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Impact of Obesity and Weight Management on Women with Polycystic Ovary Syndrome and Coexisting Obesity – A Brief Narrative Review

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Review article

Abstract

Obesity, an ongoing pandemic, is associated with obesity-related androgenic, reproductive, and metabolic comorbidities in females. Polycystic Ovary Syndrome (PCOS) is a multifaceted endocrinopathy that commonly manifests with hyperandrogenic, reproductive, and metabolic dysfunctional features. Obesity and PCOS often coexist. Insulin resistance and subsequent hyperinsulinemia are key factors implicated in the clinicopathological manifestations of PCOS and associated metabolic syndrome. Obesity may amplify these effects, thus, affecting adolescent girls and women of childbearing age. Evidence supports weight loss in achieving favourable endocrine, metabolic, and reproductive outcomes in women with Polycystic Ovary Syndrome and coexisting obesity. Therefore, an effective weight loss strategy should be considered as a front-line intervention in this patient population, with emphasis on fertility timeline-related management in reproductive-aged women, where applicable. This brief narrative review provides insight into the impact of obesity and weight loss on women with Polycystic Ovary Syndrome and coexisting obesity.

Key words: PCOS, Obesity, Overweight, Weight Loss, Polycystic Ovary Syndrome, Exercise, Lifestyle intervention, Bariatric surgery

VLIV OBEZITY A REGULACE HMOTNOSTI NA ŽENY SE SYNDROMEM POLYCYSTICKÝCH VAJEČNÍKŮ A SOUBĚŽNOU OBEZITOU – STRUČNÝ PŘEHLED

Přehledový článek

Abstrakt

Obezita, která představuje pokračující pandemii, je u žen spojena s androgenními, reprodukčními a metabolickými komorbiditami souvisejícími s obezitou. Syndrom polycystických vaječníků (PCOS) je mnohostranná endokrinopatie, která se běžně projevuje hyperandrogenními, reprodukčními a metabolickými dysfunkcemi. Obezita a PCOS se často vyskytují současně. Inzulinová rezistence a následná hyperinzulinémie jsou klíčovými faktory, které se podílejí na klinicko-patologických projevech PCOS a souvisejícím metabolickém syndromu. Obezita může tyto projevy zesilovat, a postihovat tak dospívající dívky a ženy ve fertilním věku. Důkazy podporují snížení hmotnosti při dosahování příznivých endokrinních, metabolických a reprodukčních výsledků u žen se syndromem polycystických vaječníků a koexistující obezitou. Proto by měla být účinná strategie snižování hmotnosti považována za intervenci první linie u této populace pacientek,

případně s důrazem na řízení související s časováním plodnosti u žen v reprodukčním věku. Tento stručný přehled poskytuje vhled do dopadu obezity a hubnutí na ženy se syndromem polycystických vaječníků a koexistující obezitou.

Klíčová slova: PCOS, obezita, nadváha, hubnutí, syndrom polycystických vaječníků, cvičení, intervence v oblasti životního stylu, bariatrická chirurgie

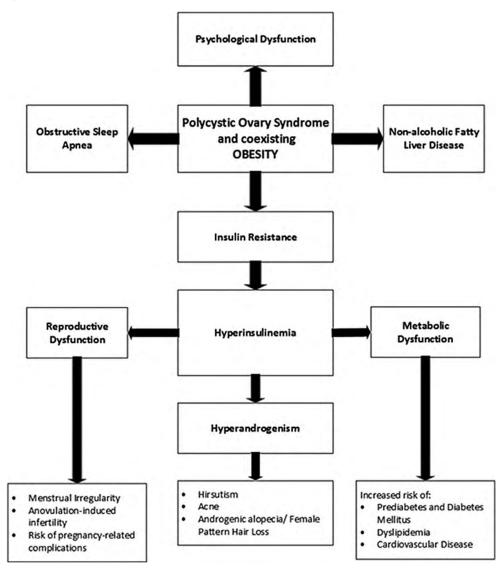
Introduction

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder with a prevalence of 5% to 15% (1). The etiopathology of this perplexing endocrinopathy is still not completely understood; however, the complex interplay of genetic and environmental traits may play some role (1,2). Due to the heterogeneous nature of the disease, women may experience a spectrum of clinical manifestations of variable intensity from adolescence to menopause (2,3).

Various mechanisms are hypothesized and proposed for the etiopathogenesis of PCOS. This multifaceted syndrome has reproductive, metabolic, and psychological dysfunctional features (summarized in *Fig. 1*) (4). Numerous evidence-based guidelines mention that PCOS diagnostic criteria require at least two of the following: ovulatory dysfunction, hyperandro-

genism, and polycystic ovaries on ultrasound-based imaging (5). Its clinical reproductive features include menstrual irregularity, hirsutism, anovulation-induced infertility, and risk of pregnancy-related complications (6,7). In PCOS, LH/FSH ratio is often altered due to disturbance in the gonadotrophin axis (8). PCOS-related metabolic disturbances increase the individual's risk of prediabetes, diabetes mellitus, cardiovascular disease, dyslipidemia, and metabolic syndrome (2,9). Emerging evidence indicates an association of PCOS with psychological features such as mood disorders, anxiety, and depression (10-12). Women with PCOS tend to have a poor mental quality of life (13). Various treatment options are available to address diverse symptoms of PCOS, but none of the therapies has been proven yet to combat and cure PCOS (14).

Fig. 1 Various dysfunctional PCOS-related manifestations



Obesity is prevalent in around 50-70% of women with polycystic ovary syndrome (15,16). Despite the availability of diverse published data, the exact etiopathogenesis of obesity is not clearly explained in the patient population affected with PCOS (16). There is research evidence suggesting androgen excess in women with PCOS, which favours abdominal fat deposition and induces obesity (2). This contributes to insulin resistance and hyperinsulinemia, thus facilitating more androgen secretion. The aforementioned vicious pathological phenomenon and hypothalamic-pituitary-ovary axis dysfunction often result in anovulation and subsequent infertility. It is noted that obese women with PCOS may enhance their ovulation rates through effective weight reduction (16)

Limited evidence is available concerning the progression of PCOS-linked comorbidities over the women's reproductive lifetime. Research shows that the risk of PCOS-related comorbidities such as dyslipidemia, cardiovascular disease, hypertension, and diabetes mellitus is amplified in the presence of coexisting obesity (4). Although PCOS is considered an obesity-related disorder, the correlation between the two conditions may not imply causation despite the increased prevalence of PCOS in obese women (17). More methodological research and RCTs are required for this patient population to define PCOS-specific weight loss stratagems and therapeutics regimens with long-term favourable clinical outcomes.

Aims and objective

Due to a lack of robust evidence-based research, the exact impact of weight loss remains unanswered for overweight/obese PCOS women in their reproductive years who are chronically struggling with reproductive, metabolic, and endocrine abnormalities. Therefore, this narrative review is sought to assess mainly two objectives: first, to assess the negative health impacts of obesity in reproductive-aged women with PCOS, and second, to review various effective weight management stratagems and related outcomes in this patient population.

Materials and methods

The current narrative review provides insight into the prolific medical literature on the impact of obesity and weight loss on women with PCOS and coexisting obesity. For this purpose, an electronic PubMed database search is performed to identify the relevant research articles. Reference lists of selected research papers are also checked and reviewed to identify the relevant studies and expand this search.

This narrative review includes much of the scholarly work published from 1992 to 2022 and is thus stretched to the last three decades. Preference was given more to recently published literature with relevance to the area of interest. One hundred scientific publications are finally identified and included in this review. These publications are selected by searching the PubMed database while using the combination of the following keywords: "polycystic ovary syndrome," "PCOS," "overweight," "obesity," "weight

loss," "exercise," "lifestyle intervention," and "bariatric surgery."

Publications evaluating the pediatric population are excluded as those are beyond the scope of this review. Duplicate articles and irrelevant papers are also excluded from the data searched via the PubMed database.

Discussion

Obesity and PCOS often coexist (2,4). PCOS is more prevalent in obese women than those with normal body weight (18,19). Research indicates a six times higher obesity risk in adolescents with polycystic ovary syndrome compared with those without PCOS (20).

The complex pathogenesis of PCOS is often accentuated in obese women (4,21). The intricate interplay of hormonal, genetic, and cardiometabolic features in PCOS with concurrent obesity makes this condition challenging (6). Insulin resistance and excessive adiposity are firmly associated with exacerbation of the clinical severity of PCOS, including anovulation and subfertility. Recent research suggests a possible link between obesity, glucagon-like peptide-1 kinetics alteration, and pathogenesis of PCOS (22). Various diverse research studies reflect on how excess weight gain plays a mediating role in underlying mechanisms implicating PCOS (6,23). The impact of obesity and various weight management strategies on women affected with PCOS and coexisting obesity is briefly discussed in the succeeding sections of this narrative review.

A. The impact of obesity on women with Polycystic Ovary Syndrome

PCOS affects up to 1 in 10 women globally (24). Based on body mass index criteria, at least 50% of PCOS patients are reported to be overweight or obese (15,25). Obesity contributes to the increasing prevalence of PCOS (18). Research-based evidence shows a causal and genetic link between obesity and polycystic ovary syndrome (4). Also, obesity enhances the expression of the PCOS phenotype, particularly in women genetically predisposed to PCOS (4). A research study based on data from the Northern Finland Birth Cohort 1966 suggests a correlation between obesity in adolescence and adulthood and self-reported PCOS-related symptoms in women aged 31 years (26)

The majority of PCOS patients (between 50-90%) are found with insulin resistance, although the underlying mechanisms implicated in insulin resistance and subsequent hyperinsulinemia are poorly understood (27,28). In PCOS, hyperinsulinemia (secondary to insulin resistance) leads to enhanced steroidogenic effect, hyperandrogenemia, ovulatory dysfunction, and dysmetabolic features (4,6,29).

Adiposity accentuates insulin resistance (30). In PCOS, excess androgen levels promote insulin resistance and hyperinsulinemia, which further worsens hyperandrogenism and enhances LH secretion, thus establishing a vicious cycle (31). In short, both obesity and PCOS synergistically contribute

to insulin resistance and high serum insulin levels, thus, intensifying the hyperandrogenic state (30,32). Successful weight loss strategies in obese women with concurrent PCOS may improve metabolic, androgenic, and biochemical parameters and clinical

outcomes such as restoration of ovulation and menstrual cyclicity and increased chances of conception (6,33,34). Literature on various impacts of obesity on PCOS is briefly summarized in **Table 1**.

Tab. 1 Summary of Main Studies exploring the Impact of Obesity on PCOS

Authors and Year (with Ref.)	Impact of Obesity on PCOS
Hoeger KM (2007) (15) Motta AB (2012) (35)	Negative impact on clinical, reproductive and metabolic features of PCOS
Hoeger K (2001) (25) Vrbikova J and Hainer V (2009) (16) Barber TM (2022) (27)	Synergistic effect on PCOS manifestations and increased risk of cardiovascular-related comorbidities
Laitinen J, et al. (2003) (26)	Self-reported PCOS symptoms due to obesity
Norman RJ, et al. (2004) (32) Hardy OT, et al. (2012) (30) Calcaterra V, et al. (2021) (31) Cunha A and Póvoa AM (2021) (36)	Amplified insulin resistance and hyperandrogenemia with concomitant obesity
Brewer CJ and Balen AH (2010) (34) Silvestris E, et al. (2018) (33) Balen AH, et al. (2016) (37)	More severe PCOS phenotype including menstrual dysfunction, anovulation and infertility
Silvestris E, et al. (2018) (33) Balen AH, et al. (2016) (37)	Delayed conception and increased miscarriage rate Reduced outcomes in assisted conception treatments Increased risks of gestational diabetes mellitus and hypertension
Navaratnarajah R, et al. (2008) (38)	Risk factor for endometrial carcinoma
Kahal H, et al. (2017) (39) Sam S and Tasali E (2021) (40)	Increased risk of obstructive sleep apnea
Tseng PH, et al. (2021) (41)	Exacerbation of sleep disorders and psychiatric illnesses in PCOS coexisting with inflammatory bowel syndrome
Dokras A, et al. (2012) (12)	Poor psychological health

PCOS accounts for 70-80% of anovulatory infertility (36,37). Apart from infertility, other common distressing symptoms of PCOS include menstrual irregularity, hirsutism, and psychological impacts such as anxiety, depression, and low self-esteem (29,42). Obesity is an independent risk factor for subfertility in obese females (without PCOS) (33,34). It is associated with diminished reproductive outcomes in women with spontaneous conception and those seeking fertility treatments such as ovulation induction and IVF (33,34). The link between excessive body weight and poor fertility outcomes is indisputable (22). Research has shown that weight loss (10% of the body weight) may help improve the pregnancy and live birth rates in overweight women (43).

Multiple studies suggest the association of PCOS with an increased risk of endometrial carcinoma (3,44,45). Other noteworthy risk factors for this malignancy include obesity, insulin resistance, hyperinsulinemia, and hyperandrogenism (38,46,47).

PCOS patients are at risk of developing a sleep disorder called obstructive sleep apnea (OSA), which is characterized by periodic partial or complete obstruction of the upper airway leading to apnea or hypoxemia, thus affecting sleep and quality of life (39,40). Obesity and PCOS are considered risk factors for obstructive sleep apnea (39,40). Like PCOS, there is an increased risk of insulin resistance with OSA, apart from other metabolic disturbances (40).

Research studies observed a high prevalence of inflammatory bowel syndrome (IBS) in PCOS patients, thus affecting their quality of life (41,48,49). Increased LH/FSH levels and stress appear to be the key factors for this high prevalence (48). Moreover, obesity may exacerbate sleep disorders and psychiatric illnesses in women who are simultaneously affected by PCOS and IBS (41).

Obese PCOS patients are susceptible to poor psychological health (12,50). Research indicates that anxiety, depression, and poor body image are more common in PCOS patients than in healthy women (11,50). PCOS-related symptomatology, such as menstrual irregularity, failure to conceive, and hirsutism, may make obese women vulnerable to emotional stress, mental health problems, and impaired psychological quality of life. A research study found that overweight women with PCOS-related infertility (who were trying to conceive and lose weight) had low scores of PCOS health-related quality of life (51).

B. The impact of weight management on women with Polycystic Ovary Syndrome and coexisting Obesity

Research has consistently shown a positive impact of weight loss in ameliorating metabolic, androgenic, and biochemical derangements in overweight and obese women with PCOS (6,33,34). Weight reduction benefits obese PCOS patients by lowering fasting

blood glucose levels and optimizing fasting insulin, serum free-testosterone levels, lipid profile, and blood pressure control (52,53). Studies indicate that weight loss (attained through lifestyle intervention) improves various reproductive parameters related to menstrual cycles, ovulation, and pregnancy rate, in overweight and obese females affected with PCOS (35,54-58).

The weight control measures and their influence on PCOS management have been explicitly discussed in the literature. The beneficial effect of even a modest weight loss on metabolic and reproductive health cannot be overemphasized in PCOS (15,59-61). Research data indicate that modest weight loss (minimum of 5% of body weight) may alleviate endocrine, reproductive, and metabolic derangements in overweight/obese women with PCOS, including improvement in hyperandrogenism, insulin resistance, and metabolic index (60-62).

Obesity is associated with adverse reproductive health consequences such as infertility, ovulation dysfunction, and miscarriages (63,64). A retrospective cohort study found weight loss (10% of the body weight) associated with significant improvement in pregnancy and live birth rates in overweight women with infertility (43). Hence, effective pre-pregnancy counselling for weight reduction should be an integral part of the management strategy of PCOS-related infertility in overweight and obese patients (32).

There is a high risk of anxiety, depression, and low self-esteem reported in women with PCOS (42). Research studies depict the beneficial impact of physical activity on psychological health in overweight and obese patients with PCOS (65,66).

Study indicates that overweight women experiencing PCOS-related infertility (while trying to conceive and achieve weight loss) tend to have poor eating behaviors and diet, thus making healthy weight goal difficult to achieve (51). Weight management is challenging in the patient population with PCOS and coexisting obesity, often leading to non-adherence and a high drop-out rate from weight control programs (4,67). This may also be attributed to the compromised lipolytic function of adipocytes under the androgenic effect (4,68). Future research must focus on androgen-mediated lipolysis dysfunction in PCOS and coexisting obesity.

Weight reduction goals can be accomplished in PCOS through intensive, structured, and sustainable strategies aimed at reasonable weight reduction (21,53,59,69). Weight management programs incorporating cognitive behavioural therapy may help obese women with PCOS attain satisfactory and sustainable weight loss (70). Based on the current evidence, various weight management strategies include lifestyle intervention, pharmacotherapy, and bariatric surgery (71). Each strategy is prioritized, considering multiple factors such as the required magnitude of target weight loss, the timeline of fertility treatment, and comorbidities associated with PCOS and concurrent obesity (71). The impact of various weight management strategies on PCOS obese/ overweight women is briefly summarized in *Table 2*. Lifestyle intervention can help overweight/obese women to achieve their target weight and favourable reproductive outcomes such as improvement in the menstrual cycles, ovulation, and pregnancy rate (35,54-58,97). Weight reduction strategy through lifestyle intervention requires three key components: Diet, exercise, and behavioral therapy (69). Weight loss program that integrates dietary approach with exercise should be tailored according to an individual's body composition requirement and nutritional assessment (72,98). The effects of various diet plans are recently investigated and considered one of the beneficial non-pharmacological strategies for weight management of overweight and obese patients with PCOS (68,75,97). Dietary models recommending food consumption with a low glycemic index and low proportion of trans- and saturated fatty acids seem promising in combating insulin resistance and achieving weight reduction in women with PCOS (61,76,77). Nutrition and exercise can be complemented by short-term pharmacotherapy to treat insulin resistance and promote weight loss in the initial management of PCOS (78).

Appropriate exercise programs and dietary approaches may help to restore ovulation and regularize the menstrual cycles in approximately 49% of patients with polycystic ovary syndrome (74). Resistance or strength training may improve androgen levels and insulin sensitivity in women with PCOS (73). How-ever, extremely heavy exercise (more than 60 minutes per day) is not recommended for women with PCOS who seek fertility because of the increased risk of anovulation (99).

An effective multidisciplinary weight management program, using a combined approach of nutrition counselling, exercise, and cognitive behavioral therapy, may encourage overweight/obese women with PCOS to lose weight and maintain it long-term after initial weight reduction (70,100,101). Behavioral strategy and optimal psychological support are likely to improve the outcomes of weight management interventions (101). Such strategies should consider the nutritional and mental health requirements of reproductive-aged women and include stress management (101). Telehealth services can be utilized to provide mental health rehabilitation as a part of reproductive care and preconception counselling in women struggling with infertility (102).

Potential pharmacotherapy in PCOS-specific weight management may comprise insulin-sensitizing monotherapy and various pharmacologic therapy options to induce weight loss (79,81-84). In a setting of PCOS and coexistent obesity, an effective weightloss pharmacotherapy may improve spontaneous conception rates and response to fertility treatments such as ovulation induction and IVF (71). An integrated weight reduction strategy, with a combined approach of lifestyle intervention and pharmacotherapy, can help reduce body weight, insulin resistance and androgen levels in PCOS patients (79,80).

Bariatric metabolic surgery is one of the weight management options to achieve a target body mass index (BMI) and the required body weight in obese

Tab. 2 Impact of Weight Management Strategy on Overweight/Obese women with PCOS

Weight Management Strategy	Impact of weight management on overweight/obese PCOS women (with Ref.)
Lifestyle intervention	 Association of 5% weight loss with the improvement in: Endocrine and reproductive derangements (60,61) Metabolic index (62) Spontaneous ovulation rates and pregnancy (35) Improvement in live birth rates in overweight, infertile patients with a meaningful weight loss target of 10% (43) Improvement in menstrual cyclicity, insulin sensitivity, cardiovascular and reproductive parameters, and psychological health achieved through weight loss with calorie-restricted dietary strategy (55,72) Improvement in insulin sensitivity and androgen levels with vigorous resistance training and aerobic exercise (73) Additional benefits of regular exercise when combined with energy restriction strategy (54) Successful management of obesity and insulin resistance in women with PCOS with a range of dietary patterns (74) Weight reduction and marked improvement in reproductive and metabolic disturbances with hypocaloric diet/calorie restriction (56-58) Significant decrease in insulin resistance in PCOS with short cycles of the ketogenic diet (75) Improvement in insulin resistance and successful weight reduction with fat restricted diet (with a low proportion of saturated and trans fats) and food with a low glycemic index (61,76,77)
Pharmaco- therapy	 Successful weight-management strategy using pharmacotherapy (aimed at improving insulin sensitivity and promoting weight loss) combined with a lifestyle management strategy (78-80) Improvement in menstrual irregularity, weight management, hyperandrogenemia, and insulin resistance with combination therapy of canagliflozin and metformin and metformin monotherapy (81) Successful weight reduction and ovulation with either of the two drugs (orlistat or metformin) in combination with lifestyle interventions, but orlistat has a better safety profile and tolerability compared with metformin (82) Better performance of liraglutide than the other drugs (orlistat and metformin) for weight loss management (83) Effective weight loss management with orlistat and liraglutide monotherapy. Orlistat improves insulin resistance and reduces androgen levels. On the contrary, liraglutide does not affect insulin resistance or androgen levels (84)
Bariatric Metabolic Surgery	 Helps to achieve PCOS regression, conception, significant weight loss, and improving insulin resistance, hormonal abnormalities, menstrual disturbances, and anovulation (85-89) Improvement in quality of life, type 2 diabetes, obstructive sleep apnea, and life expectancy (86) Possibility of complete remission of PCOS in patients with obesity after achieving target BMI with weight reduction (90,91) Improvement in the key diagnostic characteristics of PCOS (92) Aid to prevent or reverse metabolic syndrome (88) Associated with positive perinatal and obstetric outcomes and successful maternal obesity management (93-95) Successful weight loss and restoration of menstrual cycles and ovulation in PCOS patients after sleeve gastrectomy procedure (96)

patients with PCOS (85,90). This specific surgical intervention requires certain patient selection criteria for the recommendation and thorough assessment considering factors such as BMI, presence/absence of comorbidities, potential risks and benefits associated with the surgery, response to lifestyle intervention and medical therapy for weight management, and patient's fertility plan (35,37,53,85,90,91). Patient preference and informed choice are essential for shared decision-making before bariatric surgery (103). Various bariatric surgery procedures have been described in the literature, such as Roux-en-Y gastric bypass, sleeve gastrectomy, and adjustable gastric band, to name a few (85).

Multiple research studies mention bariatric surgery as an effective weight-loss procedure and relate it with positive outcomes in selected cases of PCOS, including improvement in insulin resistance, metabolic syndrome-related features, hyperandrogenism, menstrual irregularity, ovulatory dysfunction, and complete remission of polycystic ovary syndrome (85-88,90-92,96). Limited evidence suggests improved chances of conception and fertility in PCOS patients after weight loss following bariatric surgery (86,89). While increasing evidence mentions the beneficial impact of bariatric surgery on obstetric and perinatal outcomes, research data also highlights a few maternal and neonatal complica-

tions observed in pregnancies after bariatric surgery (89,93-95). Large and sufficiently powered studies are required to reflect the bariatric surgery-related specific reproductive, maternal, and neonatal outcomes in women with PCOS and concurrent obesity (85,86).

More extensive research and RCTs are required to determine short- and long-term reproductive, endocrine, and metabolic outcomes using various weight loss strategies in overweight and obese females with PCOS. Qualitative research evidence can also help formulate PCOS-specific protocols for weight reduction and clinical practice guidelines for weight management in PCOS with concurrent obesity.

Conclusion

Given the increasing prevalence of the ongoing obesity pandemic, the prevalence of PCOS is likely to rise. Polycystic ovary syndrome and obesity, both conditions, affect women through multiple complex pathogenic mediating mechanisms. The clinical manifestations of PCOS associated with reproductive, metabolic, endocrine, cardiovascular, and psychological dysfunction tend to worsen with obesity.

Hence, an effective weight reduction strategy can be considered a milestone in optimizing reproductive, endocrine, and metabolic outcomes in PCOS management of obese women.

Healthcare professionals must pursue a proactive approach to identify and timely manage both conditions, particularly in adolescent girls and young women of reproductive age. Preventing excessive weight gain from an early age should be an important part of a continuum of care. More robust interventional and methodological studies, including RCTs, are still required to examine the short- and long-term impacts of obesity on PCOS and determine the optimal magnitude of weight loss through effective obesity management programs in overweight and obese women with PCOS.

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