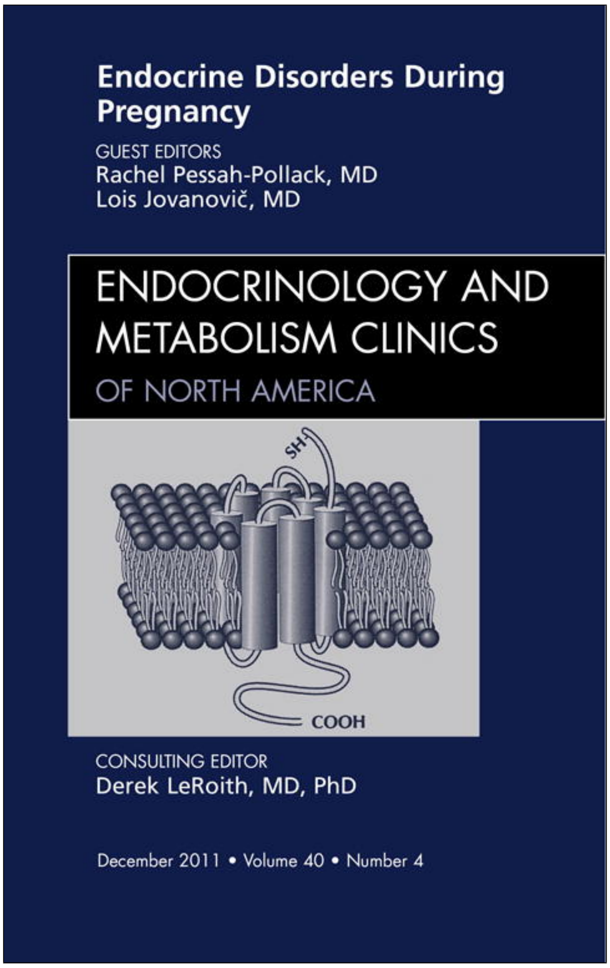
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Achieving a Successful Pregnancy in Women with Polycystic Ovary Syndrome

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KEYWORDS

• Polycystic ovary syndrome (PCOS) • Infertility • Pregnancy

DEFINITION AND EPIDEMIOLOGY OF POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS), first described by Stein and Leventhal[1] in 1935, is characterized by oligoanovulation, clinical or biochemical hyperandrogenism, and/or polycystic ovaries.[2,3] PCOS is one of the most common endocrinopathies in women of reproductive age, with prevalence estimated between 7% and 8%.[4,5] It is the most common cause of female infertility among reproductive-age women. It is also the leading cause (75%) of anovulatory infertility.[6,7] The prevalence of different phenotypes of PCOS among various populations is affected by ethnic origin, race, and environmental factors.[8]

Currently, there are 3 broadly accepted sets of criteria for diagnosis of PCOS.[2,3] After excluding all other causes of hyperandrogenism and menstrual dysfunction, National Institutes of Health (NIH) criteria (1990) require evidence of hyperandrogenism (clinical or biochemical) and evidence of anovulation or oligo-ovulation. Rotterdam criteria (2003) added the presence of polycystic ovarian morphology as an alternative (2 out of 3 criteria still need to be present for diagnosis of PCOS).[2] The Androgen Excess and PCOS Society criteria (2006) consider polycystic ovarian morphology as an alternative evidence of ovarian dysfunction (**Box 1**).[3] None of these definitions fully addresses the clinical picture of PCOS. For example, none of the sets mentioned earlier includes insulin resistance or increased circulating luteinizing hormone (LH) levels, both common features of PCOS.

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Box 1
Diagnostic criteria for PCOS

NIH (1990)

Anovulation or oligo-ovulation

Clinical and/or biochemical hyperandrogenism

Rotterdam (2003) (2 out of 3)

Anovulation or oligo-ovulation

Clinical and/or biochemical hyperandrogenism

Polycystic ovaries (morphology)

Androgen Excess and PCOS Society (2006)

Ovarian dysfunction

Either anovulation or oligo-ovulation or polycystic ovaries (morphology)

Clinical and/or biochemical hyperandrogenism

PATHOGENESIS AND MANIFESTATIONS OF PCOS

Women with PCOS may present with multiple manifestations, which include cutaneous, reproductive, and metabolic abnormalities. The symptoms are usually peripubertal in onset. The cutaneous manifestations include hirsutism, acne, and male pattern baldness, and are caused by hyperandrogenism. The reproductive manifestations include menstrual dysfunction (secondary amenorrhea, oligomenorrhea), anovulation, infertility, early pregnancy loss, and other complications of pregnancy, which are discussed in detailed later. Metabolic and endocrine manifestations include increased circulating levels of total and/or free testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS); decreased sex hormone-binding globulin (SHBG); increased insulin levels; and increased LH/follicle-stimulating hormone (FSH) ratio.

Hyperandrogenism results from abnormalities at all levels of the hypothalamic-pituitary-ovarian axis. The increased frequency and amplitude of LH pulses in PCOS seems to result from an increased frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses.[8] The increased LH secretion stimulates theca cells to increase production of androgens. The hyperandrogenic milieu alters the intrafollicular microenvironment, leading to aberrant folliculogenesis.[9]

Obesity, insulin resistance, and hyperinsulinemia are commonly present in PCOS. Approximately 40% to 50% of women with PCOS are overweight,[4] and a history of weight gain frequently precedes the onset of clinical manifestations of this syndrome. Obese subjects with PCOS tend to have more severe reproductive abnormalities and may be resistant to treatment.

In adolescent and young women, the age of onset of obesity and onset of menstrual irregularities are significantly correlated.[10] A large study conducted in the United Kingdom, which included 5800 women, showed that obesity in childhood and in the early 20s increased the risk of menstrual abnormalities.[11] In the Nurses' Health Study, the risk of anovulatory infertility increased in women with higher body mass indices (BMI).[12]

Hyperinsulinemia is present in about 80% of obese women with PCOS and in approximately 30% to 40% of those with normal weight.[13] Overall, 20% to 50% of women with PCOS have insulin resistance and approximately 10 % of women with PCOS develop type 2 diabetes by 40 years of age.[14–16]

Hyperinsulinemia may affect steroidogenesis in the human ovary both directly and indirectly.[17] Insulin receptors are present in the human ovary[18] and in vitro studies have shown that, in the ovaries of women with PCOS, insulin is capable of stimulating androgen production in the theca cells. In vivo, both acute and chronic hyperinsulinemia stimulate testosterone production in some studies, whereas suppressing insulin levels by any means uniformly decreases circulating androgen concentrations.[19] In spite of systemic insulin resistance, insulin sensitivity seems to be preserved in the human ovary.[20] In the ovaries, insulin can activate both insulin receptor and type 1 insulinlike growth factor (IGF)-1 receptor, leading to excessive stimulation of androgen production. Insulin suppresses insulinlike growth factor-binding protein type 1 (IGFBP-1) production, therefore increasing the bioavailable IGF level, which can further enhance androgen synthesis, particularly because hyperinsulinemia can also upregulate ovarian type 1 IGF receptors.[19]

Systemically, insulin inhibits production of serum SHBG in the liver, further increasing the levels of free testosterone.[21] Thus, the role of hyperinsulinemia in accelerating ovarian androgen production is multifactorial (**Fig. 1**).

The level of circulating estrogens in PCOS is commonly increased because of aromatization from the excess of androgens. High insulin levels may contribute to this process by stimulating aromatase; however, the effect of hyperinsulinemia on aromatase is controversial.[22]

The effect of hyperinsulinemia, if any, on the hypothalamic/pituitary axis in women with PCOS is controversial. Burcelin and colleagues[23] showed that LH secretion can be stimulated by insulin. In contrast, other studies in women with PCOS, as well as in animals, failed to consistently show the stimulatory effect of insulin on LH production or secretion.[24] For example, Moret and colleagues[25] assessed LH levels before and during hyperinsulinemic clamp and showed that LH levels increased in the control group but not in subjects with PCOS. Obese patients with higher insulin levels frequently do not have an increase in LH/FSH ratio.[26] LH levels are commonly low in obese women.[27] LH levels did not increase either tonically on in response to GnRH in female rats with experimental hyperinsulinemia compared with control animals.[28]

The cause of PCOS is not well understood, but it is believed to be multifactorial (**Box 2**). An abnormality in the hypothalamic-pituitary axis is considered to be one of

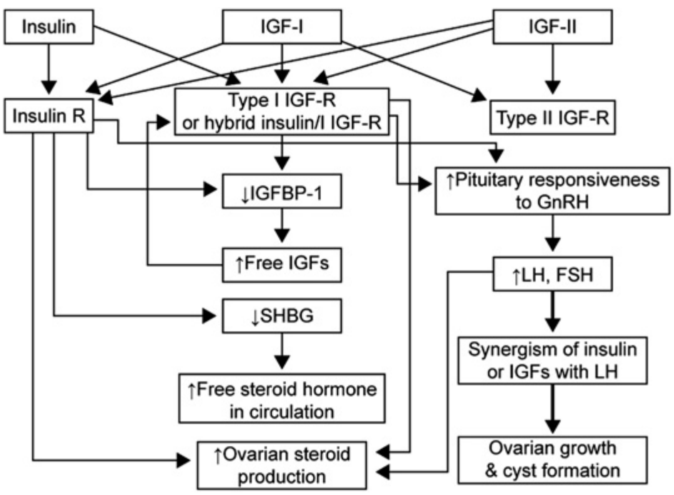

Fig. 1. Insulin-related ovarian regulatory system. (*Adapted from* Poretsky L, Cataldo NA, Rosenwaks Z, et al. The insulin-related ovarian regulatory system in health and disease. Endocr Rev 1999;20:535; with permission.)

Box 2
Hypotheses of PCOS pathogenesis

1. Central hypothesis[29–31]
2. Ovarian hypothesis[33–37]
3. Adrenal hypothesis[38–40]
4. Dual-defect hypothesis[41]
5. Programming hypothesis[41–43]
6. Genetic hypothesis[44–46]

many pathogenetic components. It seems that both the frequency and, in particular, the amplitude of LH pulses are increased in PCOS.[29–32] Although the causes of these abnormalities of LH secretion are unclear, they may be primarily caused by increased sensitivity of the pituitary to GnRH.

It has been proposed that intrinsic functional defects of theca cells and granulosa cells may be the primary feature of PCOS. Dysregulation of P-450C17 enzyme is presumed to occur in theca cells, because several studies that used GnRH agonists in PCOS showed hypersecretion of 17-OH progesterone.[33,35,36] The steroidogenic and mitogenic abnormalities have also been found in theca and granulosa cells from patients with PCOS.[47] Aromatase activity was observed to be low in PCOS granulosa cells in vivo, probably reflecting decreased FSH activity in vivo, because aromatase activity seems to be either normal or even exaggerated when granulosa cells from PCOS are examined in vitro.[34,37]

It has been hypothesized that excessive adrenal androgen production during puberty can supply substrate for extragonadal aromatization, resulting in tonic estrogen inhibition of FSH secretion. Premature adrenarche is associated with a higher incidence of functional ovarian hyperandrogenism and insulin resistance.[38–40] Hyperinsulinemia can stimulate adrenal (as well as ovarian) steroidogenesis.[48] It is unknown why pubertal insulin resistance persists in women with PCOS.

There is both in vitro and in vivo evidence that increased circulating levels of LH and hyperinsulinemia may act synergistically to enhance ovarian growth, androgen secretion, and ovarian cyst formation (**Fig. 2**).[19] The dual-defect hypothesis of PCOS postulates the presence of 2 independent primary defects in at least some women with PCOS.[41]

According to the programming hypothesis, the nutritional and endocrine environment in utero can affect development of neuroendocrine systems regulating body

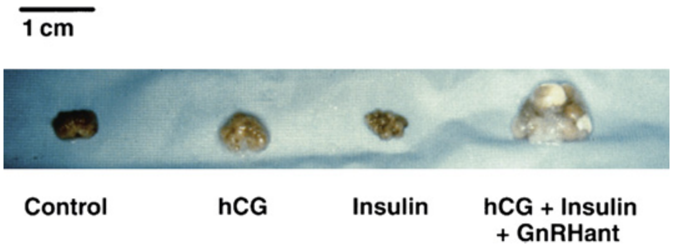

Fig. 2. Synergistic effects of insulin and LH/human chorionic gonadotropin (hCG) on ovarian morphology. (*Adapted from* Poretsky L, Clemons J, Bogovich K. Hyperinsulinemia and human chorionic gonadotropin synergistically promote the growth of ovarian follicular cysts in rats. Metabolism 1992;41:903; with permission.)

weight, food intake, and metabolism. For example, hyperinsulinemia and hyperandrogenism, which can program female reproduction, possibly producing a phenocopy of PCOS.[42,43] A genetic cause has been suspected because PCOS has strong familial clustering[44–46]; however, as discussed later, identifying the specific genetic defects that could lead to the development of PCOS, has been challenging.

INFERTILITY IN PCOS

PCOS is the most common (75%) cause of anovulatory infertility in reproductive-age women.[6,7] Prevalence of infertility among women with PCOS ranges from approximately 40% to 75%.[49–52]

Multiple approaches have been shown effective for the treatment of infertility in women with PCOS. These approaches are based on the pathogenetic mechanisms discussed earlier and include lifestyle modifications, pharmacologic therapy, and surgical interventions.

Lifestyle Modifications

Since the 1990s, when it became apparent that insulin resistance/hyperinsulinemia play a role in the pathogenesis of PCOS, weight loss and exercise have been introduced as potential methods of treatment. It is believed that the primary mechanism by which weight loss can improve reproductive outcomes in PCOS[53–56] involves reducing circulating insulin levels.[57]

Loss of 5% to 10% of initial body weight in 6 months is sufficient to reestablish ovarian function in more than 50% of obese women with PCOS.[58] Even a less significant amount of body weight loss (2%–5%) can result in restoration of regular vaginal bleeding consistent with ovulatory patterns.[55] Short periods (4 weeks) of extremely low-calorie diet (350 kcal/day, 43 g carbohydrate, 33 g protein, 2.9 g fat per 100 g) can decrease fasting insulin and free testosterone levels and increase the levels of SHBG and IGFBP-1.[59,60]

Clark and colleagues[61] conducted an observational study of behavioral modifications (diet/counseling/exercise) in 13 obese women with PCOS. After 6 months, with an average weight loss of 6.3 kg, 12 out of 13 women regained ovulatory cycles, and 11 out of 13 became pregnant. Hollman and colleagues[54] conducted an observational study in 29 obese women with PCOS. With 5.6 kg of mean weight loss in 8 months, the ovulation and pregnancy rates were improved to 80% and 29%, respectively. Fasting insulin, androstenedione, and dihydrotestosterone levels decreased after this intervention, although LH, FSH, dehydroepiandrosterone (DHEA), DHEAS, testosterone, and estrogen levels were unchanged.

Hoeger and colleagues[62] conducted a 48-week trial of diet modification (50% carbohydrate, 25% protein, 25% fat, low-glycemic-index foods) and/or metformin. Ovulation rates were increased equally in all groups, suggesting that reduction of hyperinsulinemia achieved either through lifestyle modification or metformin therapy was equally effective.

There is no clear-cut evidence that exercise, independent of weight loss, improves ovulatory function. However, the potential benefits of exercise can be expected in the overweight PCOS population,[56] because there is evidence that exercise enhances weight loss.[63]

Medical Therapy

Clomiphene citrate

Clomiphene citrate (clomiphene; Clomid), an oral synthetic triphenylethyne, is an inexpensive and safe medication that has been used for ovulation induction since the

1960s.[64] Clomiphene is a partially selective estrogen receptor modulator with antiestrogenic effect in the hypothalamus, where it induces a change in the GnRH pulse frequency. This change results in an increased FSH level, promoting follicular development and estrogen production.[65,66] High ovulation rates of 60% to 85% have been reported with administration of clomiphene[67,68] and a 30% to 40% pregnancy rate can be achieved in the first 3 months of treatment.[69]

Because of a high rate of successful ovulation and cost-effectiveness, the Thessaloniki European Society for Human Reproduction and the American Society of Reproductive Medicine (ESHRE/ASRM) consensus workshop recommended that clomiphene be the first-line therapy for ovulation induction. Clomiphene can be started at 50 mg daily for 5 days beginning on day 2 to 5 of the menstrual cycle, with incremental dose increase to a maximum of 150 mg[70] or 250 mg per day.[71]

There are several limitations to clomiphene use. Clomiphene increases the risk of multiple pregnancies (4%–10%), particularly in obese women with PCOS who are commonly resistant to clomiphene and require a higher dose.[72] Ovarian hyperstimulation syndrome (OHSS) may occur, although the risk of OHSS with clomiphene is less than that with gonadotropin therapy. It is known that obesity and clomiphene resistance correlate, and that hyperinsulinemia may account for the poor responsiveness to clomiphene, possibly because of the alterations in the IGF system.[73,74]

The discrepancy between ovulation rates (60%–85%) and successful pregnancy rates (30%–40%) in patients with PCOS receiving clomiphene therapy may be caused by the antiestrogenic properties of clomiphene, which can cause poor thickening of the cervical mucus and endometrium, rendering the uterine environment hostile for conception.[75]

Gonadotropins/GnRH

Exogenous gonadotropin therapy can be used for ovulation induction in patients who do not conceive after 3 cycles of clomiphene therapy.[76] Gonadotropins have been used in PCOS since the 1960s. Human recombinant FSH, administered subcutaneously, currently is used the most frequently. Gonadotropin ovulation induction is based on the hypothesis that the initiation and maintenance of monofollicular growth may be achieved by a transient increase in FSH to more than the threshold dose for a sufficient duration.

High starting doses of FSH (150 IU daily), which used to be conventional, resulted in high ovulation rates (70%) and a pregnancy rate of about 30%. However, the high-dose protocol increases the risk of multiple pregnancies (25%–30%) and OHSS.[77,78] To avoid these complications, various regimens have been proposed. The step-up low-dose FSH induction protocols (37.5–50 IU daily) have been shown to be safer for monofollicular development.[79] An analysis of 225 women with PCOS treated with low-dose gonadotropin regimens showed high rates of ovulation and pregnancy as well as significantly decreased frequency of multiple pregnancies (6%) and OHSS (8%).[78]

Combination trials involving gonadotropins have been performed. Comparing coadministration of metformin with FSH with FSH monotherapy, one study showed a lower incidence of ovarian hyperstimulation in the combination therapy group,[80] whereas another study showed no significant difference in ovarian response between the 2 groups.[81]

GnRH analogues are used to prevent premature LH surge during ovarian stimulation and are administered before FSH stimulation. Both forms (GnRH agonists and GnRH antagonists) are available. GnRH agonists require a longer period of administration than GnRH antagonists. In initial studies, the concomitant use of GnRH agonists and gonadotropins seemed to increase the risk of OHSS.[82] However, more recent studies showed that there is no significant difference in either reproductive outcomes or overall occurrence of OHSS with the use of either regimen.[83,84]

The drawbacks to gonadotropin therapy include its high cost, the need for frequent monitoring of serum estradiol levels, and the need for frequent ultrasound assessments to minimize the risk of multiple follicles developing.

The Thessaloniki ESHRE/ASRM Consensus Workshop (2007) recommended a low starting dose of FSH (37.5–50.0 IU daily) with a step-up regimen until 6 ovulatory cycles.[70]

Metformin

Because insulin resistance and consequent hyperinsulinemia are considered important factors in the pathogenesis of PCOS, multiple studies attempted to target these metabolic abnormalities to improve ovulation and fertility in women with this syndrome.[85]

In 1994, Velazquez and colleagues[86] published the first trial of metformin in PCOS. This trial included 29 obese women with PCOS who were treated with metformin for 8 weeks and showed improvement in metabolic parameters, as well as a noticeable increase in pregnancy rate. Since then, there have been numerous studies of metformin assessing the metabolic and/or reproductive outcomes on subjects with PCOS. Most of these studies favor metformin use, although there are some that do not.[87]

Metformin is an insulin sensitizer that decreases fasting insulin levels, hepatic gluconeogenesis, and body weight. The mechanisms of the effects of metformin on hyperandrogenism and female reproductive function are not well understood, but are believed to be primarily related to the reduction in hyperinsulinemia. Metformin enhances adenosine monophosphate–activated protein kinase (AMPK) pathway, inhibits IGF-1 signaling[88] and IGFBP-1 production both in the ovary and systemically, and produces increases in SHBG levels.[89] These changes result in improved ovulatory rates.[90]

The first head-to-head randomized controlled trial of metformin and clomiphene was published by Palomba and colleagues[91] in 2005. One hundred nonobese subjects with PCOS without glucose intolerance were randomized into metformin or clomiphene treatment groups. After 6 months, ovulation rates were not significantly different (24.4% vs 31.9%). However, there were striking differences in pregnancy rates (68.9% in the metformin group vs 34% in the clomiphene group). The investigators concluded that metformin was superior to clomiphene as a first-line therapy.

Two years later, a retrospective head-to-head study of 154 patients by Neveu and colleagues[92] showed that metformin was superior to clomiphene in inducing ovulation, but that there was no difference in the pregnancy rate in anovulatory women with PCOS. In contrast, a head-to-head randomized controlled trial by Zain and colleagues[66] in 115 Asian women with PCOS showed that metformin was inferior to clomiphene in ovulation rates but equal to clomiphene in pregnancy rates.

In 2006, Moll and colleagues[93] reported a large multicenter randomized controlled study that compared metformin plus clomiphene versus clomiphene monotherapy in nonobese women with PCOS. Two hundred and twenty-eight women were followed for up to 6 menstrual cycles. The study showed that there were no significant differences in ovulation rates or pregnancy rates between the combination therapy versus clomiphene monotherapy groups, suggesting that addition of metformin provided no benefit.

A meta-analysis by Creanga and colleagues[94] showed that metformin alone improves the odds of ovulation in women with PCOS but it does not improve rates of clinical pregnancy. This meta-analysis suggested that combination therapy increased the likelihood of both ovulation and early pregnancy, compared with clomiphene alone, especially among clomiphene-resistant and obese women with PCOS. However, the combination therapy did not improve the odds of live births.

Another meta-analysis by Moll and colleagues[5] (2007) was limited to the studies using ESHRE/ARSM Rotterdam criteria and compared the live birth rates among patients who received metformin, clomiphene, or their combination, as well as other therapeutic modalities with or without metformin. The investigators analyzed clomiphene-naive and clomiphene-resistant subgroups separately. They concluded that adding metformin did not affect live birth rates in the clomiphene-naive group, whereas there was significant increase in live birth rates in the clomiphene-resistant group.

The largest trial to date (The Pregnancy in Polycystic Ovary Syndrome [PPCOS]) was published in 2007 by Legro and colleagues.[85] This was a prospective randomized controlled trial in 626 anovulatory infertile women with PCOS with live birth rate as the primary outcome. Subjects were randomized to 1 of 3 groups: (1) clomiphene, (2) metformin, (3) clomiphene plus metformin. The live birth rate was 22.5% in the clomiphene group, 7.2% in the metformin group, and 26.8% in the combined group. The difference in live birth rates between the clomiphene group and the metformin group, as well as between the combination group and metformin group, was statistically significant (**Table 1**). There was no significant advantage of the combination therapy compared with clomiphene alone, although, when ovulation was considered to be the outcome, the combination therapy was superior. The investigators concluded that clomiphene, rather than metformin, is the most appropriate first-line treatment in anovulatory women with PCOS.

The combination therapy (clomiphene and metformin) is recommended for a subgroup of patients who have BMI greater than 35 kg/m^2, glucose intolerance, and clomiphene resistance because the only beneficial outcomes in the combination therapy group, compared with clomiphene monotherapy, were decreased BMI and improved insulin resistance, whereas pregnancy rates or live births rates were not affected (see **Table 1**).[85]

To help clinical decision making, a nomogram for clomiphene therapy was created by Imani and colleagues[95] in 2002. This nomogram was designed to predict the

Table 1
Summary of outcomes from PPCOS study

	Clomiphene (C)	Metformin (M)	Combination (comb.)	*P* value (comb. vs M)	*P* value (comb. vs C)	*P* value (C vs M)
N	209	208	209	—	—	—
Ovulation (%)	49	29	60	<.001	.003	<.001
Conception (%)	30	12	38	<.001	.006	<.001
Pregnancy (%)	24	9	31	<.001	.10	<.001
Live birth (%)	23	7	27	<.001	.31	<.001

Data from Legro RS, Barnhart HX, Schlaff WD, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 2007;356:551.

outcome (chances of ovulation and live birth) with clomiphene induction. The screening characteristics included age, BMI, presence of oligomenorrhea or amenorrhea, and free androgen index. Rausch and colleagues[96] created a more complex live birth prediction chart, using data from a large cohort from PPCOS (**Fig. 3**).[85] This live birth prediction chart was formulated with probabilities of live birth that ranged from 0% to 10% to greater than 60%. The model factored in (1) age, (2) duration of infertility, (3) severity of androgenic manifestations, and (4) BMI. Input of information is based on history and physical examination, and the modalities are not limited to clomiphene, but include the data from metformin monotherapy and combination therapy. Because timing may be a critical factor in treating infertility, the nomograms may help both clinicians and patients to make therapeutic decisions, and, in the case of very low likelihood of successful pregnancy, may help fast-track the treatment.[97]

Metformin is a category B drug for pregnancy. There is no evidence of fetus toxicity in animal studies. In humans, one study reported metformin use throughout the pregnancy in women with type 2 diabetes and gestational diabetes without teratogenic effects or adverse fetal outcomes.[98]

In summary, currently metformin is not recommended as the first-line therapy for infertility in patients with PCOS. The Thessaloniki ESHRE/ARSM Consensus Workshop advised that, thus far, studies do not show an advantage to adding metformin to clomiphene.[70] Remaining areas of uncertainty include the choice of therapy in obese versus nonobese patients with PCOS and in clomiphene-naive versus clomiphene-resistant subgroups.

Thiazolidinediones

Thiazolidinediones (TZDs) are the peroxisome proliferator–activated receptor γ (PPAR-γ) ligands that are being used as insulin sensitizers in individuals with type 2 diabetes. Several studies of troglitazone, the first TZD approved for the treatment of diabetes, have been reported in PCOS. The first pilot study, conducted by Dunaif and colleagues,[99] showed that troglitazone decreased androgen levels in obese

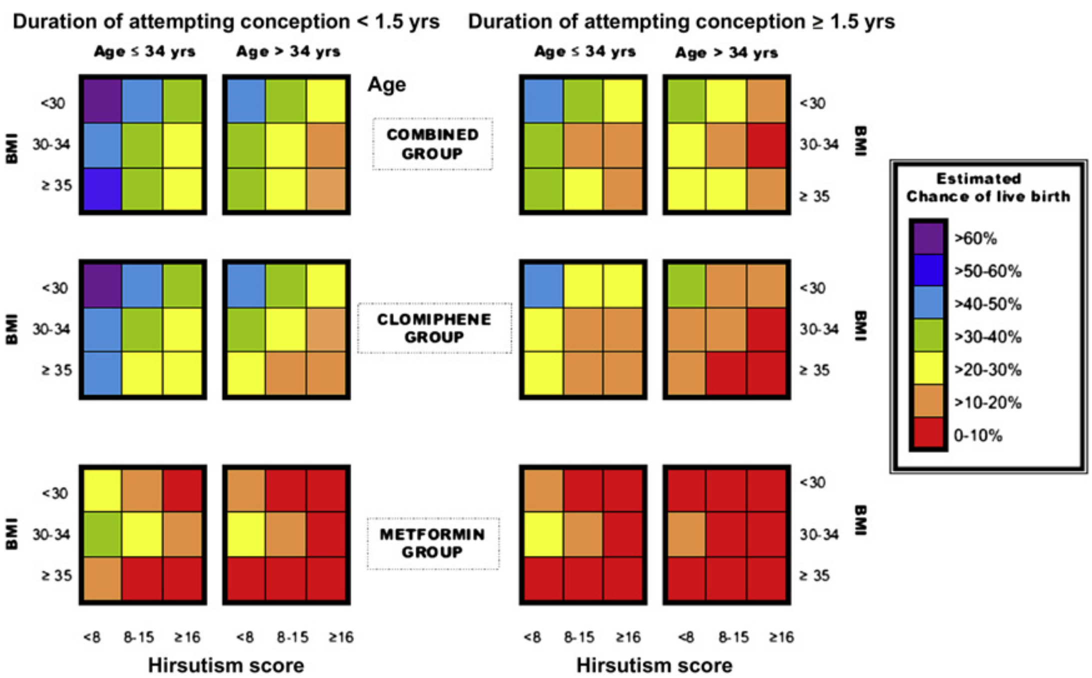

Fig. 3. Live birth prediction chart for various methods of ovulation induction. (*Adapted from* Rausch ME, Legro RS, Barnhart HX, et al. Predictors of pregnancy in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2009;94:3458; with permission.)

women with PCOS. Mitwally and colleagues[100] compared troglitazone plus clomiphene with clomiphene monotherapy and showed significant improvement of ovulation rates in the combination group. A large multicenter trial with more than 400 women with PCOS who received troglitazone in a range of doses (150 mg, 300 mg, and 600 mg daily) for 44 weeks showed a correlation between ovulation rates and the dose of troglitazone.[101] However, troglitazone has been removed from the worldwide market because of its hepatotoxicity. Two other TZDs currently available, rosiglitazone and pioglitazone, have been shown to improve ovulation, hyperandrogenism, and insulin resistance in women with PCOS[102,103]; however, there have been concerns about cardiovascular risks associated with rosiglitazone use,[104] propensity of all TZDs to induce weight gain, and their classification as category C drugs for use in pregnancy.

The mechanism of action of TZDs involves activation of the PPAR-γ ligands, which are present in the human ovary.[105] In vitro, in human ovarian cells, TZDs directly inhibit androgen production. Their action in the ovary involves activation of steroidogenic acute regulatory (StAR) protein[106] and inhibition of 3-β-hydroxysteroid dehydrogenase[107] and aromatase.[108] Systemically, TZDs reduce circulating insulin levels, which further contributes to the reduction of ovarian androgen synthesis (**Box 3**).[17]

Glucagonlike peptide-1 agonists

Glucagonlike peptide-1 (GLP-1) is an incretin, which enhances glucose-dependent insulin secretion, delays gastric emptying, and centrally controls appetite, therefore producing weight loss.[109]

Box 3
Effects of TZDs related to ovarian function

Direct: can be observed in vitro; may be present in vivo

Insulin independent

- ↑ Progesterone
- ↓ Testosterone
- ↓ Estradiol
- ↑ IGFBP-1 (in the absence of insulin)

Insulin sensitizing (enhanced insulin effect)

- ↓ IGFBP-1 production
- ↑ Estradiol production (in vivo, in a setting of high-dose insulin infusion)

Indirect: observed in vivo; caused by systemic insulin-sensitizing action and reduction of hyperinsulinemia

↓ Testosterone

↑ IGFBP-1

↑ SHBG

↓ Free testosterone

Data from Seto-Young D, Paliou M, Schlosser J, et al. Direct thiazolidinedione action in the human ovary: insulin-independent and insulin-sensitizing effects on steroidogenesis and insulin-like growth factor-binding protein-1 production. J Clin Endocrinol Metab 2005; 90:6099.

Several studies have examined GLP-1 levels in women with PCOS. One study showed that there was no difference in circulating GLP-1 levels between women with PCOS and healthy subjects.[110] In another study, Vrbikova and colleagues[111] assessed incretin levels in 34 lean women with PCOS compared with control subjects. In the early phase of the oral glucose tolerance test (OGTT), GLP-1 levels were similar in both women with PCOS and controls; however, in the later phase, the PCOS group showed a significant decrease in GLP-1 levels compared with controls matched for BMI and age. A similar postprandial pattern on the OGTT also exists in patients with type 2 diabetes.[112] GLP-1 has been shown to participate in modulation of GnRH secretion[113] and to reduce the pulsatile component of testosterone secretion in healthy men.[114] GLP-1 knockout mice had reduced gonadal weight and delayed onset of puberty in women.[113]

One pilot study compared the GLP-1 agonist exenatide, metformin, and their combination in obese patients with PCOS.[115] After 24 weeks of intervention, ovulation rates improved by 50%, 29%, and 86%, respectively. The average weight loss was most significant in the combination arm, with 6.0 kg, versus 3.2 kg in the exenatide arm, and 1.6 kg in the metformin arm. Total testosterone levels were reduced in all groups. The preliminary evidence of potential benefits of incretin therapy in PCOS, coupled with the evidence that weight reduction has consistently led to improvement in ovarian function in women with PCOS, suggests that GLP-1 agonists may have a role in therapy for PCOS.

Aromatase inhibitors

Aromatase inhibitors block the biosynthesis of estrogens from androgens. Aromatase inhibitors cause a reversible uncoupling of the hypothalamic/pituitary axis from negative estrogen feedback, leading to FSH and LH secretion and induction of ovulation. Unlike clomiphene, aromatase inhibitors do not block the estrogen receptor, and therefore the potential negative effects on cervical mucus and the endometrium are usually not seen.

Aromatase inhibitors were first introduced for ovulation induction by Mitwally and colleagues[116] in 2001, with promising data. In a prospective study, letrozole, the most commonly used aromatase inhibitor, was administered in the early part of the menstrual cycles to 12 clomiphene-resistant women with PCOS. The results included an ovulation rate of 75% and clinical pregnancy (presence of a gestational sac on ultrasound[117]) rate of 17%. Letrozole treatment also produced a thicker endometrium compared with clomiphene therapy.

Badawy and colleagues[118] compared 115 patients with PCOS given anastrozole 1 mg/d (a third-generation aromatase inhibitor), on cycle days 3 to 7 (for 5 days), to a matched group of 101 patients with PCOS given clomiphene 100 mg/d. The anastrozole group (243 cycles) had a thicker endometrium and fewer mature and growing follicles compared with the clomiphene group (226 cycles). The pregnancy rate per cycle was slightly higher in the anastrozole group but did not reach statistical significance. The investigators concluded that anastrozole should be considered whenever the risks of OHSS and multiple pregnancies are high. Currently, aromatase inhibitors are not recommended for use in treating infertility (except if there is a history of estrogen sensitive tumors), because of the potential embryotoxicity of letrozole.[119]

Glucocorticoids

Glucocorticoids suppress adrenal androgen production and therefore may improve ovulation. Several studies have shown an improvement in reproductive outcomes with glucocorticoid therapy in anovulatory patients, including women with PCOS,[120–122] whereas others have shown no beneficial effects.[123,124] At this time, glucocorticoid therapy is not recommended for treatment of infertility in women with PCOS.

Oral contraceptives/antiandrogens

Oral contraceptives (OCPs) reduce hyperandrogenism via suppression of LH secretion as well as by stimulating SHBG production.[125,126] OCPs can be the first-line therapy for the treatment of hirsutism.[126] Spironolactone, an aldosterone antagonist and competitive inhibitor of the androgen receptor, is also commonly used to treat hirsutism in women with PCOS. A systemic review showed that spironolactone (100 mg daily), compared with placebo, produced a greater reduction in hirsutism (−4.8 in Ferriman-Gallway scores).[127] Cyproterone acetate, a 17-hydroxyprogesterone acetate derivative, blocks androgen receptors and has been used for the treatment of hirsutism and acne; however, it is not currently available in the United States. Finasteride, an inhibitor of 5 α-reductase, produces a 30% to 60% reduction in hirsutism score in most studies.[128] Because none of these agents has been shown to produce consistent improvement in either ovulation or pregnancy rates, and because of concerns regarding their teratogenicity, antiandrogens are not used in treating infertility in PCOS, although contraceptives can be used as part of in vitro fertilization protocols (discussed later).

Surgical management

Surgical management of anovulatory infertility includes traditional ovarian wedge resections, laparoscopic diathermy, and laser drilling.[129] These procedures may restore ovulatory cycles; however, given the invasive nature of these surgical procedures and the development of other medical treatment options, today these surgical management techniques are seldom used for treatment of infertility. In addition, some of the side effects from surgery (pelvic adhesions) may impair fertility.[130] In summary, surgical procedures for treating infertility in PCOS are mostly of historical significance.

In vitro fertilization

In patients with PCOS, in vitro fertilization (IVF) should be considered for the following indications: failure of nonpharmacologic and clomiphene treatment, failure of gonadotropin/intrauterine insemination, or in cases of a high response to FSH (4 or more follicles) despite low gonadotropin dose. As in all patients, when PCOS is combined with tubal disease, male factor infertility, severe endometriosis, and/or patients requiring a preimplantation genetic diagnosis, IVF should be considered. A limited report with a small number of patients (N = 16) suggested that, in women who are older than 30 years and who have increased androgen levels, proceeding directly to IVF may be most cost-effective once clomiphene treatment fails.[131]

A variety of stimulation regimens for patients with PCOS undergoing IVF have been reported, including protocols based on GnRH agonists and GnRH antagonist. Before the use of GnRH antagonists in IVF stimulation, we developed a protocol that involves dual pituitary suppression with oral contraceptives for 28 days with a GnRH agonist overlap during the last 7 days of the OCP (**Fig. 4**).[132] Low-dose stimulation with FSH (150 IU/d) is started on the third day of withdrawal bleeding. Among 73 patients with a total of 99 cycles, only 13 cycles (13.1%) were canceled before embryo transfer. The causes for cancellation included poor response (low estrogen level and few follicles), hyperresponse (>25 follicles with a high estrogen level of >3000 pg/mL), or estrogen reduction of more than 20% after human chorionic gonadotropin (hCG) trigger. Eight patients experienced mild to moderate OHSS. The clinical and ongoing pregnancy rates were 46.5% and 40.4%, respectively.

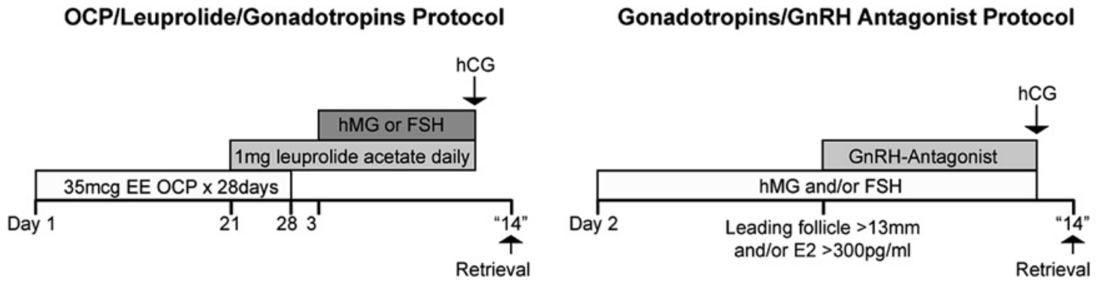

Fig. 4. Representative IVF ovulation induction protocols used at the Center for Reproductive Medicine at Weill Cornell Medical College.

Recently, a randomized controlled trial comparing GnRH agonist–based versus GnRH antagonist–based protocols in 220 women with PCOS showed that the clinical pregnancy rates were similar in the two groups (50.9% vs 47.3%, respectively).[133] However, the incidence of moderate OHSS was higher in the agonist, compared with the antagonist, group (60% vs 40%, respectively, *P*<.01).

Ovarian stimulation for IVF can be achieved using pure FSH,[134] human menopausal hormones (hMG) alone,[135] or a combination of the two.[136] Addition of clomiphene (100 mg, cycle days 3 to 7, for 5 days) to hMG/GnRH antagonist may produce improved results.[137] A meta-analysis that compared the overall IVF outcome in women with PCOS using different stimulation protocols with controls without PCOS, revealed a higher cancellation rate, an increased number of oocytes per retrieval and a lower fertilization rate in the PCOS group.[138] However, both groups had a similar clinical pregnancy and live birth rates. Regardless of the type of gonadotropins used (pure FSH or hMG, with or without clomiphene), GnRH antagonist–based protocols significantly reduce the incidence of OHSS,[133,139] especially if GnRH agonist is used to trigger ovulation.[140,141] Metformin cotreatment before or during IVF stimulation also reduces the risk of OHSS.[142]

An early report of patients with PCOS undergoing IVF showed that stimulation of ovulation was associated with a sharp increase of E2 levels and an exceedingly high number of developing follicles. The excessively high follicle number and E2 levels are associated with a high incidence of severe OHSS after hCG administration.[143] Several approaches have been suggested to decrease the incidence of OHSS in patients with PCOS. Our approach includes individualization of stimulation protocols (using the lowest effective gonadotropin dose) based on antral follicle count and anti-mullerian hormone levels, using antagonist-based protocols with a GnRH agonist triggering, and coasting. Coasting is a term to describe the technique of withholding gonadotropins when E2 levels exceed 3000 pg/mL during stimulation in an effort to starve small follicles and allow larger follicles to continue to develop. Coasting seems to reduce (but not to eliminate) the incidence of OHSS.

More recently, the advent of GnRH antagonist protocols has allowed us to trigger an endogenous LH surge with GnRH agonist, resulting in a short-lived LH surge compared with the longer surge observed after hCG, which has a longer half-life.[144] If the E2 level is more than 3000 pg/mL on the triggering day, we recommend using GnRH agonists instead of hCG to trigger ovulation. When a GnRH agonist trigger is used, luteal estrogen and progesterone supplementation should be prescribed.[140]

In vitro maturation (IVM) involves the recovery of immature oocytes from women with PCOS on cycle day 10 to 14 after a withdrawal bleed.[145] The immature oocytes are then incubated in maturation medium in the presence of FSH and LH. Following maturation, the oocytes are fertilized by intracytoplasmic sperm injection (ICSI), and the resulting embryo is transferred into the uterus on day 2 or 3 after ICSI.[145] Before immature oocyte retrieval, FSH priming has been reported to produce varying results.[146,147] Compared with conventional IVF, the advantages of IVM include lower risk of OHSS, less complicated stimulation procedures, and reduced cost. At experienced centers, the clinical pregnancy and implantation rates in women with PCOS following IVM are 30% to 35% and 10% to 15%, respectively.[146] Despite the lack of randomized trials comparing IVM with conventional IVF in women with PCOS,[148] we suggest that IVM should be considered if the patient has a history of poor oocyte quality.

Currently, we recommend the use of an antagonist-based protocol with and without clomiphene. We initiate coasting when the E2 level exceeds 3000 pg/mL, as mentioned earlier, or in the setting of numerous immature follicles (<16 mm) with a rapidly increasing E2 level. If the E2 level does not decrease to less than 3000 pg/mL after 4 days of coasting, we cancel the cycle. If the patient has progressive clinical signs of OHSS after oocyte retrieval, we consider canceling the transfer and freezing all the embryos. In the absence of pregnancy, OHSS is generally limited to the luteal phase in the setting of a conservative stimulation protocol. The avoidance of hyperstimulation syndrome is most effectively accomplished with a conservative approach to stimulation. Once hCG is administered in the setting of greater than 30 follicles or E2 greater than 6000 pg/mL, OHSS is almost unavoidable, even in the absence of pregnancy.

RISK OF PCOS FOR THE OFFSPRING DURING PREGNANCY AND BEYOND

During pregnancy, women with PCOS have a significantly increased risk of complications, both maternal and fetal. These complications include early pregnancy loss, gestational diabetes mellitus (GDM), pregnancy-induced hypertension, preeclampsia, delivery by cesarean section, premature delivery, and increased perinatal mortality.

Early Pregnancy Loss

Early pregnancy loss, defined as miscarriage of a clinically recognized pregnancy during the first trimester, occurs in 30% to 50% of women with PCOS compared with 10% to 15% of women without PCOS.[149–151]

Mechanisms of early pregnancy loss in women with PCOS are not well understood. Obesity and hyperinsulinemia (insulin resistance) are independent risk factors for early pregnancy loss.[152] Decreased levels of glycodelin, a glycoprotein produced from endometrium to protect the embryo from immune response, and reduced IGFBP-1, as well as increased levels of plasminogen activator inhibitor-1 (PAI-1), seem to increase the risk of early pregnancy loss.[153,154] Previous studies have suggested that women who hypersecrete LH are at increased risk for miscarriage[149]; however, a study by Clifford and colleagues[155] failed to show an improvement in miscarriage rates after suppression of endogenous LH before conception.

Small studies have suggested a protective effect of metformin on early pregnancy loss in women with PCOS. For example, in a study by Glueck and colleagues,[156] the rate of first-trimester pregnancy loss was significantly decreased to 11% in the metformin group, whereas it was 39% in the control group. In a retrospective study, Jakubowicz and colleagues[150] reported 8.8% pregnancy loss in the metformin group compared with 41.9% in the control group. The mechanism of metformin action responsible for the reduced early pregnancy loss is not understood but may include reduced glucose and insulin levels as well as PAI-1 activity. The assessment of the effect of metformin withdrawal on pregnancy is further complicated by the possibility of metformin withdrawal unmasking preexisting diabetes. Further studies are needed to examine the effect of metformin therapy on early pregnancy loss.

GDM

Insulin resistance develops during pregnancy because of the secretion of human placental lactogen (hPL). Because women with PCOS often have preexisting insulin resistance, they may be at an increased risk of GDM.

Studies of the correlation between GDM and PCOS produced conflicting results. Holte and colleagues[157] found a remarkably high prevalence of PCOS in the GDM population (41%). Other studies have been controversial, with both positive[158,159] and negative correlations between PCOS and GDM reported.[160] Higher incidence of GDM was observed in a lean PCOS population compared with women without PCOS; however, BMI values were not matched in this study (mean BMI 25 kg/m^2 in the PCOS group vs 23 kg/m^2 in the control group).[161] According to the meta-analysis by Boomsma and colleagues,[162] after weight matching, women with PCOS still had a significantly higher chance of developing GDM (odds ratio [OR] 2.94, 95% CI 1.70–5.08), with the increased risk of developing GDM being independent of obesity. However, Toulis and colleagues,[163] in a recent systematic review and meta-analysis, concluded that there was no consistent evidence for a higher risk of GDM in women with PCOS.

These conflicting results may be caused by the heterogeneity of PCOS and the diversity in screening methodology, diagnostic criteria, and predisposing factors for GDM (eg, ethnicity).[164]

In the first study to assess the impact of metformin on the risk of GDM, Glueck and colleagues[165] compared 33 nondiabetic women with PCOS who took metformin throughout the pregnancy versus 28 pregnant women with PCOS who did not receive this intervention. The incidence of GDM decreased significantly in the metformin group compared with the nonmetformin group (3% vs 31% respectively). A recent study in 137 pregnant women with PCOS compared pregnancy complication rates in 3 metformin intervention arms that differed in the duration of metformin therapy (4–8 weeks of gestation, 32 weeks, and throughout the pregnancy).[166] There was no significant difference in occurrence of GDM, but the rate of GDM requiring insulin therapy was significantly lower in the continuous metformin group compared with other groups.

Pregnancy-induced Hypertension and Preeclampsia

Women with PCOS are at high risk of pregnancy-induced hypertension (PIH). PIH occurs in 3% to 5% of pregnancies in previously normotensive women and usually develops during the third trimester.[167] The cause of PIH is likely multifactorial, involving immune, genetic, and placental abnormalities.[168]

The data on the association between PCOS and PIH are still conflicting. Initially, Diamant and colleagues[169] reported an increased incidence of preeclampsia in patients with PCOS, but the groups in this study were not matched for BMI. Gjonnaess[170] suggested that there was increased risk of preeclampsia (13%) in women with PCOS who have moderate to severe obesity. However, Mikola and colleagues[158] showed that PCOS had no predictive value for PIH, regardless of BMI, and a retrospective analysis by Haakova and colleagues[160] showed that there was no statistically significant difference in the rates of occurrence of PIH among PCOS and non-PCOS populations.

More recent studies have shown that PCOS may be an independent risk factor for PIH. Radon and colleagues[159] showed a significant increase in incidence of PIH in women with PCOS (OR 15.0, CI 1.9–121.5) after matching for BMI. Similarly, a recent meta-analysis by Boomsma and colleagues[162] showed a significantly higher chance of developing PIH in pregnant women with PCOS (OR 3.67, 95% CI 1.98–6.81). The rates of preeclampsia in this study were also higher among the women with PCOS (OR 3.47, 95% CI 1.95–6.17). De Vries and colleagues[171] reported a case-controlled study in pregnant women with similar BMI with and without PCOS . In spite of a similar occurrence of PIH, a significantly higher occurrence of preeclampsia was observed in the PCOS group (14%) compared with controls (2.5%).

Several studies noted an association between PIH and hyperinsulinemia. Hamasaki and colleagues[172] conducted a prospective study that showed that hyperinsulinemic pregnant women have higher systolic and diastolic blood pressures, with hyperinsulinemia appearing to constitute an independent risk factor of PIH. The hypothetical mechanisms for this association include endothelial dysfunction caused by hyperinsulinemia, or the stimulatory effect of insulin on blood pressure via stimulation of the sympathetic tone.[173]

Nawaz and colleagues[166] presented data on 137 pregnant women with PCOS divided into 3 different metformin intervention arms to compare pregnancy complications. Rates of PIH were 43.7% in group A (metformin continued until 4–16 weeks of pregnancy), 33% in group B (metformin continued until 32 weeks of pregnancy), and 13.9% in group C (metformin continued throughout the pregnancy), suggesting the benefit of continuous use of metformin during pregnancy for reduction of PIH. There were no adverse fetal or maternal effects of metformin.

Perinatal Care

According to a meta-analysis by Boomsma and colleagues,[162] there is a significantly higher rate of premature delivery (OR 1.75, 95% CI 1.16–2.62), admissions to an neonatal intensive care unit (OR 2.31, 95%CI 1.25–4.26), and perinatal mortality (OR 3.07, 95% CI 1.03–9.21) in PCOS pregnancies. However, there seems to be no significant differences in the rates of cesarean sections,[174] Apgar score,[158] or the occurrence of neonatal malformations.[162]

Birth Weight

It remains controversial whether offspring of women with PCOS are large, normal, or small for gestational age. Several early studies and case reports suggested that offspring of women with PCOS tended to have low gestational weight. Low birth weight has been associated with the development of type 2 diabetes and cardiovascular disease later in life.[175] In contrast, maternal obesity and diabetes are known to pose an increased risk for large fetal size, obesity, and glucose intolerance in the offspring.[176] Several lines of evidence support a hypothesis that there is an association between low birth weight and PCOS.[177] Female sheep treated prenatally with testosterone had reduced birth weight and impaired insulin sensitivity in early postnatal life.[178] Girls with premature pubarche and features of PCOS have a history of being significantly smaller for gestational age.[179,180] A prospective study by Sir-Petermann and colleagues[181] showed that there is increased prevalence of infants who are small for gestational age in women with PCOS compared with normal women.

However, several other studies failed to confirm association between PCOS and alterations in birth weight in singleton pregnancies. According to the meta-analysis by Boomsma and colleagues,[162] when only higher validity studies were considered (for example, those that matched BMI between women with PCOS and controls), no significant difference in birth weight was observed.[162] Legro and colleagues[177] recently published a family-based study of birth weight in PCOS that included approximately 1000 individuals, consisting of both women with PCOS and their family members. Compared with controls, PCOS family members in this study did not have any significant alterations in birth weight.

Risk of PCOS for Female Offspring

Female offspring of women with PCOS may have a higher risk of developing PCOS,[46,182,183] although the precise incidence in the offspring is unknown. The genetic component, supported by strong familial associations,[44–46] and the environmental component, including programming from intrauterine hyperandrogenemia, may affect the risk of developing PCOS.[43]

Prenatally androgenized female monkeys have approximately 40% to 50% fewer menstrual cycles than normal females.[42] In addition, 40% of prenatally androgenized women, compared with ~14% of controls, have polyfollicular ovaries that resemble the morphology of polycystic ovaries.[42] In one cross-sectional study, daughters of women with PCOS had increased LH and testosterone levels, hyperinsulinemia, and an increase in ovarian size during puberty.[184]

Risk of Metabolic Disorders for the Female Offspring

Offspring of PCOS mothers tend to suffer from metabolic abnormalities in later life.[185,186] Prenatally androgenized female rhesus monkeys develop metabolic problems characteristic of women with PCOS, namely decreased insulin sensitivity and abnormal pancreatic β cell function, as well as increased total body adiposity.[187] The timing of fetal androgen exposure seems to be an important factor in determining phenotypic presentation of the offspring.[42] Eisner and colleagues[188] showed that the offspring of the female monkeys that were treated early (from gestational day 40) had impaired insulin secretion, whereas the offspring of the late-treated (from gestational day 100–115) females showed decrements in insulin sensitivity with increasing adiposity, but preserved normal insulin secretory function.[187] Early androgen–treated female monkeys also had increased visceral fat compared with controls, even after correcting for BMI and total body fat.

Risk for the Male Offspring

Multiple possible phenotypes for male offspring of women with PCOS have been proposed. Manifestations include increased body hair growth, premature male balding, and metabolic abnormalities, such as insulin resistance.[185] There seems to be an increased risk of coronary heart disease in male offspring of mothers with PCOS. The mechanism is not clear, but may involve insulin resistance that develops because of exposure to intrauterine hyperandrogenemia.[43,185] Adult male rhesus monkeys exposed to exogenous testosterone in utero have insulin resistance and impaired insulin secretion.[189]

Norman and colleagues[190] was the first study to report hyperinsulinemia in male first-degree relatives of women with PCOS, although only 5 families were studied. Recabarren and colleagues[185] recently conducted a controlled study of male offspring of women with PCOS (80 boys from women with PCOS vs 56 boys from a control population), to assess the metabolic profiles in different chronologic stages. They found that there was no significant difference in birth weight between the 2 groups; however, there was an increase in body weight in the male offspring of women with PCOS beginning in early infancy (2–3 months). This excessive body weight persisted into adulthood. In addition, insulin resistance developed during adulthood and was independent of body weight.

GENETICS/GENETIC COUNSELING

PCOS has strong familial clustering,[44–46] therefore, as mentioned previously, a genetic cause has been suspected. Several lines of evidence suggest that PCOS is heritable, and various approaches have been used in an attempt to define a specific genetic risk. Despite the extensive studies, the lack of reliable associations between genotype and phenotype raises the possibility that inheritance of PCOS, if any, is probably multifactorial and modified by environmental factors. Thus far, all initial examined candidate genes (**Box 4**), including those involving insulin signaling pathways, regulation of ovarian folliculogenesis, or theca cell androgenesis, have failed to maintain the strong linkage to a PCOS phenotype.[191]

The strongest evidence for an association of a single gene with PCOS is the nucleotide repeat microsatellite marker, D19S884, which lies within intron 55 of the fibrillin-3 gene. This gene is located on chromosome 19, close to the insulin receptor gene and resistin gene, and may relate to insulin resistance and β cell dysfunction.[192,198,209–211] However, because the m-RNA expression of fibrillin-3 in the human ovary is less pronounced than that of other fibrillins (1 or 2), it is still not clear whether or how fibrillin-3 contributes to the pathogenesis of PCOS. Recently, a new single-nucleotide polymorphism linked to PCOS in the pro-opiomelanocortin (POMC) gene

Box 4
PCOS candidate genes

Pathway and protein

Insulin secretion and action related

- Insulin receptor (INSR)[191,192]
- Insulin receptor substrate[193]
- Calpain 10 (CAPN10)[194,195]
- PPAR γ[196,197]

Gonadotropin secretion and action

- Follistatin (follistatinlike 3) (FST)[191]
- Activin receptor (ACTR2A)[191]
- Inhibin (INHBA, INHBB)[191]

Obesity and energy metabolism

- Pro-opiomelanocortin (POMC)[198,199]

Androgen biosynthesis

- Androgen receptor (AR)[200]
- Small glutamine-rich tetratricopeptide repeat (TPR)-containing protein α (SGTA)[201]
- Cytochrome P-450c17 (CYP17)[202]
- Cytochrome P-450c11α (CYP11 α)[203,204]
- Sex hormone-binding globulin (SHBG)[205,206]

Others, unclear role

- Feminization-1B (FEM 1A, FEM 1B)[207,208]
- Fibrillin-3 (FBN3)[192,198,209–211]

was also reported[198,199] but, once again, the significance of this finding remains unclear. Similar to other complex diseases, including diabetes, genetic research in PCOS remains challenging and is confounded by the extreme heterogeneity of PCOS.

SUMMARY

PCOS is a complex disease, characterized by variable phenotypes, and whose cause remains unclear. It is characterized by anovulation, hyperandrogenism, and polycystic ovaries. Infertility is commonly present and a variety of methods have been used successfully to achieve pregnancy in women with PCOS. Maintenance of pregnancy is complicated by a higher rate of premature spontaneous abortions and an increased risk of GDM, hypertension, and preeclampsia. However, with careful monitoring and treatment, the outcome of pregnancy in most women with PCOS is excellent.

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