Republic of Iraq
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POLY CYSTIC OVARIAN SYNDROME RELATED TO OBESITY

A scientific dissertation Submitted to the College of Medicine- Diyala University in partial fulfilment of the requirement of M.B.Ch.B

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April 2022

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1.INTRODUCTION

Polycystic ovary syndrome (PCOS) is recognized as the most common reproductive disorder in women. Obesity is believed to play a central role in the development of PCOS,as many women with this condition are reported to be overweight or obese.A strong correlational relationship exists between PCOS and obesity. [1]This paper examines the relationship between PCOS and obesity in order to determine whether PCOS causes obesity as opposed to obesity causes metabolic changes that lead to PCOS. Analysis was conducted by reviewing and comparing many studies related to the topic . Factors such as insulin resistance, hyperandrogenemia and body fat distribution were examined in obese and non-obese PCOS subjects. [2] Most studies included in this review could not conclusively determine whether PCOS contributed to obesity or vice versa. The important points raised in the literature showed thatobesitycouldbeanimportantfactortopredictPCOS. InwomenwhoarepredisposedtoPCOS,the metabolic and hormonal issues that are present such as insulin resistance and hyperandrogegism, can lead to weight gain and eventually obesity. Obesity in turn can exacerbate the symptoms of PCOS such as further metabolic issues and reproductive abnormalities.[3]

1.1 What is PCOS.

Polycystic ovaries contain a large number of harmless follicles that are up to 8mm (approximately 0.3in) in size.
The follicles are underdeveloped sacs in which eggs develop. In PCOS, these sacs are often unable to release an egg, which means ovulation does not take place.
It's difficult to know exactly how many women have PCOS, but it's thought to be very common, affecting about 1 in every 10 women in the UK.
More than half of these women do not have any symptoms.[4]

1.2 Symptoms of polycystic ovary syndrome (PCOS).

If you have signs and symptoms of PCOS, they'll usually become apparent during your late teens or early 20s.
They can include:
• irregular periods or no periods at all
• difficulty getting pregnant as a result of irregular ovulation or failure to ovulate
• excessive hair growth (hirsutism) – usually on the face, chest, back or buttocks
• weight gain
• thinning hair and hair loss from the head
• oily skin or acne
PCOS is also associated with an increased risk of developing health problems in later life, such as type 2 diabetes and high cholesterol levels. [5]

1.3Diagnosis of PCOS.

The 3 main features of PCOS are:
• irregular periods – which means your ovaries do not regularly release eggs (ovulation)
• excess androgen – high levels of "male" hormones in your body, which may cause physical signs such as excess facial or body hair
• polycystic ovaries – your ovaries become enlarged and contain many fluid-filled sacs (follicles) that surround the eggs (but despite the name, you do not actually have cysts if you have PCOS)

If you have at least 2 of these features, you may be diagnosed with PCOS.[6]

1.4Management of PCOS.

There's no cure for PCOS, but the symptoms can be treated. Speak to a GP if you think you may have the condition.
If you have PCOS and you're overweight, losing weight and eating a healthy, balanced diet can make some symptoms better.
Medicines are also available to treat symptoms such as excessive hair growth, irregular periods and fertility problems.[7]
If fertility medicines are not effective, a simple surgical procedure called laparoscopic ovarian drilling (LOD) may be recommended. This involves using heat or a laser to destroy the tissue in the ovaries that's producing androgens, such as testosterone.
With treatment, most women with PCOS are able to get pregnant. [8]

1.5 What are the mechanisms by which obesity cause PCOS

Obesity has been linked to abnormal function of the hypothalamic-pituitary-ovarian (HPO) axis through multiple mechanisms that contribute to a development of PCOS. Although it is often difficult in a feedback endocrine system to isolate single influences because all participants in the loop can be affected, I explore each component of the feedback loop, acknowledging that effects are likely interactive and in some cases additive.[9]

Ovarian Effects

Obesity is associated with insulin resistance and compensatory hyperinsulinemia. Insulin has been shown to serve in culture as a co-gonadotropin to stimulate ovarian androgen production. Several severely insulin-resistant hyperinsulinemic states in women have been associated with marked hyperandrogenemia, such as leprauchaunism. [10] Small increases in circulating ovarian androgens have been noted with insulin infusions to women with normal ovaries, as well as when women with type 1 diabetes are treated with insulin.The administration of anti diabetic drugs that lower insulin levels or improve insulin sensitivity has been associated with decreases in circulating androgen levels and increases in ovulation rates.[11]

Multiple other growth factors and inflammatory factors are increased in obesity and may further stimulate excess ovarian androgen production or inhibit aromatisation of androgens to oestrogens.[12]

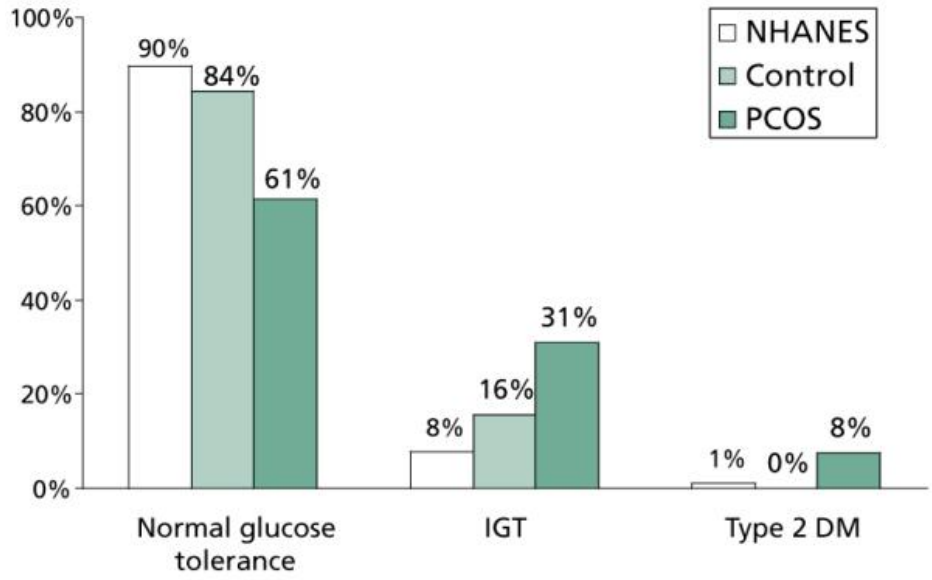
Hypothalamic-Pituitary Effects

Obesity is associated with multiple factors that may influence hypothalamic pituitary function. Insulin resistance and/or hyperinsulinemia has been associated with direct hypothalamic effects that may favour disordered gonadotropin secretion.[13] Obese mice with selective knockout of the insulin receptor in the pituitary have resolution of normal gonadotropin secretion and improved fertility, implying a direct role for insulin action in PCOS.[14] Such experiments are obviously more difficult to perform in humans, but there are multiple other mechanisms through which obesity could affect HPO function.[15] Inputs from adipokines such as leptin are key to controlling ovulatory function. This is well illustrated by the example of anorexia nervosa or hypothalamic amenorrhea where gonadotropin secretion is suppressed with a corresponding loss of ovulatory function. [16]The fact that leptin replacement alone can result in resumption of gonadotropin secretion, follicular development, and in some cases ovulation in women with hypothalamic amenorrhea supports a direct role for markers of fat and energy metabolism on reproductive function.There have been fewer studies of the effect of eating behaviour and such hormones released during digestion as incretins on reproductive function. But it is possible that such hormones and other appetite regulators may also affect gonadotropin secretion. [17]

1.6 Glucose Tolerance in PCOS : related to obesity

Considering the baseline defects in insulin sensitivity and secretion in PCOS and the deleterious impact of obesity on these measures, women with this condition are expected to have a high prevalence of impaired glucose tolerance
(IGT, defined by a 2h post-challenge glucose level 140–200 mg/dl) and type 2 diabetes. [18] A number of studies have confirmed a high prevalence of these abnormalities in obese reproductive-age women with PCOS. In a study of reproductive-age women with PCOS and control women of comparable ethnicity, age, and weight. [19]the prevalence of glucose intolerance in women with PCOS (~40% combined IGT and type 2 diabetes) was much higher than that reported in the control women from the same study (14% with IGT and 0% with type 2 diabetes) as well as that reported in a major population-based study.

Furthermore, the risk for developing glucose intolerance increased with increasing body mass index (BMI); the prevalence of IGT and type 2 diabetes were much lower in non obese women with PCOS (10.3% and 1.5%, respectively) compared to the obese and the overall population. [20] The study also revealed that normal fasting glucose levels in women with PCOS does not exclude glucose intolerance in these women. Of women diagnosed with type 2 diabetes, 58% had normal fasting glucose levels and were identified based on elevated 2h glucose levels by an oral glucose tolerance test. [21]



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). [22][23]

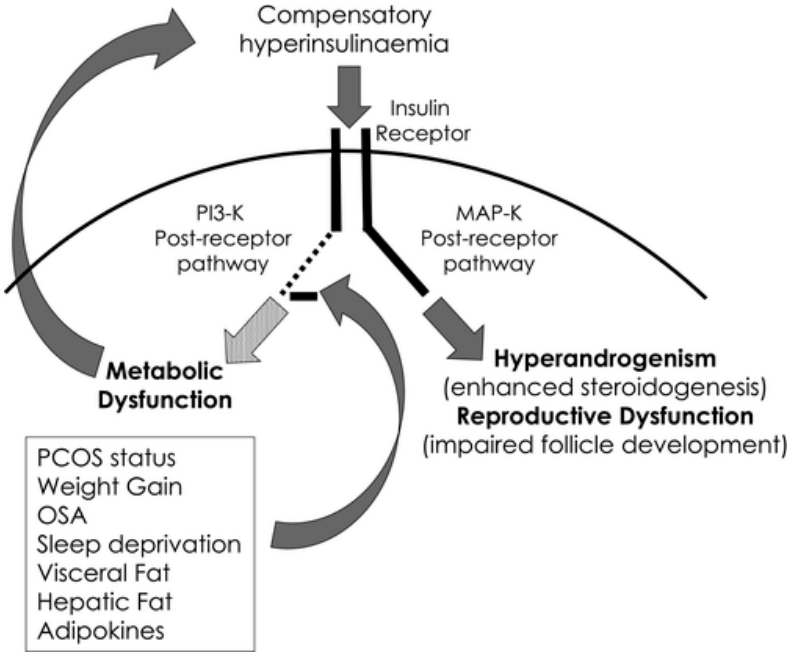
In another study of women with PCOS,5 the overall prevalence of glucose intolerance was 45% (35% with IGT and 10% with type 2 diabetes). [24]Women with PCOS and type 2 diabetes were significantly more obese than their counterparts with normal glucose tolerance. Moreover, repeat determination of glucose tolerance after 2.5 years revealed an accelerated rate of conversion from IGT to type 2 diabetes that was strongly dependent upon BMI. [25]Similarly in this study, the fasting glucose levels did not reliably predict the 2h glucose levels after a glucose tolerance test. Studies from Australia have also revealed a high prevalence of abnormal glucose tolerance in women with PCOS in association with
obesity;6 obese women (BMI≥30 kg/m2) had a 10-fold increase and over-weight women (BMI

25–30 kg/m2) had a 7-fold increase in the risk of abnormal glucose tolerance [26] compared with
normal weight (BMI<25 kg/m2) women with PCOS. 4,5,6
In summary, PCOS is associated with high rates of glucose intolerance resulting from defects in insulin action and β-cell function.[27]

1.7Insulin tolerance in PCOS :related to obesity

Insulin resistance is present in many, if not most, women with PCOS.28_29 Although the mechanism of insulin resistance in PCOS remains incompletely understood, the underlying defect is reported to occur within the post-receptor phosphatidylinositol 3-kinase (PI3-K) insulin pathway that mediates the metabolic effects of insulin.30_31 Other factors may also contribute towards the establishment of insulin resistance in women with PCOS.[32]These include increased levels of plasma testosterone (both in adulthood and prenatally, with evidence of the latter from an ovine model of PCOS33) and enhanced sensitivity of the androgen receptor (determined by the androgen receptor CAG repeat number).34 Furthermore, suppressed levels of serum adiponectin in women with PCOS compared with BMI-matched control women (demonstrated in a large meta-analysis on >3400 subjects) may further contribute towards the establishment of insulin resistance in PCOS.36_35 The role of high molecular weight adiponectin in PCOS remains incompletely understood 37 and should form a focus for future research as there may be implications for therapy, as suggested by a recent study in a rodent model of PCOS.38

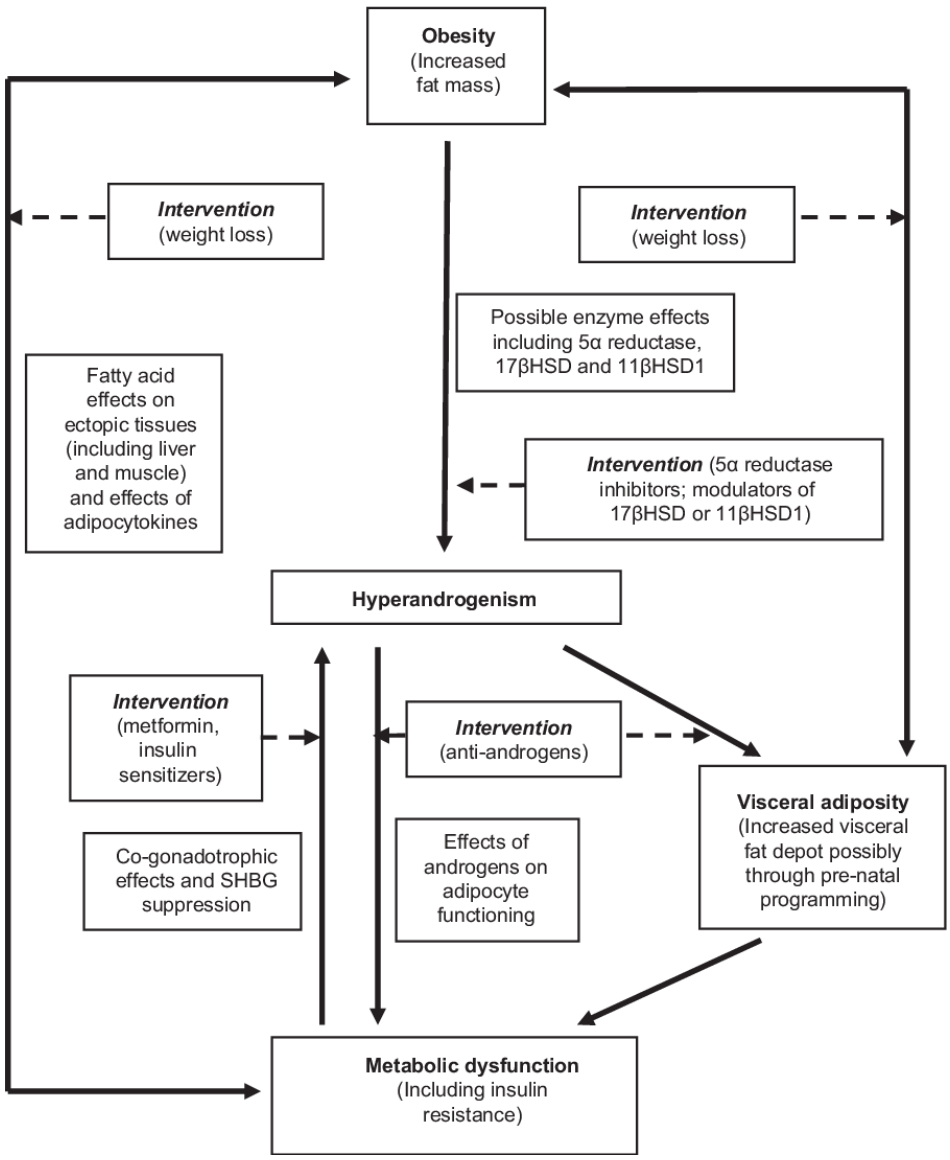
The severity of insulin resistance in women with PCOS is increased by subsequent weight gain, 39 possibly mediated through inflammatory pathways.40 Similar to the insulin resistance that characterize T2D and PCOS, only the PI3-K post-receptor insulin pathway becomes resistant to the effects of insulin following weight gain and obesity.41 Perhaps the umbrella term ‘insulin resistance’ should be replaced by the more descriptive term ‘metabolic insulin resistance’,41 that results from selective dysfunction of the PI3-K post-receptor insulin pathway in PCOS that is augmented commensurately with weight gain. Importantly, in both PCOS and obesity, the other main post-receptor insulin pathway, the ‘mitogen-activated protein kinase’ (MAP-K) pathway remains unaffected., 42 Compensatory hyperinsulinaemia ensues in an unsuccessful attempt to overcome the selective metabolic dysfunction stemming from the defective PI3-K insulin pathway.41 The resulting preferential activation of the MAP-K post-receptor insulin pathway results in atherogenic, steroidogenic and mitogenic effects.43 Furthermore, the preserved MAP-K insulin pathway confers much of the pleiotropic and deleterious effects of hyperinsulinaemia in obese women with PCOS that result in much of the hyperandrogenic and reproductive dysfunction that typify this condition



Hyperandrognism in PCOS : related to obesity.

Androgen excess is often associated with obesity states, at any age of life, because of changes in the pattern of secretion or metabolism of androgens and in their actions at the level of target tissues, particularly the adipose tissue. Androgen excess plays an important role in favouring the expansion of visceral fat, which characterize so-called visceral obesity. [44] Moreover, there is evidence that the combination of androgen excess and obesity may favour the development of metabolic disorders, such as the metabolic syndrome and type 2 diabetes. In obese adolescent girls, androgen excess may also suggest the potential development of the polycystic ovary syndrome (PCOS). [45]A new hypothesis, based on long-term lifestyle intervention programs or bariatric surgery, supports the concept that a "PCOS secondary to obesity" may exist, as confirmed by the complete resolution of all features defining PCOS after considerable weight loss. Obesity can also develop after long-term exposure to chronic stress, which is characterized by increased activity of the hypothalamic-pituitary-adrenal axis and the sympathetic system combined with higher than normal androgen production rates in women. This increasingly observed condition, often underestimated, should be considered more carefully, not only in mature women but also in girls during adolescence. [46]The presence of a hyperandrogenic state can also be detected in menopausal women, as a consequence of the rearrangement of the sex hormone balance which, in turn, may play some role in determining the development of both visceral adiposity and even obesity and, consequently, metabolic disorders. Undoubtedly, the recognition of the potential negative effects of androgen

excess in obese women may open new therapeutic perspectives aimed at achieving a sustained weight loss and its maintenance for as long as possible.



1.8 Obesity as risk factor for development of PCOS.

In women who are genetically predisposed to development of PCOS, weight-gain and obesity often result in its clinical and biochemical manifestation. Accordingly, there are close links between obesity and PCOS. The majority of women with PCOS (38%-88%) are either overweight or obese. Data from the Northern Finland Birth Cohort (NFBC) 1966 show a significant association between body mass index (BMI) and features of PCOS at all ages. Furthermore, modest weight-loss (around 5%) often results in clinically meaningful improvements in the reproductive, hyperandrogenic, and metabolic features of PCOS,

Outlined below are factors that mediate the effects of weight-gain and obesity on the pathogenesis of PCOS.[47]

1.9 PCOS as risk for development of obesity.

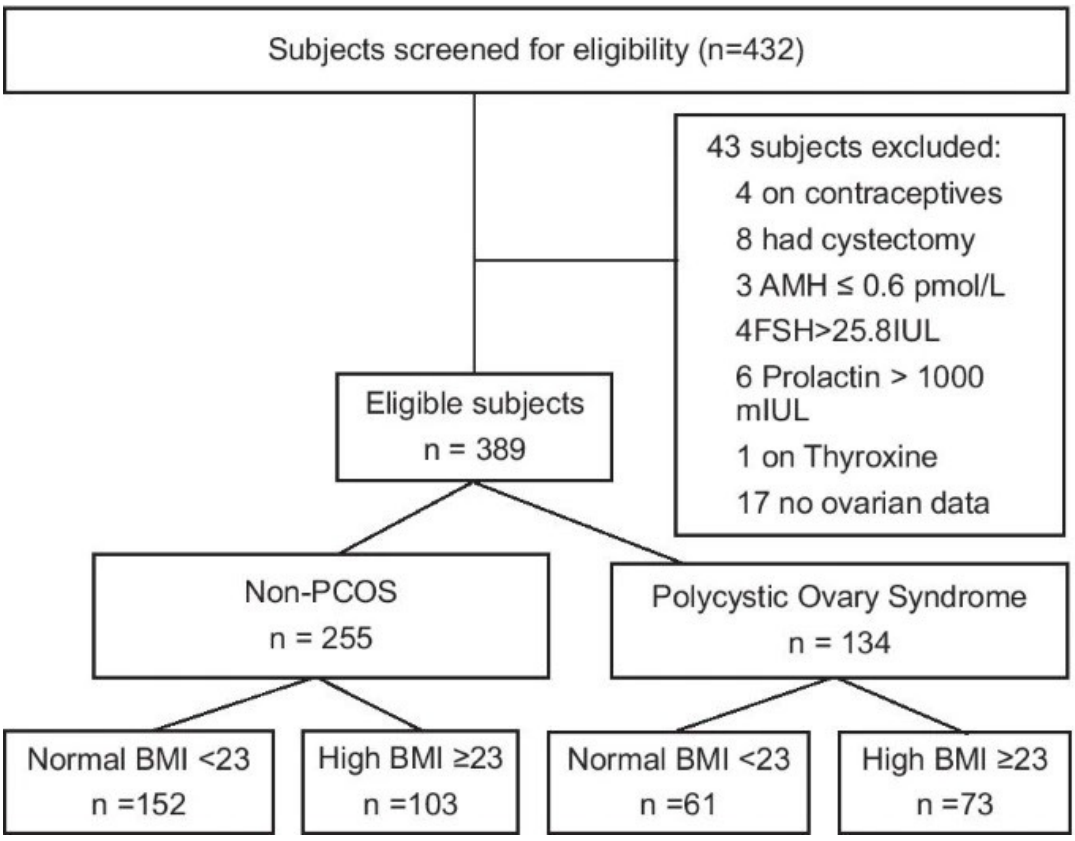
Much epidemiological data confirm a close association between obesity and PCOS. As outlined earlier, much evidence confirms a clear effect of weight-gain on development of PCOS and weight-loss on its alleviation, mediated, for example, through effects on insulin sensitivity. [48]However, PCOS is a complex condition, and it is likely that its relationship with obesity is also complex. It is important to consider possible mechanisms whereby PCOS may contribute towards further weight-gain or hamper successful attempts at weight-loss and maintenance of body weight through lifestyle means in women with this condition, outlined in this section .[49]

1.5 study design.

This is a prospective cohort study involving healthy women and "clinically-suspected" PCOS cases. All eligible participants were assessed similarly, and were classified into two groups: healthy (Non-PCOS) and PCOS (Fig. 1). Details of the protocol have been described previously . Women were diagnosed with PCOS if they presented with at least two out of three features of the Rotterdam criteria [50]. Diagnostic thresholds for AFC (≥ 22), ovarian volume (≥ 8.44 ml) and biochemical hyperandrogenism (serum testosterone ≥ 1.89 nM) have previously been established for this cohort [51]. Hirsutism was defined as mFG score ≥ 5 according to East Asian criteria . Women who were not PCOS served as healthy controls (Fig. 1). The study was approved by the Domain Specific Review Board of the National Health

Healthy women, aged 21 to 45 years, were recruited from participants in an annual corporate health screen in National University Hospital (NUH) and volunteers from the university community. "Clinically-suspected" PCOS cases were referred from gynecological clinics at NUH and KK Women's and Children's Hospital. Subjects were recruited from 2011 to 2019. Informed written consent was obtained from all participants.[52]

Exclusion criteria were pregnancy, breastfeeding, hyperprolactinaemia (previously diagnosed, or with prolactin > 1000 mIU/L), congenital adrenal hyperplasia, adrenal tumours, androgen-secreting tumours, thyroid disease, severe cardiovascular disease, or history of



hysterectomy and/or oophorectomy, ovarian failure (anti-müllerian hormone [AMH] levels ≤ 0.6 pmol/L, or follicle stimulating hormone [FSH] levels > 25.8 IUL). Participants on lipid-lowering, and/or contraceptives, diabetic or other medications known to affect reproductive function within 60 days of study entry were also excluded from the study.

Results

Of 389 participants, 134 (34.4%) were classified as PCOS and the remaining 255 (65.6%), as the non-PCOS population. Overall 45.2% of women had high BMI (≥ 23). Compared to non-PCOS subjects, women with PCOS had a higher BMI . Women with PCOS and high BMI had increased hair growth with modified Ferriman-Gallwey (mFG) scores that were 2.96-fold higher versus healthy-normal BMI women. Compared to healthy-high BMI women, PCOS women with high BMI had significantly higher mean differences in mFG scores . In PCOS women, having high BMI also significantly increased mFG scores by 1.85-fold . This effect was mirrored by the additive effect of BMI and PCOS on free androgen index. No independent effect of high BMI on

rates of oligomenorrhoea, antral follicle count, ovarian volume or serum androgens were observed.

1.13 Management Strategies for obesity and PCOS.

There are multiple methods to treat obesity within PCOS. These include lifestyle changes, with alterations in diet and increases in physical activity; pharmaceutical treatments that may have some mitigating effects on weight, such as metformin; anti-obesity drugs; and finally bariatric surgery. Most of these methods have limitations in terms of long-term compliance and weight maintenance with perhaps the exception of bariatric surgery. [53]

1.14 Lifestyle Therapy in PCOS

There are many hurdles to lifestyle therapy in women with PCOS. First is what to recommend in terms of lifestyle. Studies of exercise alone have been inadequate to show meaningful change in the PCOS phenotype[54] suggesting that some amount of dietary modification is also necessary. Additionally, there can be major orthopedic limitations to weight bearing exercise in morbidly obese women with joint problems and even arthritis, so exercise must be tailored to their abilities.
Most studies of lifestyle therapy have generally involved both an exercise component and a dietary component with varying degrees of caloric restriction. [55] Many have mimicked the Diabetes Prevention Program60 and aimed for 150 minutes a week of aerobic exercise in divided sessions and a 500 kcal/day deficit (which ideally should produce a 1 pound/ week weight loss, although counter regulatory responses and changes with weight loss significantly blunt this generous estimate). The role of dietary composition versus calorie restriction in improving aspects of PCOS is uncertain. [56]In the larger population, diets low in carbohydrates are certainly associated with more rapid weight loss, but these equalize over time in longer studies such that macronutrient dietary composition is irrelevant to weight loss.
Lifestyle studies are very labor intensive and involve personnel with nutritional, kinesiological, and behavioral backgrounds who are[57] traditionally not part of outpatient clinical care in women's health. Thus such interventions are difficult to introduce in clinical practice in the United States, where such services or treatment of obesity per se is not covered by medical insurance.

Another major hurdle is retention of subjects. Most women who are contacted to participate in such studies elect not to participate, and even after consenting to participate, there is substantial dropout in a time-dependent manner, such that longer studies (and here in the PCOS literature we are talking ~6-month studies as opposed to shorter ones) can have dropout rates that approach or exceed 50%. Thus it is difficult to extrapolate the results to a larger population of women with PCOS because only a fraction will elect to participate or will participate long enough to develop meaningful effects. [58]Overall, however, lifestyle therapy does show some benefit with changes in body composition, improvements in insulin sensitivity, and improvement of hyperandrogenism. There was no evidence of effect for lifestyle intervention on improving glucose tolerance or dyslipidemia and no adequate studies assessing clinical reproductive outcomes, quality of life, and treatment satisfaction.[59]

1.15 Effects of Insulin-Sensitizing Agents in PCOS.

The use of metformin in many studies of women with PCOS as well as in the Diabetes Prevention Program (which recruited men and women on the basis of impaired glucose tolerance) has been associated with weight loss. There is also a meta-analysis in adolescents that supports metformin use associated with weight loss , but there is another in women with PCOS that does not support it.Metformin does not have an indication by the Food and Drug Administration (FDA) as a weight loss drug, and studies in other populations did not support this as a uniform and reproducible effect of metformin. Therefore the use of metformin to achieve weight loss remains an off-label indication.[60]
Older insulin sensitisers such as troglitazone and, to a lesser extent, rosiglitazone were associated with a dose–response increase in weight, whereas pioglitazone appears to be more weight neutral[61]
However, given the other unfavorable effects of thiazolidinediones, their use at all in women with PCOS is debatable. Newer insulin-sensitizing agents, such as injectable glucagon like peptide-1 analogs, have been associated with weight loss when used in type 2 diabetes. However, there are only limited studies in women with PCOS. In one head-to-head study of

metformin versus exenatide in women with PCOS, the weight loss with both treatments was comparable.[62]

1.16 Effect of anti-obesity drugs in pcos

Overall, these data indicate that obesity only modestly increases the risk of PCOS, if at all, and that the prevalence of obesity in PCOS most strongly reflects environmental factors. In this study we have not assessed the potential contribution of any specific environmental factor. However, it is likely that changes in the quantity, type, and quality of dietary intake and in the degree and type of physical activity over time may have had significant influence on the prevalence of obesity among PCOS women, as they have in the general population [63]. Finally and notwithstanding our observation that the role of obesity in altering the development or prevalence of PCOS appears to be modest, it is also clear that the concomitant presence of obesity will worsen the phenotypic and

metabolic presentation of the disorder 33 and that weight loss and lifestyle management offers a beneficial effect on the ovulatory and metabolic dysfunction of obese women with PCOS.[64] .

There are currently few agents available with a specific indication for weight loss. The anorexiant agents have generally had a checkered history (e.g., fen-phen), and most have eventually been removed from the market for adverse cardiovascular effects. The most recent agent to be removed from the worldwide market was sibutramine, a [65]selective serotonin-norepinephrine reuptake inhibitor that was thought to exert an amphetamine-like anorexic effect but that eventually was found to increase the risk for cardiovascular events and strokes. Although some anorexiant agents remain on the market for short-term use of weight loss, [66]these mainly have amphetamine-like effects and likely are poor choices given the underlying metabolic dysfunction including .hypertension found in many obese women with PCOS

That leaves only one FDA-approved drug for the treatment of obesity: orlistat. Orlistat works through a different mechanism (i.e., by inhibiting intestinal lipase activity and thus inhibiting fat absorption). Adverse effects include steatorrhea and flatulence that are reduced with adherence to a low-fat diet and, in rare cases, hepatic damage. Nevertheless, orlistat is available in prescription strength (120 mg/meal) or over the counter (brand name Alli in the United States at 60 mg/meal). The amount of weight loss (in combination with lifestyle change) is relatively modest, ~5 to 7 lbs after a year of use. Limited studies in women with PCOS also show modest improvements in biochemical measures of insulin sensitivity and hyperandrogenism .[67]

1.17 Effect of Bariatric Surgery in PCOS.

Bariatric surgery has been increasingly used in the United States to treat morbid obesity associated with PCOS. In the larger population as the surgery has become safer with primarily a laparoscopic approach and selection of a healthier population for surgery, long-term survival is now superior with versus without the surgery.Clearly this form of therapy is the one most likely to result in massive and sustained weight loss, especially compared with the therapies described earlier.Initial case series describe primarily positive effects on PCOS.[68] One large case series from Spain that characterized subjects both before and at varying time points after surgery reported marked resolution of multiple biochemical abnormalities, as well as improvements in menses and hirsutism after bariatric surgery, implying the procedure was a “cure” for PCOS and morbid obesity.Other series report similar results as well as improved fertility among women with PCOS undergoing surgery.However, more rigorous studies, preferably multicenter .and prospective, are needed to confirm these results.[69]

2.CONCLUSION.

It is widely accepted based on current evidence that, weight-gain and obesity are important risk factors for the clinical and biochemical manifestations of PCOS in those women who are genetically[70] predisposed. The multiple mechanisms mediating this process are complex. However, the association between obesity and PCOS is more complex than a simple cause-and-effect process and likely includes complicated interlinks between multiple factors. As outlined, it seems likely that in at least some obese women with PCOS, development of PCOS through indirect mechanisms (including depression and perceived lack of self-control and increased distress) may hamper ongoing attempts at lifestyle change and therefore effective weight-loss. Indeed, such factors may even promote further weight-gain, thereby setting in play a vicious circle that can be difficult to vanquish . [71]

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