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Review Article

Polycystic Ovary in Obesity

Polycystic Ovary Syndrome as A Cause of Obesity in Females

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Abstract: Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age, that develops in girls and women who are genetically predisposed to its development. PCOS affects between 6%-10% of reproductive- age women. and often develops during adolescence. PCOS manifests with the typical clinical features of hyperandrogenism. Lifestyle interventions are the first- line treatment for PCOS, especially when it is accompanied by obesity. This suggested priority is based on the fact that reduction of central fat ameliorates the PCOS phenotypes, inter alia improved cyclicity and resumption of ovulation. This review focuses on PCOS in Overweight and Obese Women, in development of Obesity and in Adolescents, Diagnostic Criteria in Adolescents, Risk Factor, Insulin Action in PCOS, Glucose Tolerance in PCOS, Epigenetic factors and Novel Management Strategies.

Keywords: Polycystic Ovary Syndrome, Obesity, Metabolism

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1. INTRODUCTION

The polycystic ovary syndrome (PCOS) is a condition categorized by hyperandrogenism and chronic oligo-anovulation. However, many structures of the metabolic syndrome are inconsistently present in the popular of women with PCOS. About 50% of PCOS women are overweight or obese and most of them have the abdominal phenotype. Obesity may play a pathogenetic part in the development of the syndrome in susceptible individuals. In fact, insulin has true gonadotrophic function and an increased insulin availability at the close of ovarian tissue may favour excess androgen synthesis. Obesity, mainly the abdominal phenotype, may be partly responsible for insulin resistance and linked hyperinsulinemia in women with PCOS. Therefore, obesity-related hyperinsulinemia may drama a key role in favouring hyperandrogenism in these women. Other factors such as enlarged estrogen production rate, enlarged activity of the opioid system and of the hypothalamic-pituitary-adrenal axis, diminished sex hormone binding globulin synthesis and, possibly, high dietary lipid intake, may remain additional mechanisms by which obesity favours the expansion of hyperandrogenism in PCOS. Irrespective of the pathogenetic mechanism involved, obese PCOS women have extra severe hyperandrogenism and related clinical landscapes (such as hirsutism, menstrual abnormalities and anovulation) than normal-weight PCOS women. This depiction tends to be more noticeable in obese PCOS women with the abdominal phenotype.Body weight loss is associated with beneficial properties on hormones, metabolism and clinical features. An extra clinical and endocrinological improvement can also be achieved by totaling insulin-sensitizing agents and/or antiandrogens to weight reduction programmes. These visibly emphasize the role of obesity in the pathophysiology of PCOS [1]. Over the last 40 years, the global prevalence of obesity in women has amplified 2.5- fold from 6% to 15%[1]. Over a comparable timeframe, the prevalence of obesity- related co-morbidities, of which there are >50 that cooperatively account for a substantial global health and socio-economic burden[3,4]. has enlarged commensurately. The development of many obesity-related conditions is interceded through the deleterious effects of insulin resistance (a value of weight gain) or compensatory hyperinsulinaemia, and its connected metabolic dysfunction[5].These include landscapes of the metabolic syndrome (type 2 diabetes mellitus [T2D], dyslipidaemia and hypertension) and obesity-related malignancies such as endometrial carcinoma[6]. Polycystic ovary syndrome (PCOS) is a significant and highly prevalent obesity-related comorbidity[7], that progresses in girls and women who are genetically predisposed to its expansion[8,9]. PCOS marks between 6%-10% of reproductive-age women[10,11]. and often develops during adolescence[12]. PCOS establishes with the typical clinical landscapes of hyperandrogenism (including acne, hirsutism and male-pattern alopecia) and reproductive dysfunction (comprising oligo-amenorrhoea and associated sub-fertility)[13]. Although not an essential of its diagnostic criteria[14]. metabolic dysfunction also often forms a vital component of the clinical presentation of PCOS. There are also distinctive biochemical and radiological structures. For billions of years, the eukaryotic cell and, extra recently, its multi-cellular manifestations have evolved to mitigate against nutrient scarcity. This, mutual with oxygen free radicals and hypothermia, represents chief threats to species survival. In response to these threats, our complex physiology has modified through diverse mechanisms. Provision of a ready supply of nutrients over storage of energy in the liver and adipose tissue in times of sufficiently and use of alternate fuel sources such as ketone bodies when food is scarce mitigate in contradiction of starvation. Efficientand timely eradication of oxygen free radicals, generated over mitochondrial oxidative respiration through enzymes such as superoxide dismutase, mitigates against the harmful effects of oxygen free radicals. Conservation of a constant body temperature, through shivering movement and activation of brown adipose tissue in response to cold acquaintance, mitigates against hypothermia. For the last 50 years, Homo sapiens has been navigating a white water ride. Though environmental turbulence is frequently necessary for evolutionary change, what is unusual about our current 'white water ride' is the supposition of its cause being antipodal to a more familiar threat of nutrient scarcity: that of nutrient plenty. (Abundance of a material essential for life is not altogether unprecedented: oxygen abundance during the Cambrian era may have occasioned the Cambrian explosion of multi-cellular life.) Of course, this perspective is almost positively a gross over- simplification. The development of the worldwide obesity epidemic over the last halfcentury is likely to be multi-factorial and complex, and go far elsewhere simple food abundance. However, whatever its actual cause(s), obesity explanations for a huge component of global ill health and is associated with at minimum 50 obesity-related comorbidities[15,16]. Global obesity also deliberates a substantial socio-economic burden. Expenditure on obesity and its numerous sequelae versions for a substantial proportion of healthcare expenses globally. PCOS in Overweight and Obese Women, in development of Obesity and in Adolescents, Diagnostic Criteria in Adolescents, Risk Factor, Insulin Action in PCOS, Glucose Tolerance in PCOS, Epigenetic factors and Novel Management Strategies.

2. *PREVALENCE AND OF THE POLYCYSTIC OVARY SYNDROME IN OVERWEIGHT AND OBESE WOMEN*

Of a total of 113 consecutive women appraised, 32 were diagnosed as having PCOS for a 28.3% prevalence of this syndrome in overheavy or obese women (95% confidence interval, 20.0%-36.6%). Another 3 women presented with hyperandrogenemia minus oligo-ovulation, 2 had idiopathic hirsutism, 2 had isolated chronic oligomenorrhea deprived of clinical or biochemical hyperandrogenism, and 2 had oligomenorrhea and hyperprolactinemia, precluding the diagnosis of PCOS. The outstanding 72 women (63.7%) had no evidence of hyperandrogenism or reproductive irregularities and were considered as the nonhyperandrogenic control group for further comparisons. The commonness of PCOS was not statistically different when considering the gradation of obesity, as classified according to the guidelines available by the National Institutes of Health[17]

3. *CHARACTERISTICS OF WOMEN DIAGNOSED AS HAVING PCOS*

The PCOS and nonhyperandrogenic control collections had similar mean body mass index values, but PCOS patients were meaningfully younger than the nonhyperandrogenic controls. Therefore, we comprised age as a covariate in the general linear model to correct for this variance when studying the possible differences between PCOS patients and nonhyperandrogenic panels in other variables. Compared with nonhyperandrogenic controls, PCOS patients obtainable with increased hirsutism scores; amplified triglycerides, fasting insulin, total and free- testosterone, 17-hydroxyprogesterone,

androstenedione and luteinizing hormone levels; increased HOMA-IR and HOMA-β values; and reduced composite insulin sensitivity index values. The other clinical and biochemical variables thoughtful were not different among the PCOS and non hyperandrogenic regulator groups

4. DEVELOPMENT OF OBESITY AND POLYCYSTIC OVARY SYNDROME IN ADOLESCENTS

4.1 1-A Diagnostic Challenge

There is debate about the aptness of using the Rotterdam criteria for a diagnosis of PCOS in adolescents since they were industrialized for use in women. Other criteria for diagnosing PCOS come from the NIH and AES. Just comparable the Rotterdam criteria, they also include HA as a diagnostic parameter, and these standards have been proposed for use in adolescents. In adolescence, the usual changes during puberty can bias the interpretation of the biochemical measures classically used in the diagnosis of PCOS. For example, during usual pubertal development in girls, hypothalamic pulsatile secretions of gonadotropin-releasing hormone (GNRH) are established, and these developed dynamic and cyclic. During puberty, the growth hormone (GH)-mediated release of insulin-like growth factor-1 increases, which in turn decreases insulin sensitivity and increases insulin secretion [18]. The resultant hyperinsulinemia (HI) declines liver production of SHBG, which rises the bioavailability of steroids, resulting in raised cFT. Thus, in adolescent girls preeminent levels of circulating androgens are not necessarily a sign of HA per se. Additionally, the reproductive capacity of adolescents also endures non-pathological changes during pubertal development that are influenced by the excretion of gonadotropins. These changes are uttered by irregular menstrual patterns and PCOM on ultrasonography, and may even persevere for 2 years after menarche[16-19]. Because all three sets of criteria include irregular ovulatory patterns and PCOM, the diagnosis in adolescence remnants challenging. Taken together, these biochemical and physiological aspects of pubertal progress suggest that the diagnosis of PCOS in adolescents should be assigned using diverse criteria from thosein women.

4.2 2-Diagnostic Criteria in Adolescents

Given these unique aspects of pubertal advance, diagnosing PCOS in adolescent girls is a challenge. In a sample of 250 adolescent girls, PCOS was greatest characterized by clinical HA (hirsutism) and/or biochemical HA and oligomenorrhea [22]. Other groups have suggested that menstrual patterns are confidential as pathological in adolescents when menstruation is absent-minded for ≥90 days, or if cycles persistfor ≥45 days *[23]. Biochemically, HA can be resolute by levels of cFT, and dehydroepiandrosterone in adolescent girls [23]. Physiologically, ovarian capacity and antral follicle count can be measured by transabdominal ultrasonography, although these measures may be operator reliant on and also of limited use in adolescents [19]. Transvaginal or transrectal ultrasonography in adolescents is questionable or even unethical in young girls prior to sexual debut. Abundant like in adult women, the diagnostic dependability of AMH in adolescents has yet to be resolute [24].

Table (1): Diagnostic criteria for PCOS [16]

NIH/NICHD Criteria*	Rotterdam Criteria*
Diagnosis requires both features:	Diagnosis requires 2 of 3 features:
1. Oligo and/or anovulation	1. Oligo and/or anovulation
2. Hyperandrogenism Clinical or biochemical	2. Hyperandrogenism Clinical or biochemical
	3. Polycystic ovary morphology**

Other androgen excess or related disorders have to be excluded prior to diagnosis of PCOS.

Defined by at least one ovary demonstrating an ovarian volume>10 ml or presence of 12 or more follicles measuring 2-9 mm in size.

5. THE RELATIONSHIP BETWEEN PCOS AND OBESITY: WHICH COMES FIRST?

Polycystic ovary syndrome (PCOS) is a mutual metabolic and endocrine disorder effecting 15- 20% of women of reproductive age. This complaint, originally known asStein-Leventhal syndrome, was discovered in 1935. Its scientific features include obesity, hirsutism, spots, infertility, and oligomenorrhea. PCOS is also attributed toseveral hormonal and metabolic disturbances, including enlarged androgen production and disordered gonadotropin secretion principal to menstrual irregularity, hirsutism, and infertility. Aside from meddlesome with reproductivefunction, PCOS also disrupts the metabolism of women, upsetting insulin action and β-cell function, increasing the risk for glucose prejudice and type 2 diabetes [25,26]. The origin of PCOS remains unclear, but exploration has shown that one of thecharacteristics of this disorder is the extra production of androgens in the ovaries[27]. Androgen secretion is the result of irregular response of the ovary to go-nadotropins, insulin and insulin-like hormones such as insulin-like growth factor-1 (IGF-1), which enhances LH-stimulated androgen production by theca cells. Althoughthe condition is not life threatening, the lack of treatment could chief to moreserious health issues in the future, such as enlarged risk of infertility, dysfunctionalbleeding, endometrial carcinoma, obesity, type 2 diabetes mellitus, dyslipidemia,hypertension, and enlarged risk for cardiovascular diseases[26]. Among the risk factors related with PCOS, overweight (body mass index (BMI) 25–29.9 kg/m2) and obesity (BMI ≥30 kg/m2) have been measured as major contributingfactor to overall health worries among women worldwide. Obesity has also been a determined as a contributing influence to reproductive health problems such as anovulation. As body weight increases, incidence of anovulation also rises significantly. Another contributor to reproductive dysfunction is the accretion of abdominal fat, indicating a higher risk associated with insulin conflict (IR). IR in obesewomen has been associated with anovulation and increased androgen secretion [28]. Several studies relay obesity as a risk factor of PCOS [29,30]. Some studies report that overweight and obesity frequency in females with PCOS is as high as 80%. The mechanisms by which obesity impacts PCOS 'pathophysiology and clinical expression are not fully understood, but obesity is individually associated with IR [31] and sex steroid imbalances that may prime to an increased risk of menstrual irregularities and hyperandrogenemia, like to

PCOS symptoms [32]. On the other hand, others proposed that irrespective of physical condition PCOS could occur.PCOS may develop in women with a BMI in any range counting both underweight and overweight women[33]. The consistent association amid PCOS and obesity suggests a biological basis for this observation. Obesity aggravates many of the reproductive and metabolic abnormalities related with PCOS. To understand which comes first, obesity or PCOS, studies have explored this relationship in girls and adolescents. It was well-known that girls with a high BMI in childhood had an enlarged risk of oligomenorrhea and a diagnosis of PCOS in young adulthood (age 24), yet the possibility that features of PCOS were previously present in these girls cannot be excluded. The researchers examined if PCOS (or its features) in adolescents is predictive of later class III obesity. In spite of not using pelvic ultrasonography, PCOS was diagnosed by the Rotterdam criteria in 12 (40%) of 30 oligomenorrheic girls at age 14 years. Of these girls, 33% shown class III obesity by24 years of age versus 8.4% of girls without PCOS. Additional predictors of class III obesity included low sex hormone required globulin (SHBG), oligomenorrhea, high childhood insulin levels, increased cFT and MetS, all of which are documented as PCOS phenotypes [34]. Meanwhile, others conducted a probable study on 244 randomly particular postmenarchal girls from a large population-based birth cohort to investigate the influence of obesity on the expansion of abnormal ovarian morphology. They found PCOS in 61.1% of the obese girls, but solitary in 32.1% of the normal- weight girls, suggesting that obesity is a causative factor [35]. These educations illustrate that obesity and PCOS are correlative in their pathogenesis.

6. *OBESITY AS A RISK FACTOR FOR THE DEVELOPMENT OF PCOS*

In women who are genetically disposed to development of PCOS, weight-gain and obesity often result in its clinical and biochemical manifestation. Consequently, thereare close links between obesity and PCOS. The mainstream of women with PCOS (38%-88%) are both overweight or obese. Data from the Northern Finland Birth Cohort (NFBC) 1966 show a significant suggestion between body mass index (BMI) and features of PCOS at all ages. Furthermore, diffident weight-loss (around 5%) often results in clinically meaningful enhancements in the reproductive, hyperandrogenic, and metabolic topographies of PCOS. Outlined below are factors that mediate the properties of weight-gain and obesity on the pathogenesis of PCOS[36].

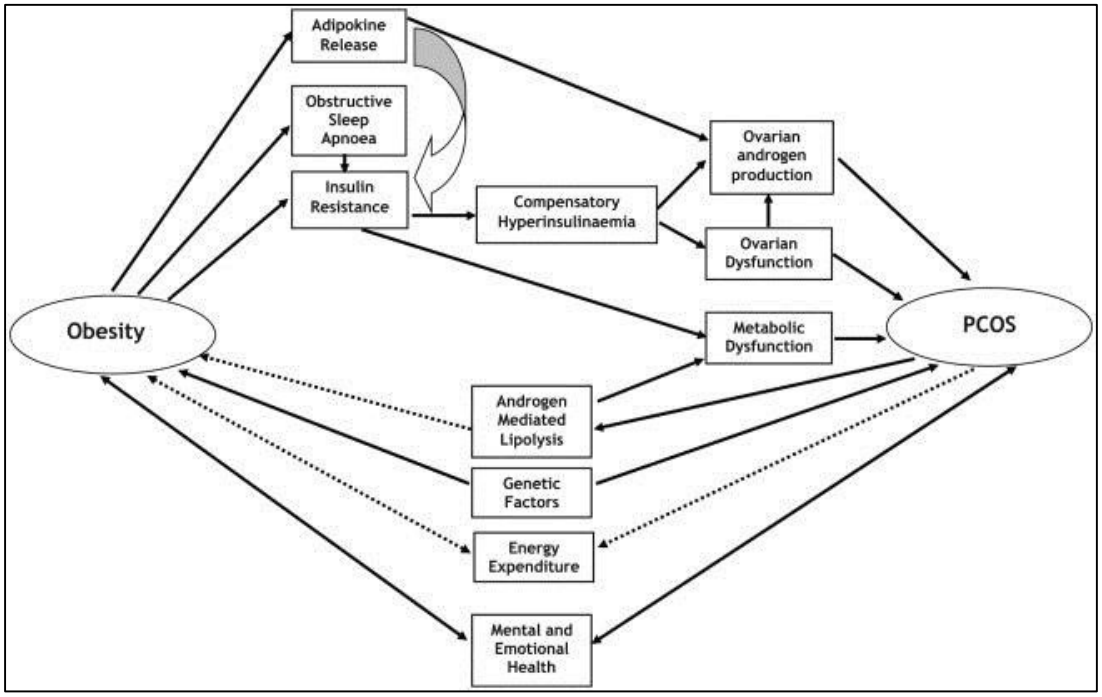

Fig (1): Summary of mechanisms linking obesity with PCOS. PCOS indicates polycystic ovary syndrome.

7. *INSULIN ACTION IN PCOS: RELATION WITH OBESITY*

Insulin resistance is a common finding in PCOS that is self-governing of obesity. Insulin-mediated glucose disposal, reflecting mainly insulin achievement on skeletal muscle is decreased by 35–40% in women with PCOS likened to weight comparable reproductively normal women. This defect is independent of but considerably worsened by obesity. In contrast, hepatic insulin resistance, considered by both increased postabsorptive glucose production and abridged sensitivity to insulin mediated suppression of endogenous glucose manufacture, is present only in obese women with PCOS compared to control women of analogous body weight. Thissynergistic deleterious consequence of obesity and PCOS on endogenous glucose production may be an important influence in the pathogenesis of glucose intolerance. Fasting insulin levels are increased in PCOS. Nonetheless, there are faults in insulin secretion that are independent of obesity. These irregularities are more pronounced in women with

PCOS who have a first-degree relative with type 2 diabetes. In PCOS, basal insulin secretion is enlarged, but insulin responses to glucose are inappropriately low. Under normal circumstances, the relative between insulin secretion and sensitivity is constant so that deviations in insulin sensitivity are accompanied by reciprocal variations in insulin secretion that preserve normal glucose tolerance; this relationship is identified as the "disposition index." Bothobese and nonobese women with PCOS have lower a disposition index associated to weight-matched reproductively usual women. Furthermore, disposition index is significantly lowered by PCOS as well as obesity. In instant, PCOS is associated with defects in insulin sensitivity and secretion that are supplementary exacerbated by obesity[37].

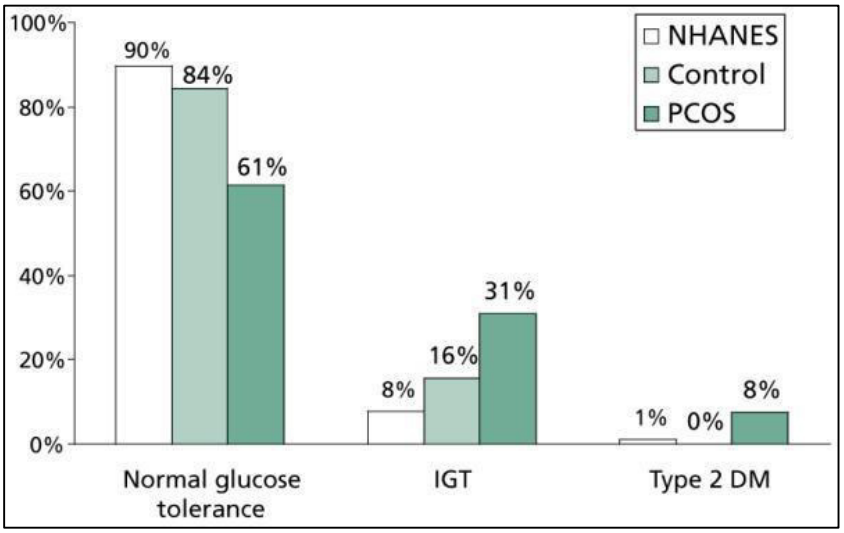

Fig 2: Women with PCOS (black bars) had much higher prevalence of abnormal glucose tolerance compared to control women of similar ethnicity, age, and weight (gray bars) (P=0.02) as well as compared to reproductive-age women from the Second National Health and Nutrition Examination Survey (NHANES) (white bars).[16]

8. GLUCOSE TOLERANCE IN PCOS: RELATION WITH OBESITY

Considering the baseline defects in insulin compassion and secretion in PCOS and thedeleterious impact of obesity on these measures, women with this complaint are expected to have a high frequency of impaired glucose tolerance (IGT, defined by a 2h post-challenge glucose level 140–200 mg/dl) and type 2 diabetes. A amount of studies have confirmed a high prevalence of these irregularities in obese reproductive-age women with PCOS. In a training of 254 reproductive-age women with PCOS and 80 control women of analogous ethnicity, age, and weight[38], the prevalence of glucose prejudice in women with PCOS (~40% combined IGT and type2 diabetes) was much higher than that described in the control women from the same study (14% with IGT and 0% with type 2 diabetes) as well as that described in a major population-based study. Furthermore, the risk for evolving glucose intolerance increased with increasing body mass index (BMI); the pervasiveness of IGT and type 2 diabetes were much lower in nonobese females with PCOS (10.3% and 1.5%, respectively) compared to the obese and the overall populace. The study also revealed that normal fasting glucose levels in females with PCOS does notexclude glucose intolerance in these women. Of women detected with type 2 diabetes, 58% had normal fasting glucose levels and were recognized based onraised 2h glucose levels by an oral glucose tolerance test.

8.1 Hormonal Regulations of Weight and Appetite

Compared to weight-matched control women, women with PCOS have been found to have lower fasting ghrelin levels. The gastric endocrine cells that produce ghrelin have been linked to the control of appetite and body weight. Before meals, ghrelin levels spike sharply, causing hunger and the start of food intake, and they fall sharply after meals, causing an appetite suppression and satiety. Because of their persistently positive energy balance, obese people are said to have lower fasting ghrelin levels. However, there is proof that PCOS patients may have dysregulated ghrelin homeostasis. Women with PCOS also have less pronounced post-parandial reductions in ghrelin levels, as well as less satiety after a test meal, in addition to having lower fasting ghrelin levels.[29]

8.2 Areas of Controversy

The pathophysiology of PCOS, including its heritability, epidemiological and genetic links with obesity, and the crucial role of insulin resistance, have been the subject of substantial agreement between clinicians and researchers thanks to research published over a number of decades. In spite of this development and broad consensus, there are still significant areas of the pathophysiology of PCOS that are unclear and contentious. These hot-button topics most prominently concern the function of epigenetic factors and the developmental causes of PCOS.

8.3 Epigenetic Factors

The heritability of PCOS is undeniable, as stated above. Furthermore, recently released PCOS GWAS study data have revealed novel insights into the genetic makeup of the condition. According to our traditional understanding of heritability, variations in our DNA's nucleotide sequence can affect how encoded proteins are expressed. Consider the DNA nucleotide sequence as the genetic machinery that is also studied in GWAS studies. The DNA nucleotide sequence itself is not implicated in the novel perspective on heritability that has recently emerged, but rather additional proteins that bind to the DNA molecule and change its expression profile. These extra proteins can be thought of as the genetic code, and it's important to note that they don't change the nucleotide

sequence of the DNA molecule in any way, making them invisible to conventional GWAS methods. The term "epigenetic" refers to protein modifications that bind to DNA molecules without altering the nucleotide sequence but have an impact on the gene expression profiles (through transcription and/or translation)[39]. In the context of the pathogenesis of PCOS, the idea of epigenetics is compelling. A variety of genetic pathways involved in steroid synthesis, insulin signalling, cell communication, reproductive function, and carbohydrate metabolism are just a few examples of those that have been linked to altered gene expression and have the potential to be significant players in the pathogenesis of PCOS. In fact, epigenetic modifications are likely responsible for at least some of the hidden heritability in the case of other diseases with complex pathophysiologies (such as T2D, depression, and some cancers), for which GWAS data also only reveal a small portion of the overall heritability[40]. Histone modifications, DNA hypo- or hypermethylation, and other protein-based alterations to the DNA molecule itself are examples of epigenetic modifications that result from exposure to environmental factors, including the environment in utero. Micro-RNA (miRNA)-induced changes, which affect the expression of miRNA directly through epigenetic changes, mediate these protein-based modifications either directly or indirectly. Small, non-coding single-stranded RNA molecules known as miRNAs (length: 20–24 nucleotides) have the ability to regulate gene expression in a variety of ways. This includes controlling the translation of mRNA, degrading mRNA transcripts, and specifically targeting the epigenetic machinery (also known as "epi-miRNA" and including genes for the "polycomb repressive complex" and DNA methyltransferases as examples) [39, 40].

9. NOVEL MANAGEMENT STRATEGIES FOR OBESITY AND PCOS

Although many therapies exist for management of PCOS, greatest of these target manifestations of PCOS rather than underlying causal mechanisms. Operative weight-loss implementation remainders the most effective and promising management strategy for women with PCOS. However, this contribution a problem: weight-loss maintenance through lifestyle application is challenging and has a high failure rate [41]. While bariatric surgery represents an outstanding alternative strategy to lifestyle implementation for actual and long-term weight-loss[42]. surgical management strategies for obesity related with PCOS will never be scalable to a population level. Our recent therapeutic armamentarium for obesity in the United Kingdom is diminutive. Novel administration strategies for PCOS in the context of obesity should therefore focus on actual means of maintaining weight- loss over the longer tenure on a population level.

10. SUGGESTED TREATMENT IN CASE OF POLYCYSTIC OVARY SYNDROME

Lifestyle interventions are the first-line management for PCOS, especially when it is accompanied by obesity. This suggested priority is based on the fact that decrease ofcentral fat ameliorates the PCOS phenotypes, inter alia better-quality cyclicity and resumption of ovulation [43]. Also weight loss improves the rank of cardiovascular risk factors accompanied by a reduced intima media thickness [44]. The effects of lifestyle intervention on normal-weight PCOS patients, though, could not be identified in the literature. Nonetheless, it is plausible that these females could also benefit from these types of interventions. In addition, it is of countless importance to address and improve the psychological facets of the condition (i.e. self-image, depression). Further, given the negative effects of PCOS on procreative function[45],these issues need to be deliberated with the patient and/or their parents. This consequence is not obvious, and it is typically not the cause why adolescents or their parents seek treatment for obesity, especially since the phenotypic outcome (anovulation) is not clinically visible beforehand entry into puberty. In a sample of 59 obese girls with PCOS aged 12–19 years, 26 girls reduced theirbody weight after 1 year of lifestyle intervention containing of physical exercise, nutritional education, and behavioral regulation. These patients reduced their cFT, insulin concentrations and homeostatic model valuation and increased SHBG concentrations during the intervention[44]. Similar consequences have been reported in other studies [46]. The fundamental trial in relation to lifestyle treatment is how to sustain the effect, i.e. preserve children/adolescents at a lower or normal weight, and stay physically active and healthy over longer stages of time. Arecent study in our clinic [47] showed that it is possible to decrease the degree of obesity in 62.5% of children and youths in up to 2 years of obesity management with a relatively high retaining irrespective of baseline adiposity, age, puberty, and social class and with no early eligibility criteria.

11. CONFLICT OF INTEREST

Conflict of interest declared none.

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