Obesity and PCOS: Implications for Diagnosis and Treatment

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Abstract

There appears to be an epidemic of both obesity and polycystic ovary syndrome (PCOS) in the world today. However, obesity per se is not a part of the phenotype in many parts of the world. Obesity is likely not a cause of PCOS, as the high prevalence of PCOS among relatively thin populations demonstrates. However, obesity does exacerbate many aspects of the phenotype, especially cardiovascular risk factors such as glucose intolerance and dyslipidemia. It is also associated with a poor response to infertility treatment and likely an increased risk for pregnancy complications in those women who do conceive. Although most treatments of obesity, with the exception of bariatric surgery, achieve modest reductions in weight and improvements in the PCOS phenotype, encouraging weight loss in the obese patient remains one of the front-line therapies. However, further studies are needed to identify the best treatments, and the role of lifestyle therapies in women of normal weight with PCOS is uncertain.

Keywords
- anovulation
- weight
- androgen excess
- insulin

The epidemic of obesity in the developed world came upon us unawares until it became a major worldwide public health problem today. Along the way an obscure endocrine disorder known as polycystic ovary syndrome (PCOS) also took us by surprise. Where, we ask ourselves, did all this PCOS come from, and more importantly, what are we to do about it?

The common rise of both has led us to link them together in some cause-and-effect manner. As women became fatter, they became more hirsute with fewer menses; the epidemics go hand in hand. This concept if true would inform both the treatment and the prevention of the disorder (i.e., treat PCOS with weight loss, and prevent it by trying to keeping adolescents and young adults at a normal weight).

This is an appealing concept, but perhaps too simple a one for such a complex and heterogeneous disorder as PCOS. This article explores the alternative hypothesis, specifically that obesity does not cause PCOS and therefore the treatment of obesity is unlikely to "cure" PCOS. Obesity clearly modifies the PCOS phenotype, especially metabolically, and it blunts responses to treatment, especially infertility treatments. This article acknowledges the adverse metabolic effects of obesity on the PCOS phenotype. However, the take-home message is not to ignore obesity when it presents with PCOS, but rather not to ignore the PCOS that presents with obesity.

Relationship between Obesity and PCOS: Influence of Time and Location

Koch's postulates were developed to prove a causative relationship between a specific microbe and a disease. They can be adapted to the relationship between obesity and PCOS. Obesity is acquired through changes in diet and lifestyle that are acquired through contact with others in our society. The first postulate thus paraphrased with obesity as the acquired infectious agent would read, "Obesity must be found in abundance in all suffering from the disease but should not be found in thin healthy organisms." However, clearly PCOS is found commonly in thin women.

The original description of Stein and Leventhal noted the association of obesity with the combination of anovulation, hirsutism, and polycystic ovaries.[1] However, although sufficient, it was not necessary to the phenotype. Many of the original women with so-called Stein-Leventhal syndrome were thin. The preponderance of evidence since suggests that women with PCOS are as thin or fat as the other women

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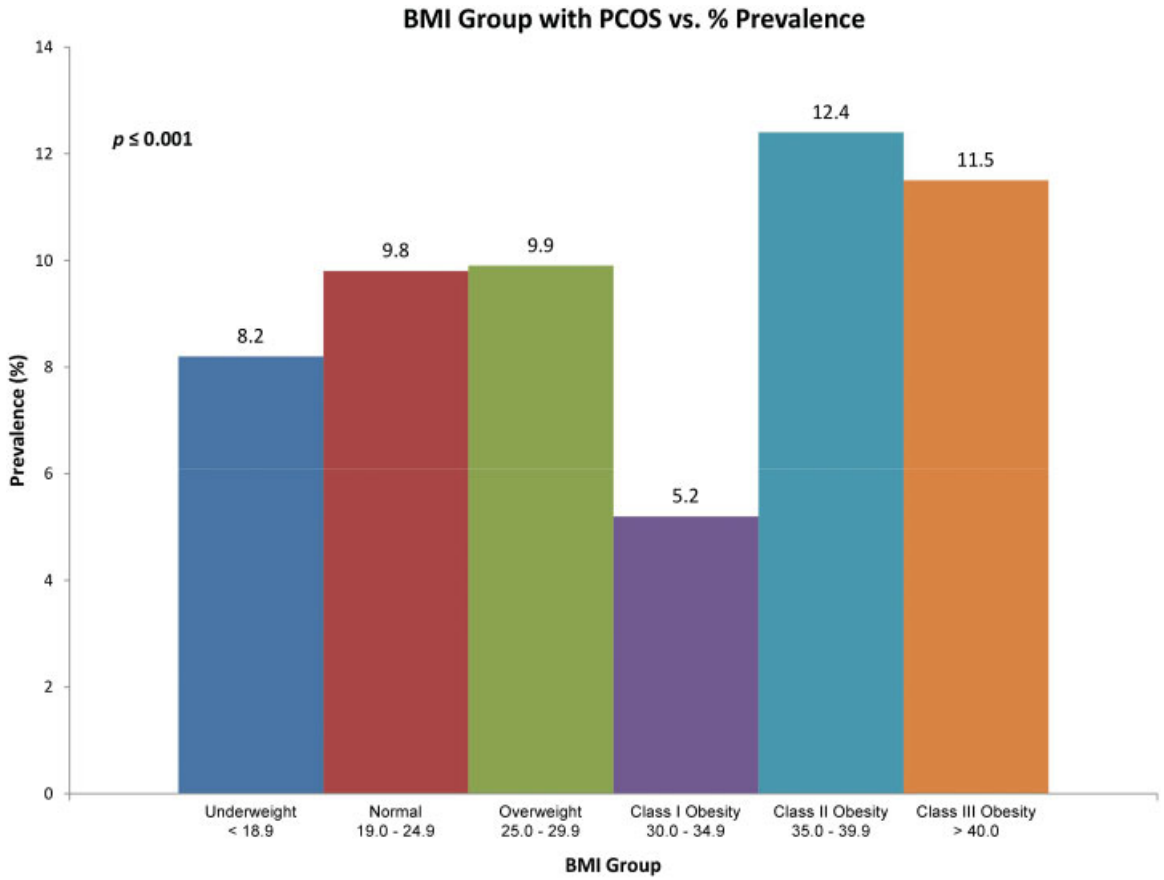

Figure 1 Prevalence of polycystic ovary syndrome (PCOS) by body mass index (BMI) category in an unselected group of women applying for jobs at an academic health center in the southeastern United States. Adapted from Yildiz et al.[8]

in the surrounding population. The best examples are to look at the classic studies of PCOS by Sam Yen et al from the 1960s and 1970s, where the mean weights of women with PCOS are <150 lbs (body mass indexes [BMIs]were not reported in these articles).[2,3] These women were normal weight to at best overweight. As America gained weight, so did the women with PCOS, so that by the 21st century the women with PCOS grew along with the rest of society. For example, the mean BMI of women was 35 in two large multicenter trials of treatment for women with PCOS, one conducted in the 1990s with troglitazone[4] and one in the 2000s with metformin and clomiphene.[5] Both of these trials recruited subjects on the basis of unexplained hyperandrogenic chronic anovulation.

This hypothesis can be explored by looking at recent prevalence studies of PCOS in an unselected population in the United States (►**Fig. 1**) or in varying populations throughout the world (►**Table 1**) and the mean BMIs or weights in these affected women with PCOS. There are few studies that have prospectively studied an unselected population of women. The studies by the Azziz group that systematically phenotyped women who applied for jobs at an academic health center (as opposed to those who presented to clinics)[6,7] eliminated much of the selection bias that any clinic-based study would introduce (i.e., women with PCOS are more likely to seek out medical treatment due to hirsutism, menstrual disorders, infertility, obesity, etc.). In an unselected population, increasing BMI has a minimal effect on the prevalence of PCOS (►**Fig. 1**).[8] When we accept that other prevalence studies may be flawed due to varying degrees of selection bias, we note that the prevalence of PCOS tends to be fairly constant, whereas the weights and BMIs vary greatly. These weights and BMIs tend to mirror those of women in the larger population.

These studies also highlight the confounding effects of diagnostic criteria on the PCOS phenotype.[9] Multiple studies have now confirmed that diagnostic criteria that center on polycystic ovaries, with either hyperandrogenism or oligomenorrhea, tend to identify a population that is thinner and has a lower prevalence of metabolic abnormalities such as hyperglycemia, dyslipidemia, or hypertension.[10–12] Polycystic ovaries are common if not normal in younger women.[13] Therefore, diagnostic schema that overly rely on the presence of polycystic ovaries are likely to identify a younger population, which is likely healthier and thinner. Increasing age during the reproductive years remains one of the most significant associations or predictors of increasing weight as well as the development of major morbidities such as cardiovascular disease and cancer.

What Are the Mechanisms by Which Obesity Causes PCOS?

Obesity has been linked to abnormal function of the hypothalamic-pituitary-ovarian (HPO) axis through multiple

Table 1 Body Mass Index in Women with and without Polycystic Ovary Syndrome around the World as Reported in Prevalence Studies of Unselected Populations

Author	Year	Country	Diagnostic Criteria of PCOS	Population Prevalence of PCOS	Mean BMI of Women with PCOS	Mean BMI of Women without PCOS
Knochenhauer et al[7]	1998	United States	1. Oligoovulation 2.Clinical hyperandrogenism and/or hyperandrogenemia 3. Exclusion of other related disorders such as hyperprolactinemia, thyroid abnormalities	4.6% (including black and white women)	White: 24.8 Black: 29.1	NA
Diamanti-Kandarakis et al[77]	1999	Greece	Combination of oligomenorrhea and hyperandrogenism (FT levels ~95th percentile of the levels detected in the group of normal cycling nonhirsute women)	6.8%	28.7 and 28.9 for two groups	25.9
Michelmore et al[78]	1999	United Kingdom	Presence of polycystic ovaries on ultrasound plus one additional feature including menstrual irregularity, acne, hirsutism, BMI >25 kg/m^2, raised serum testosterone (>3 nmol/L), or elevated LH (>10 IU/L)	26%	23.7 (median)	22.4 (median)
Alvarez-Blasco et al[79]	2006	Spain	Oligoovulation, clinical and/or biochemical hyperandrogenism with exclusion of other causes	6.5%	34.8	35.2
Chen et al[80]	2008	South China	Combination of oligomenorrhea and evidence of hyperandrogenism	2.2%	22.7	20.8
Tehrani et al[81]	2011	Iran	Combination of menstrual dysfunction and clinical hyperandrogenism and/or hyperandrogenemia	8.5%	26.2	24.5

PCOS, polycystic ovary syndrome; BMI, body mass index; NA, not applicable; FT, free testosterone; LH, luteinizing hormone.

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.

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.[14] Several severely insulin-resistant hyperinsulinemic states in women have been associated with marked hyperandrogenemia, such as leprauchaunism.[15] Small increases in circulating ovarian androgens have been noted with insulin infusions to women with normal ovaries,[16] as well as when women with type 1 diabetes are treated with insulin.[17] The administration of antidiabetic drugs that lower insulin levels or improve insulin sensitivity has been associated with decreases in circulating androgen levels and increases in ovulation rates.[4,18]

Multiple other growth factors and inflammatory factors are increased in obesity and may further stimulate excess ovarian androgen production or inhibit aromatization of androgens to estrogens.[19]

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 favor disordered gonadotropin secretion.[20] 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.[21] Such experiments are obviously more difficult to perform in humans, but there are multiple other mechanisms through which obesity could affect HPO function.

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. 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.[22] There have been fewer studies of the effect of eating behavior

and such hormones released during digestion as incretins on reproductive function.[23–25] But it is possible that such hormones and other appetite regulators may also affect gonadotropin secretion.

Other Effects of Obesity on HPO Function

Obesity may affect peripheral metabolism of sex steroids or regulators of sex steroids. Androgen action is related not only to levels of circulating androgens and local receptors, but also to peripheral metabolism of androgens and to binding proteins such as sex hormone-binding globulin (SHBG) that limit peripheral androgen bioavailability. Further metabolism of androgens at peripheral sites affects action. For example, androgens are thought to undergo peripheral aromatization in multiple sites that could have both local effects related to PCOS as well as systemic actions if these metabolites are secreted. One example is the conversion of weak androgens to 5α reduced potent androgens in the pilosebaceous unit encouraging terminal hair differentiation.[26] Another example of the local effects is the aromatization hypothesis, which states that the blood–brain barrier is relatively impervious to estrogens but can transport androgens across the barrier that are then aromatized in the cells of the central nervous system.[27] This process may be critical to normal male neurodevelopment. Testosterone secreted by the fetal testis diffuses into the male brain where it is locally aromatized to estradiol, which is critical to the onset of masculinization.

There are also examples where peripheral metabolism can have distant endocrine effects. Adipose tissue contains aromatase, which can promote increased levels of bioactive estrogens from androgens, which are then released into the circulation. This can result in delayed puberty in boys as well as accelerated puberty in girls.[28] It can also lead to increased estrone levels noted in women with PCOS.[29] This mechanism is also associated with male feminization with breast development seen in states of male obesity. In PCOS this may one of the mechanisms that contributes both to anovulation as indicated by the success of such antiestrogens as clomiphene and letrozole in inducing ovulation. This milieu is thought to contribute to a state of unopposed estrogen favoring the development of endometrial hyperplasia.[30] The relative distribution and amount of fat may affect the metabolic and reproductive phenotype of women with PCOS. Women with increased central adiposity and increased visceral fat generally display higher levels of metabolic dysfunction, inflammation, and hyperandrogenism.[31]

Finally, a relatively androgenic state and a relatively insulin-resistant state is associated with the suppression of

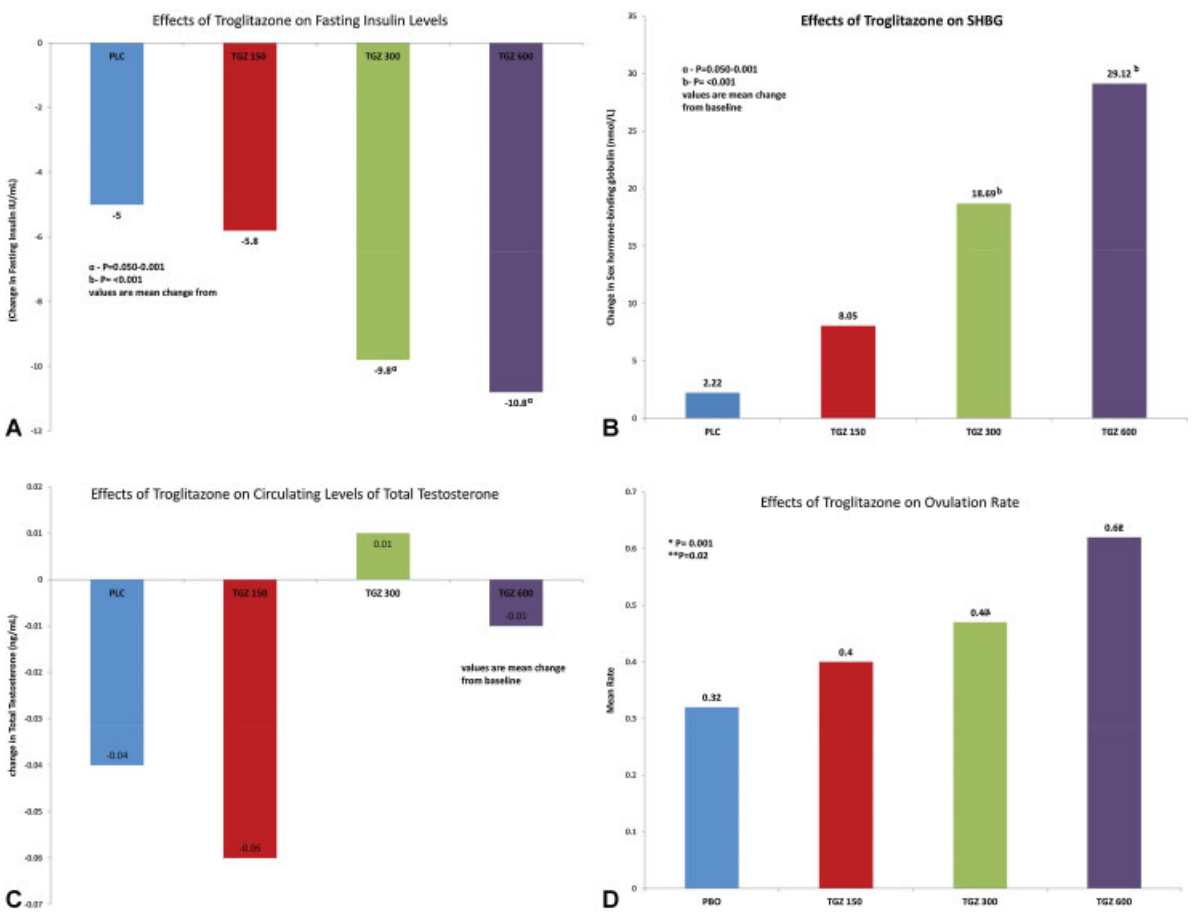

Figure 2 (A) Effects of troglitazone (TGZ) on circulating levels of fasting insulin, (B) testosterone, (C) sex hormone-binding globulin (SHBG) (all compared with baseline levels), and (D) the ovulation rate (number of [observed/expected] ovulations averaged for each treatment group). PLC, placebo. Note that there is no significant effect of increasing doses of TGZ on total testosterone; however, there are dose-related increases in body weight (data not shown). Adapted from Azziz et al.[4]

hepatic secretion of SHBG.[32] This leads to increased bioavailability of androgens in the periphery, in the brain as noted earlier, at the pilosebaceous unit, the liver, and so on.[33] Increases in estrogen, either through administration of estrogenic substances such as clomiphene or the oral contraceptive pill or through pregnancy have been associated with marked increases in SHBG in women with PCOS.[5,34,35] Similarly, decreases in insulin, such as achieved through insulin-sensitizing agents (►**Fig. 2**) have been associated with similar increases in SHBG, further limiting androgen action in the periphery.[4]

Why Don't All Morbidly Obese Women Have PCOS?

Given the multiplex actions of obesity on the HPO axis, it is remarkable that every obese women does not eventually develop PCOS, especially those with morbid obesity. In fact, as noted earlier, the prevalence of obesity in the population does not appear to be associated with a clear increase in the prevalence of PCOS. Among obese women (mean BMI: 47.2) seeking bypass surgery in a multisite bariatric surgery consortium sponsored by the National Institutes of Health, 13% reported being diagnosed with PCOS by a physician prior to surgery.[36] A total of 41% reported a history of infertility; 73% reported a prior live birth. Although this may exceed population-based prevalences (range: 5 to 10% of reproductive-age women), this still suggests that most morbidly obese women do not have PCOS and in fact have achieved a live birth in the past. Clearly, other factors are necessary to develop PCOS. One Koch postulate that would uphold the theory that obesity causes PCOS would be to induce obesity in a healthy (and thin) organism and examine the changes. Although not possible in humans due to ethical concerns, an abundance of animal data has shown that knockout phenotypes leading to obesity or feeding/lifestyle changes encouraging obesity lead to cycle disturbances and infertility in animal models.

What Are the Effects of Obesity on Metabolic Abnormalities in PCOS?

Obesity is associated with an increased likelihood of metabolic sequelae. The effects of obesity and PCOS was well illustrated by the classic experiments of Dunaif et al.[37,38] These experiments showed that the influence of obesity and PCOS are independent and additive. However, the major determinant of the two is obesity, such that obesity per se in normal women is associated with diminished insulin action compared to PCOS per se in normal weight women (►**Fig. 3**).[38] Further obesity is associated with an increase

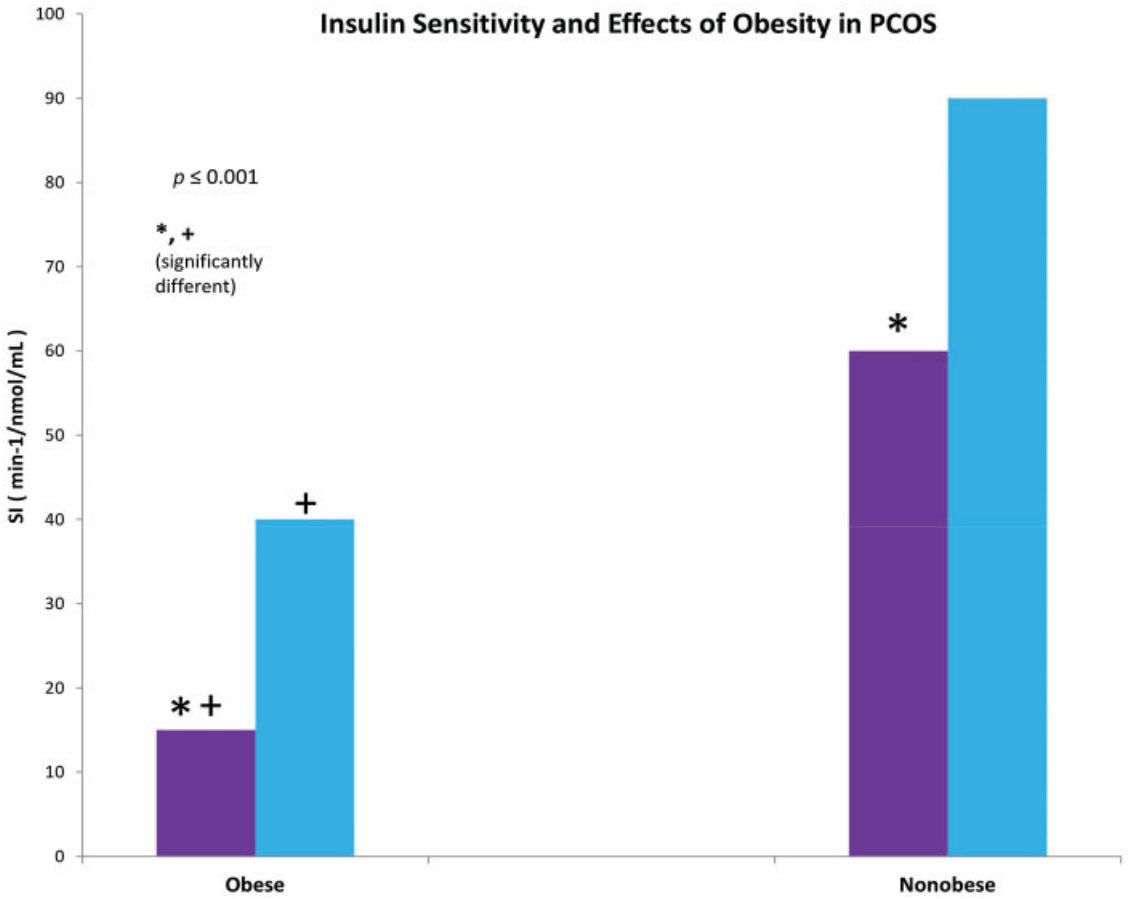

Figure 3 Insulin sensitivity by diagnosis (polycystic ovary syndrome [PCOS]: purple bars; control women: blue bars) and weight group (lean versus obese) as determined by a frequently sampled intravenous glucose tolerance test. Adapted from Dunaif et al.[82]

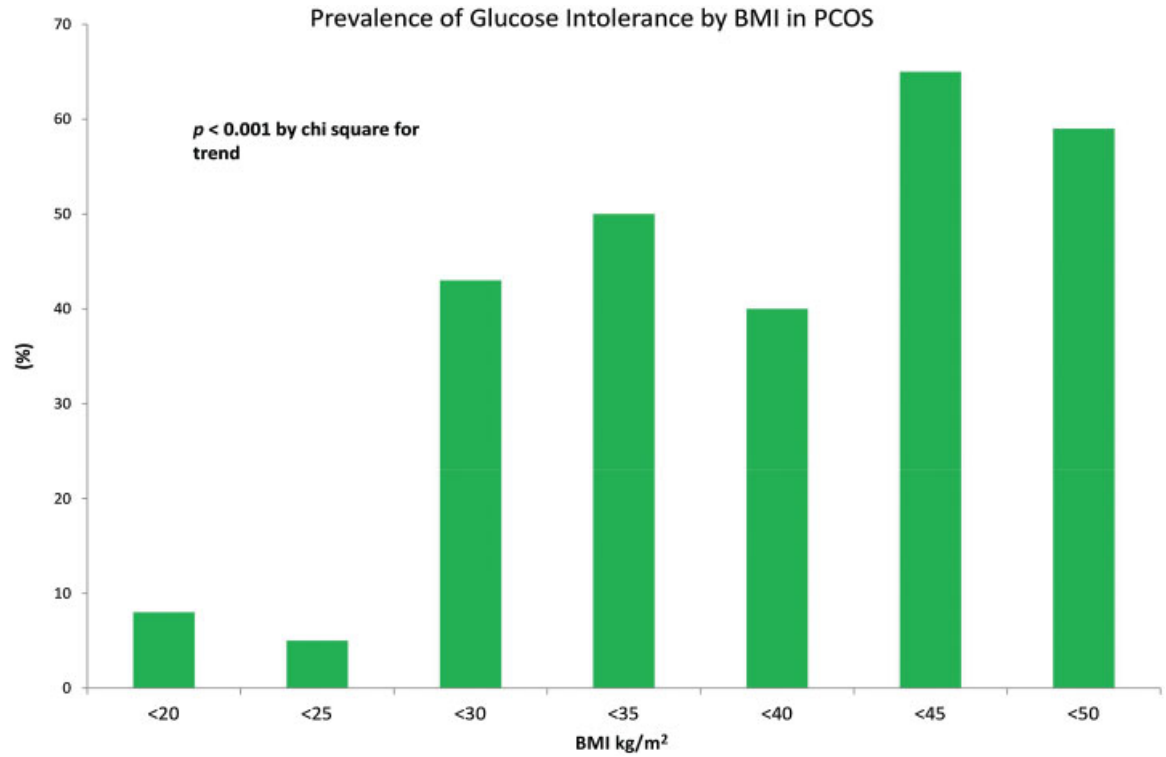

Figure 4 Prevalence of glucose intolerance (2-hour glucose level ≥140 mg/dL on 2-hour oral glucose tolerance test) by body mass index (BMI) category in women with polycystic ovary syndrome (PCOS) from academic health centers in urban and suburban settings in the United States. Adapted from Legro et al.[39]

in the risk for developing impaired glucose tolerance (►**Fig. 4**), and normal weight women with PCOS are relatively protected compared with overweight and obese women.[39–41] The high prevalence rate of glucose intolerance among obese adolescents with PCOS suggests that the normal time-related ontogeny of insulin resistance to diabetes, that is, initial compensation through excess β-cell secretion of insulin with an eventual time-related decline in insulin section followed by the development of glucose intolerance and fasting hyperglycemia, has been subverted by the obesity.[42,43]

The prevalence of dyslipidemia is similarly increased with increasing obesity.[44,45] The metabolic syndrome has a similar relationship.[46] However, it is interesting to note that a large multicenter trial of women with PCOS found no metabolic syndrome in women with PCOS and a BMI <27.[46] In terms of waist circumference and PCOS, a normal weight circumference is almost always associated with a normal metabolic profile and lack of the metabolic syndrome.[46]

In the larger population, obesity has been associated with an increased risk for several cancers including breast and endometrial cancers.[30,47] Similarly, multiple epidemiological articles have suggested that women with PCOS are at increased risk for these cancers,[48–50] although the level of epidemiological evidence is less for breast cancer within the subpopulation of PCOS. Most of these studies have lacked the power either of numbers or longitudinal follow-up to look at the mitigating effects of obesity on cancer risk in women with PCOS.

What Are the Effects of Obesity on Reproductive Abnormalities in PCOS?

The relationship between PCOS and obesity and reproductive abnormalities is less certain. For example, there is no clear dose–response relationship between obesity and the presence of anovulation, hyperandrogenemia, and hirsutism or the prevalence of polycystic ovaries within the population of women with PCOS.[51–53] Obesity, however, is clearly a baseline predictor of response to treatment including both the likelihood of ovulation and the likelihood of pregnancy. Increasing BMI within PCOS predicts clomiphene resistance and failure to respond to gonadotropins or to conceive with in vitro fertilization.[54,55] Based on these various models, likely a large change in BMI would be needed to improve the chance for treatment success (►**Fig. 5**). A decrease in 5 BMI units produces no or minimal increase in live-birth rates. BMI, however, may be the most modifiable baseline predictive variable, compared with age, duration of infertility treatment, and hirsutism. Further change in weight may lead to favorable changes in circulating biochemical predictors, such as the free androgen index or of insulinlike growth factor-1, that have been identified in other predictive modeling of treatment success.[56]

Obesity is clearly associated with adverse pregnancy outcomes in the larger population, and it likely increases the risk for adverse pregnancy complications within PCOS. One meta-analysis that looked at pregnancy in women with PCOS and adjusted for differences in obesity in women with PCOS did note increased rates of gestational hypertension,

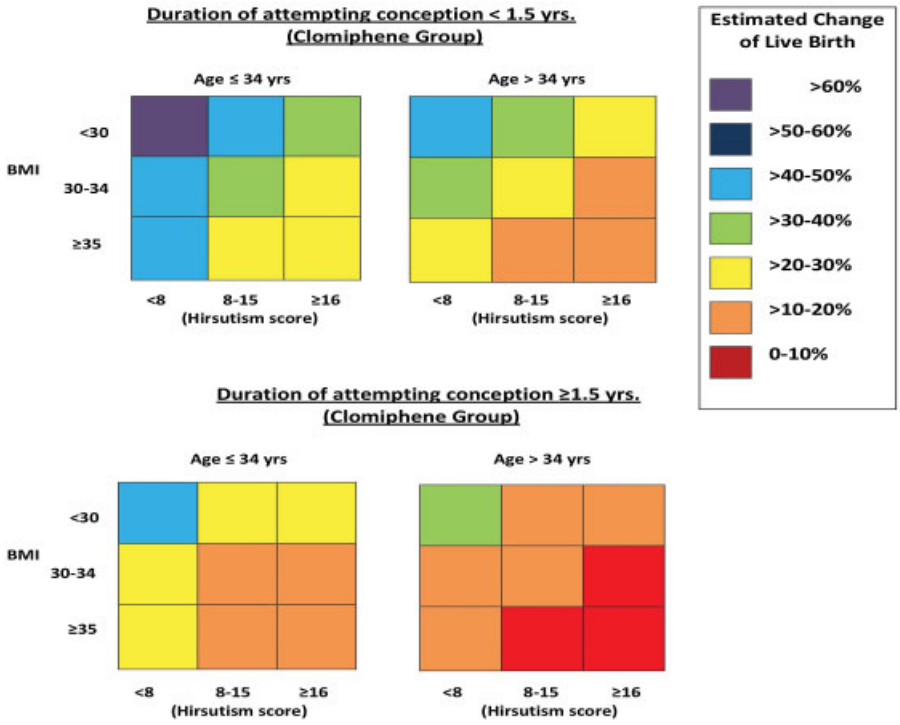

Figure 5 A baseline model for chance of live birth with up to 6 months of therapy with clomiphene citrate in women with polycystic ovary syndrome (PCOS) using age, duration of infertility treatment, body mass index (BMI), and degree of hirsutism on Ferriman-Gallwey assessment. Adapted from Rausch et al.[55]

gestational diabetes, preterm labor, and infant mortality among women with PCOS.[57] However, a large multicenter trial of metformin use during pregnancy in normal weight women with PCOS in Scandinavia found normal rates of major pregnancy complications (preterm labor, preeclampsia, small for gestational age) with and without metformin supplementation.[58] Unfortunately, there remain no adequate trials that demonstrate a preconception intervention to lose weight actually improves maternal or neonatal outcomes.

Effects of Treatment of Obesity on 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; antiobesity 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.

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,[59] suggesting that some amount of dietary modification is also necessary. Additionally, there can be major orthopedic limitations to weightbearing 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. Many have mimicked the Diabetes Prevention Program[60] 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 counterregulatory 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.[61] 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.[62]

Lifestyle studies are very labor intensive and involve personnel with nutritional, kinesiological, and behavioral backgrounds who are 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%.[63–65] 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. Overall, however, lifestyle therapy does show some benefit with changes in body composition, improvements in insulin sensitivity, and improvement of hyperandrogenism.[66] 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.[66]

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.[5,60] There is also a meta-analysis in adolescents that supports metformin use associated with weight loss,[67] but there is another in women with PCOS that does not support it.[68] 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.

Older insulin sensitizers 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. 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 glucagonlike 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.[69]

Effect of Antiobesity Drugs in PCOS

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 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, 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.[70] Limited studies in women with PCOS also show modest improvements in biochemical measures of insulin sensitivity and hyperandrogenism.[71,72]

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.[73] 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.[74] Initial case series describe primarily positive effects on PCOS. 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.[75] Other series report similar results as well as improved fertility among women with PCOS undergoing surgery.[76] However, more rigorous studies, preferably multicenter and prospective, are needed to confirm these results.

Conclusions

It is difficult to link the worldwide epidemic of obesity with a similar epidemic of PCOS. Likely the increased recognition of PCOS is related to increased physician and patient recognition of the symptoms through well-publicized and broader diagnostic criteria created by several groups of specialty experts. Obesity is likely not a cause of PCOS, and in many parts of the world, most women with PCOS are of normal weight. However, obesity does exacerbate many aspects of the phenotype, especially cardiovascular risk factors. It is also associated with a poor response to infertility treatment and likely an increased risk for pregnancy complications. Although treatments, with the exception of bariatric surgery, achieve modest reductions in weight and improvements in the PCOS phenotype, encouraging weight loss in the obese patient remains one of the front-line therapies.

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