Obesity and polycystic ovary syndrome

ARLETA SZCZEŃSA, BŁAŻEJ MĘCZEKALSKI

Abstract

Obesity in polycystic ovary syndrome (PCOS) patients poses a significant clinical problem not only due to their fertility issues, but also because of the co-existence of metabolic disorders and their long term health consequences. Obesity leads to increased morbidity, impairs Quality of Life (QoL) and might be the cause of early mortality. Polycystic Ovary Syndrome is one of the most frequent endocrinopathies affecting women in reproductive age. Obesity can be found in 18-80% of PCOS patients depending on geographical latitude. The correlation between insulin resistance and elevated androgens level in serum is a complex one. Hyperinsulinemia and insulin resistance lead to a gradual development of the elements of the metabolic syndrome which can be frequently found in PCOS patients. Long-term consequences of metabolic syndrome should be the primary focus here. These include: arterial hypertension, peripheral arterial disease, impaired carbohydrate metabolism and type 2 diabetes. To a large extent, obesity influences the phenotype of PCOS. It is probably related to menstrual cycle irregularities, miscarriage following ovulation induction and failed in vitro fertilization attempts. Body weight normalization has a number of benefits for the patient – it improves the overall metabolic profile and good results in treatment of menstrual disorders.

Key words: PCOS, obesity, metabolic disorders

Introduction

Obesity in polycystic ovary syndrome (PCOS) patients poses a significant clinical problem not only due to their fertility issues, but also because of the co-existence of metabolic disorders and their long term health consequences. Scientists have found a statistically significant correlation between obese PCOS patients, infertility, menstrual cycle irregularities and hirsutism [1-3]. Obesity leads to increased morbidity, impairs quality of life (QoL) and might be the cause of early mortality [4]. PCOS patients often report depressive mood; they feel unacceptable in their social environment not only because of their infertility issues and hyperandrogenism symptoms (such as hirsutism, acne and alopecia), but mostly because of their obesity. In societies where excessive body weight is more accepted, the influence of obesity on psychological well-being is less frequently observed.

Definition

There has been a significant degree of ambiguity in trying to establish the diagnostic criteria for PCOS. Current definition is based on the third ESHRE/ASRM PCOS – Amsterdam 2010 consensus and contains the diagnostic criteria from 2003 (ESHRE/ASRM Sponsored PCOS Consensus Workshop Group). To diagnose a given patient with PCOS, at least two out of the following three symptoms must be manifested: anovulatory cycles or infrequent ovulation, biochemical or clinical symptoms of hyperandrogenemia, and polycystic ovaries in ultrasound examination. Other endocrine causes of these abnormalities must be ruled out. Obesity may accompany the symptoms listed above, but it is not a decisive factor in the diagnostic process [5-8]. In the diagnostic process of adolescent patients, all three criteria must be observed, with a menstrual disorder recorded at least two years after menarche, and the second criterion being hyperandrogenemia (not just its symptoms) [9-10].

According to World Health Organization (WHO), obesity is an abnormal or excessive fat accumulation in adipocytes which has a negative impact on health. It is a metabolic imbalance caused by an excessive supply of energy from nourishment. Obesity is currently becoming a multifactorial civilization disease characterized by metabolic and endocrine changes [11-13].

Epidemiology

Polycystic ovary syndrome is one of the most frequent endocrinopathies affecting women in reproductive age with a prevalence around 6-15% depending on diagnostic criteria used (NIH, Rotterdam) [14].
Obesity can be found in 18-80% of PCOS patients depending on geographical latitude. It seems women suffering from PCOS are more often overweight than obese. The lowest percentage of obese PCOS patients was found in Pakistan (25%), and the highest in The United States of America (61%) and Australia (76%)[15-17]. Women with a BMI over 25 kg/m² (which indicates excessive weight or obesity) and co-existing PCOS comprise around 90% in Poland, USA and Great Britain [18-19].

The highest percentage of adolescent patients diagnosed with PCOS has been found in the United States (approximately 18-22%) [20].

In Asia, women are classified as overweight if their BMI exceeds 23 kg/m². Despite the fact that the BMI criterion is more restrictive in that area, there are still fewer overweight and obese women in Asia in comparison to the Western world. Obesity is found in 50-60% of PCOS patients, with abdominal obesity reaching 50-60% [21-23].

It is still unclear whether ethnicity is correlated with the occurrence of obesity in PCOS.

Hyperinsulinemia was found in approximately 80% of obese PCOS patients and in 30-40% of those with appropriate body weight. While 20-50% of Polycystic Ovary Syndrome patients suffer from insulin resistance, approximately 30% of them have an impaired glucose tolerance, and 8% are diagnosed with type 2 diabetes.

Etiology

Although the etiopathogenesis of Polycystic Ovary Syndrome is still unknown, it is possible that the disorder has a number of causes. It is believed that steroidogenesis disorders in ovarian theca cells resulting in excessive androgens production are its initial factor.

It has not been established whether obesity escalates PCOS symptoms or induces the disease. Alternatively, it is possible that PCOS leads to obesity (in most cases abdominal). Some scientists are concerned with early childhood obesity – there is no consensus among researchers about it being the trigger of PCOS. Some scientists suggest it could be a signal of PCOS which is to be developed in the future.

It is certain that obesity prior to menarche is highly correlated with high androgen level at the beginning of maturation. A correlation between obesity, menstrual cycle disorders and hirsutism intensity has also been observed [1].

Developing type 1 diabetes mellitus (DM1) at maturation or prior to maturation may be the cause of menstrual cycle disorders in the future. Girls suffering from DM1 show higher free testosterone levels and an increased LH secretion in comparison to FSH secretion, and enlarged ovary volume. In that particular case, exogenous hyperinsulinism (DM1 treatment) at the time of increased ovary activity during maturation reprograms the ovaries to produce more androgen which leads to developing hyperandrogenism and PCOS later in life [24-26].

Pathophysiology

Disorders of GHRH-GH-IGF1 axis regulation may be classified as one of the pathogenetic factors of PCOS. However, hypothalamus-pituitary-ovary axis aberrations are still believed to be a significant cause of the syndrome. In PCOS pathogenesis, aberrations of ovarian secretion of inhibins, activins and follistatin may also play an important role. Abnormalities in production and synthesis of these proteins may inhibit normal follicle development [27].

For some patients suffering from the condition, a familial occurrence of polycystic ovary syndrome on the basis of autosomal dominant inheritance has been observed. There is not enough evidence to determine whether PCOS is genetically determined. A multigenetic background of PCOS etiology can involve the following phenomena: aberration in gonadotropins synthesis, mutation of sex steroids synthesis and function gene, mutation of the genes responsible for carbohydrates metabolism (i.e. synthesis and function of insulin and its receptor). While the presence of CYP 17 gene generally predisposes to development of PCOS, polygenic cellular resistance to insulin triggers the condition. Insulin (hyperinsulinemia and insulin resistance) are universally believed to play a vital role in the pathogenesis of PCOS [28].

The correlation between insulin resistance and elevated androgens level in serum is a complex one. Hyperinsulinemia causes hyperandrogenism by elevating ovarian production of androgens in thecal cells. It also encourages growth of free IGF-1 concentration which stimulates 5-alpha-reductase to testosterone transformation to its active form - dihydrotestosterone by means of IGF-1 receptor. It inhibits the production of IGF-binding protein (IGFBP). IGF-1 has only 1% of insulin's biological activity. Hyperinsulinemia directly affects the liver by SHBG synthesis depletion. Lowering the level of SHBG automatically increases the level of free testosterone. The correlation between hyperinsulinemia and hyperandrogenism are still unclear [29-31].
Insulin and LH have different physiological cell mechanisms; combined together, they increase steroidogenesis in the thecal cells which brings about a specific interaction between these two hormones. Insulin significantly increases the accumulation of LH-dependant cAMP in ovarian thecal cells. This insulin-stimulated increase of cAMP may be stimulated by phosphatidylinositol 3-kinase (PI-3K) and/or protein kinase C (PKC).

In PCOS patients, abnormalities in both LH and insulin on ovarian production of androgen occur. A pathologic influence of insulin on ovarian granulose cells has been observed. It is synonymous to an increase of proliferative activity due to metabolic resistance. In women suffering from PCOS, a selective defect of insulin and its impact on androsynthesis correlates with insulin resistance or is its cause. It depends on the metabolic pathway [32].

Recent evidence suggests that medication normalizing insulin sensitivity in non-obese PCOS patients with a good level of insulin leads to normalization of testosterone levels and restores ovulation. Even patients with a normal level of insulin experience the lowering of insulin level. This suggests that some women suffering from PCOS have an increased ovarian insulin sensitivity without developing insulin resistance or hyperinsulinemia. In the light of clinical and physiological research, it can be assumed that some patients develop PCOS because of the growth of the selective and tissue-specific ovarian insulin sensitivity.

Appetite is mostly regulated by neurotransmitters and hormones such as: leptin, ghrelin, neuropeptide Y, galanin, orexin-A and orexin-B, serotonin, CRH, dopamine, noradrenaline, insulin, visfatin and resistin [33]. Each organic or functional irregularity within these may result in eating habit changes which may eventually lead to obesity. Androgens, estrogens, TNF-α, cholecystokinin, adiponectin, aquaporin, calpain-10 and β-catenin are also believed to be linked to obesity, although final evidence is still unavailable.

Neuropeptide Y excreted by arcuate nucleus stimulates food intake, decreases thermogenesis and increases the amount of insulin and cortisol. It interacts with estrogen – it stimulates GnRH release in its presence and blocks it in the case of lack of estrogen. NPY and galanin modulate appetite in the central and peripheral mechanism and play a vital role in LHRH secretion process. The interaction between central and peripheral signal (which stimulates food intake) is regulated by leptin. Leptin can also regulate NPY activity and other hypothalamic peptides, which have a significant influence on appetite. Neuropeptide Y can be treated as a link between nutrition and the reproductive system. Research on ghrelin seems to indicate that it is closely related to appetite, body weight gain and the process of body weight reduction [34].

Ghrelin stimulates food intake and has an influence on metabolic balance of the body. Due to its multiple interactions with the neurotransmitter system, it regulates appetite and has an influence on the hormonal system. In vitro studies suggest that ovaries are largely affected by the hormone which can be found in the organ in large quantities. A negative correlation between the level of ghrelin and androgen in the serum of PCOS patients has also been observed [35].

Patients suffering from PCOS seem to have lower levels of ghrelin than healthy women. However, data available on the subject is ambiguous [36-38].

Ghrelin is inextricably linked to metabolic balance, obesity, insulin resistance and reproductive functions of the body. Resistin is a recently discovered hormone which can modulate glucose tolerance and influence insulin, which in turn is related to obesity [39].

Visfatin is another recently discovered metabolic factor which is similar to insulin in the way it works. It is produced mostly in the visceral adipose tissue and, to a smaller extent by subcutaneous adipose tissue. Research shows that an elevated level of visfatin in serum is typical of obese patients. It also proves that visfatin is similar to insulin in its property of lowering the level of glucose in serum.

The discovery sheds new light on a number of phenomena such as insulin resistance, metabolic syndrome and its pathogenesis, and, most importantly, obesity and its role in PCOS.

The exact manner of estradiol’s influence of on food intake has not yet been determined, but it seems that it acts as a modulator [40-41].

Steroid hormones are believed to foster obesity, perhaps due to their influence on lipoprotein lipase activity, which is the main enzyme hydrolyzing circulating triglycerides into lipid acids and glycerol. The highest activity of lipoprotein lipase, which is recorded in adipose tissue, plays a vital role in storing fat in adipocyte, which in turn fosters obesity. Catecholamine, insulin, IGF-1, and steroid hormones influence lipoprotein lipase. The presence of estrogen, progesterone and androgen receptors on the surface of the adipocyte has been proven. It is believed that estrogens minimize the lipolytic activity of the adipose tissue and limit IGF-1 production [42-43].
Obesity can be familial where common habits (nutritional and non-nutritional) typically affect whole families. In research carried out on twins, genetic factors tend to comprise 70% of all obesity causes, and environmental factors reach approximately 30%. More than one gene can be involved in food intake and calorie expenditure (single gene mutation and multigenic mutation).

Leptin, leptin receptor, proopiomelanocortin and proopiomelanocortin receptor 4 can be listed as examples of single gene mutations. Most of these forms are inherited autosomally recessively. It is believed that leptin is coded by ob gene which is a transmitter between the adipocyte and the brain. Single gene mutation causing obesity can only be diagnosed in extremely obese patients, and it seems that only a small percentage of all obese people have a mutated leptin gene or leptin receptor.

Most forms of obesity can be classified as multigenic obesity – substitution in promoter region of uncoupling protein (UCP2) is the perfect example of such polymorphism. Some of its variants slow down the metabolism by increasing the efficiency of energetic processes leading to ATP synthesis in mitochondria.

Hereditary factors can play a vital role in passing down psycho-physical constitution and diseases causing secondary obesity such as diabetes or familial hyperlipoproteinemia. Genetic tendency to put on weight may stem from the person’s susceptibility to environmental stimuli which foster weight gain. However, increased calorie intake and decreased physical activity is not correlated with genetic factors [44-51].

Metabolic consequences

Hyperinsulinemia and insulin resistance lead to a gradual development of the elements of the metabolic syndrome which can be frequently found in PCOS patients. Long-term consequences of metabolic syndrome should be the primary focus here. These include: arterial hypertension, peripheral arterial disease, impaired carbohydrate metabolism and type 2 diabetes.

PCOS, obesity and diabetes mellitus

Due to the fact that obesity potentiates insulin resistance, it is treated as an independent risk factor in developing glucose intolerance and type 2 diabetes.

Extensive research shows that 54% of patients progress from glucose intolerance to type 2 diabetes within 6.2 years. Data gathered in a long-term cohort study suggests that the risk of PCOS patients developing type 2 diabetes when they reach middle age varies from 10 to 20%. For PCOS patients with a phenotype typical of the condition, high body mass index, abdominal obesity and positive family history of diabetes increase the risk of developing type 2 diabetes. However, because non-obese women are also at risk of developing type 2 diabetes, PCOS is an independent risk factor for middle-aged women [52]. The research also shows an increased risk of gestational diabetes in PCOS women, which is higher than those of obese women in general [53-54].

Screenings have shown that in many cases pregnant women diagnosed with gestational diabetes have been found to suffer from PCOS, especially if they were overweight or obese [55].

Risk of cardiovascular disease

PCOS patients face a number of risk factors of cardiovascular diseases, such as obesity, hyperinsulinemia, insulin resistance, hyperlipidemia and hyperandrogenism. Obese PCOS patients show an increase in cardiovascular disease markers such as CRP proteins, endothelin 1, adiponectin, homocysteine, von Wilebrand factor, PAI-1, and oxidative stress markers.

Insulin resistance leads to high blood pressure through the activity of the sympathetic system, its influence on the transport of cations in vascular wall cells, an increase in sodium reabsorption in proximal tubule of the nephron, sodium and water retention, and direct increase in proliferation of miocytes of the vascular wall. However, the data pointing to the correlation between PCOS and arterial hypertension is not coherent [56].

It can be assumed that increased risk factors typical for young PCOS patients make them more prone to developing atherosclerosis early in their life, which may eventually lead to heart attack [57]. Extensive population research carried out in Pittsburgh and the Czech Republic has shown that cardiac incidents were four times more frequent in PCOS patients in comparison to healthy women [58].

Dyslipidemia

Dyslipidemia occurs frequently in PCOS patients – in most cases, it manifests itself as hypertriglyceridemia and elevated LDL cholesterol levels. An elevated level of non-HDL cholesterol which leads to a shift in proportion of ApoB/A1 is most frequent and may result in a cardiovascular disease. Excessive body weight also has an impact on the abnormalities in lipid apoproteins in patients suffering from PCOS [59].
Obstructive sleep apnea

Obstructive sleep apnea is an independent risk factor in cardiovascular disease. It has been established that the disorder can be found mostly in obese PCOS patients. The most predictive factor of obstructive sleep apnea is the level of insulin in fasting state and glucose/insulin ratio [60-62].

Reproductive issues of obese women with PCOS

To a large extent, obesity influences the phenotype of PCOS. It is probably related to menstrual cycle irregularities, miscarriage following ovulation induction and failed in vitro fertilization attempts [9].

Metabolic PCOS phenotype (obesity, acanthosis nigricans, insulin resistance) increases the risk of pregnancy induced hypertension, preclampsia, eclampsia and gestational diabetes. It also leads to delivery complication, causes overdue pregnancy, lengthens the second stage of the delivery, leads to shoulder dystocia and often results in instrumental delivery. Metabolic phenotype of PCOS also influences the fetuses and the newborns – children of PCOS patients manifest a higher degree of morbidity and an increased mortality rate [9].

Management of metabolic disorders in PCOS

Treating obese PCOS patients should be individualized but never restricted to alleviating a few selected symptoms. In each case, the patient should be encouraged to change her lifestyle, her eating habits and make sure her diet is appropriate. Regular physical activity should be advised and psychological support should be given at all times.

The authors of this article believe that frequent contact with an obese PCOS patient plays a vital role in the treatment.

It has been proven that significant weight loss leads to reinstatement of ovulation and a general improvement in fertility. It leads to an increase in the level of SHBG and lowers the basic level of insulin followed by normalization in glucose metabolism.

Introducing lifestyle changes decreases the likelihood of developing type 2 diabetes in the future [63-66]. Physical activity should be regular and should last 90 minutes at least 3 times a week in the form of aerobe training. Until now, it has been believed that 30-40 minute long exercise every other day is sufficient.

Pharmacological treatment includes metformin and other oral medications which increase insulin sensitivity, such as thiazolidinedione, which lowers the risk of diabetes mellitus and other metabolic disorders by decreasing insulin resistance. Metformin has a positive influence on normalizing the lipid system, it lowers the level of total cholesterol, triglycerides, LDL and VLDL. There is a significant amount of evidence suggesting that thiazolidinedione can be used safely, however, there seems to be no data on its long term consequences. Therefore, in women in the reproductive period, thiazolidinedione should be administered with great caution, or not used at all. It must be emphasized that both metformin and thiazolidinedione are not registered as PCOS medication. Before she starts the treatment, each patient should be informed about their status.

Thanks to its influence on insulin resistance, metformin can slightly decrease the level of androgens in PCOS patients. However, it must be stressed that it should only be used in hyperinsulinemia, glucose intolerance or diabetes. It seems that it also fuels weight loss.

In obese PCOS patients, bariatric surgery may be performed to reverse metabolic disorders. According to WHO guidelines, patients can qualify for surgical obesity treatment if their BMI is over 35 kg/m² with the existence of one risk factor.

Arterial hypertension should be treated in accordance with current guidelines. Normalization of lipid levels therapy is not universally prescribed and should always be supervised by a specialist.

Body weight normalization has a number of benefits for the patient – it improves the overall metabolic profile and has a great influence on the mental condition of the patients, which in turn can be crucial in treating the main symptoms of PCOS (including infertility).

It must be reiterated that according to some theories, obesity as such is not stress-inducing. However, pressure to get back in shape and follow a healthy diet can lead to the development of depressive disorders which can significantly impede the outcome of the treatment.

Conclusion

Polycystic ovary syndrome is characterized by multiple metabolic aberrations, which are important because of their lifelong consequences. Treatment should be individualized and it should not target only isolated symptoms. Lifestyle modification based on the principles of caloric restriction and exercise remains a primary therapy for the management of obesity in PCOS.
References

[5] ESHRE/ASRE
[9] ESHRE/ASRE
[14] ESHRE/ASRE


Arleta Szczęsna
Department of Gynecological Endocrinology
Poznan University of Medical Sciences
33 Polna Street, 60-535 Poznan, Poland
e-mail: arleta.szczesna@op.pl