RS, Cooney RN. Effects of gastric bypass surgery on female reproductive function. The Journal of Clinical Endocrinology and Metabolism. 2012 Dec;**97**(12):4540-4548 Epub 2012 Oct 12

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