Obstetric complications in women with IVF conceived pregnancies and polycystic ovarian syndrome

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is often accompanied by infertility that necessitates ovulation induction using clomiphene citrate, gonadotropins or even *in vitro* fertilization (IVF). These treatment methods are known to increase the incidence of multiple pregnancies as well as some negative consequences, including a rise in the risk for gestational diabetes mellitus, pre-eclampsia, etc., Furthermore, pregnancies established after IVF carry an increased risk for maternal complications. However, the increased risk of developing adverse obstetric complications has been suggested to occur independently of obesity as well as in populations without assisted reproductive techniques. Many studies have been performed to study the effect of PCOS on pregnancy and the effect of pregnancy on PCOS. The hormonal milieu that is exaggerated in PCOS women is quite well understood at the biochemical and genetic levels. The maternal and neonatal outcomes of PCOS women who have undergone *in vitro* fertilization-embryo transfer (IVF-ET) have not been widely studied till date. This review aims to evaluate the current evidence regarding adverse obstetric outcomes of PCOS women undergoing IVF–ET. The rationale of this review is to study whether the adverse obstetric outcomes are increased in PCOS women in general, or particularly in those PCOS women who are undergoing IVF–ET. It is also important to analyze via a literature review whether the increased adverse outcomes are due to infertility in general or PCOS *per se*. An attempt has been made to give evidence regarding preventive strategies for obstetric complications in PCOS women who have undergone IVF-ET.

KEY WORDS: ART, assisted reproduction, *in vitro* fertilization, obstetric outcomes, pregnancy outcomes, polycystic ovaries, polycystic ovarian syndrome

INTRODUCTION

Polycystic ovarian syndrome (PCOS) has always been an enigma, and it still continues to be. Stein and Leventhal were the first to recognize an association between the presence of polycystic ovaries and signs of hirsutism and amenorrhea.[1] But, the PCOS that Stein and Leventhal discovered is much beyond what they had thought. Further biochemical, clinical and endocrinologic studies revealed an array of underlying abnormalities, and the impact of this heterogeneous endocrine syndrome is not only on the physical characteristics, ovulation and infertility but also after conception.

PCOS is one of the most common endocrine disorders in reproductive age group women. Typically, PCOS is first identified during the early reproductive years, either due to irregular menses, hirsuitism, weight gain or, very commonly, as a workup for infertility. PCOS is of clinical and public health importance as it is very common, with a prevalence of 6-10% and up to 15% in the reproductive age group, if the Rotterdam criteria are broadened.[2]

RATIONALE

Many studies have been performed to study the effect of PCOS on pregnancy and the effect of pregnancy on PCOS. The hormonal milieu, which is exaggerated in PCOS women, is quite well understood at the biochemical and genetic levels. The maternal and neonatal outcomes of PCOS women who have undergone *in vitro* fertilization-embryo transfer (IVF-ET) have not been widely studied till date. This review aims to evaluate the current evidence regarding adverse obstetric outcomes of PCOS women undergoing IVF–ET.

The rationale of this review is to study whether the adverse obstetric outcomes are increased in PCOS women in general, or particularly in those PCOS women who are undergoing IVF–ET. It is also important to analyze via a literature review whether the increased adverse outcomes are due to infertility in general or PCOS *per se*. An attempt has been made to give evidence regarding preventive strategies for obstetric complications in PCOS women who have undergone IVF–ET.

HORMONAL MILIEU IN NORMAL PREGNANCY

Normal pregnancy is characterized by the induction of insulin resistance associated with compensatory hyperinsulinemia in the second and third trimesters. This insulin resistance of normal pregnancy is a physiologically advantageous adaptation designed to restrict maternal glucose uptake and to ensure shunting of nutrients to the growing fetus. It is probably mediated by increases in the hormonal levels of estradiol, progesterone, prolactin, cortisol, human chorionic gonadotropin, placental growth hormone (PGH) and human placental lactogen (HPL).

HPL and PGH are the hormones mainly responsible for insulin resistance in pregnancy. HPL is responsible for the adaptive increase in insulin secretion necessary for pregnancy and for diversion of maternal carbohydrate metabolism to fat metabolism in the third trimester. PGH seems to be a paracrine growth factor probably regulating the metabolic and growth needs of the fetus partially. The induction of hyperinsulinemic insulin resistance in transgenic mice with PGH has recently been demonstrated.[3] They also demonstrated abnormalities in insulin signaling in the skeletal muscle tissue of these mice, which bear a remarkable similarity to the tissue found in normal pregnant women.

There is an approximately 200–250% increase in insulin secretion in lean women with normal glucose tolerance with advancing gestation.[4] However, there is comparatively less-robust increase in insulin levels of obese women with normal glucose tolerance. In normal pregnancy, there is a decreased expression of the Glucose transporter type 4 (GLUT-4) transporter in maternal adipose tissue,[5] but not in skeletal muscle. Skeletal muscle is the main site of insulin-mediated glucose disposal *in vivo*. Hence, the mechanisms for insulin resistance in normal pregnancy lie in the skeletal muscle either in the insulin signaling pathways or in the abnormal GLUT-4 translocation.[6]

DISTURBED HORMONAL MILIEU IN PCOS WOMEN DURING PREGNANCY

Hyperandrogenism and insulin resistance form the metabolic hallmark of PCOS women. A significant section of lean PCOS women have baseline intrinsic insulin resistance. Those with superimposed obesity have additional insulin resistance contributed by the excess adipose tissue. The baseline insulin resistance seems to be exacerbated with entry into pregnancy. There is an increased risk of pregnancy complications in PCOS women.

There is an increasing body of evidence suggesting a negative effect of PCOS on pregnancy outcome. Normal pregnancy induces a state of insulin resistance, which may become manifest as impaired glucose tolerance or gestational diabetes.[7] Because women with PCOS have an incidence of insulin resistance of 50-70%, they would appear to be at an increased risk of developing gestational diabetic complications.[8] Moreover, the "Barker hypothesis" of fetal programming *in utero* suggests that the fetal nutrition and endocrine environment (e.g., hyperinsulinemia) may effect neuroendocrine systems regulating body weight, food intake and metabolism, with consequences for long-term health in the offspring.[9]

Consequently, the extent to which the risk of adverse pregnancy outcomes in women with PCOS is attributed to the underlying disorder or infertility treatment is uncertain. The following article reviews the adverse obstetric outcomes in PCOS women who have undergone IVF–ET.

EARLY PREGNANCY LOSS

PCOS women are at a risk of early pregnancy loss (EPL), defined clinically as the first trimester miscarriage. EPL occurs in 30-50% of PCOS women compared with 10–15% of normal women.[10,11]

The probable pathophysiology for EPL in PCOS can be explained by Chart 1 below.

When the EPL rates were studied in PCOS women who concieved spontaneously, and compared with the EPL rates among PCOS and non-PCOS women who conceived with IVF–ET, there was no statistically significant difference between the two groups; PCOS IVF–ET group - 17% miscarriage, non-PCOS IVF-ET group - 15% miscarriage.[12]

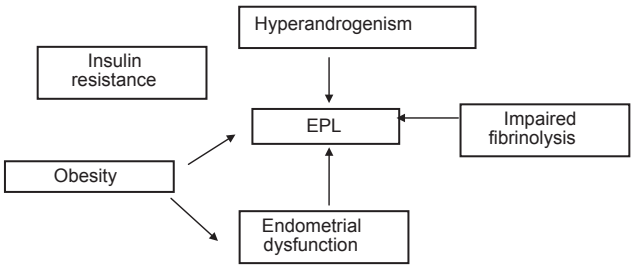

Chart 1: Pathophysiology of early pregnancy loss in PCOS

It has also been noted that the rate of polypoid embryos was increased after IVF in PCOS compared with non-PCOS patients.[13] Hypofibrinolysis due to increased plasminogen activator inhibitor might also be an independent risk factor for miscarriage in PCOS.[14] Finally, insulin resistance, the major pathophysiology of PCOS, has been proposed to play an essential role in the development of spontaneous abortion.

Irrespective of whether PCOS women conceived with or without IVF–ET, metformin has proven to reduce EPL in these women with disturbed hormonal milieu.[10,15]

OVARIAN HYPER STIMULATION SYNDROME

For obvious reasons, because there are a higher number of follicles in PCOS women, even a smaller dose of gonadotropin can blast the ovaries. Although a minority of PCOS is known where the follicles do not respond to even higher doses of gonadotropin, this remains a small group of women. Majority of PCOS women undergoing controlled ovarian stimulation (COH) require lower gonadotropin than controls (women without PCOS undergoing IVF–ET). In a study that compared the OHSS rates between PCOS and non-PCOS women undergoing IVF–ET, they found that the dosage of gonadotropin was significantly lower and the OHSS rate higher in PCOS and polycystic ovary groups than in the control group ($P < 0.05$).[16]

ECTOPIC PREGNANCY

The association between ectopic pregnancy in PCOS versus non-PCOS women undergoing IVF–ET has also been studied. In a study that included 5339 women who had clinical pregnancies after IVF treatment (PCOS, 205 women; non-PCOS, 5134 women) sought to assess the association between PCOS and ectopic pregnancy after IVF–ET. PCOS was associated with an increased risk of ectopic pregnancy after COH in fresh ET cycles but not in cryo-thawed ET cycles. A possible explanation is that compared with women without PCOS, women with PCOS appear to hold a lower threshold of hyperphysiologic estradiol level, which triggers the occurrence of ectopic pregnancy after COH.[17]

CERVICAL INCOMPETENCE

In a large, diverse, community cohort of pregnant PCOS women, a surprisingly high frequency of CI was found, with a prevalence in the range of 3% and incidence rate of 18 per 1000 births compared with lower reported estimates of CI in the general obstetric population.[18-20]

PCOS women with CI were also more likely to have received gonadotropin therapy.[21] Future studies should examine whether natural and hormone-altered PCOS is a risk factor for CI, the role of race/ethnicity, fertility drugs and consideration for heightened mid-trimester surveillance in higher risk subgroups of pregnant women with PCOS.

Gestational diabetes mellitus

GDM is defined as the onset or first recognition and diagnosis of glucose intolerance during pregnancy. The diagnostic criterion for GDM is the 75 g, 2-h oral glucose tolerance test (OGTT).

Chronically elevated luteinizing hormone (LH) and insulin resistance are two of the most common endocrine aberrations seen in PCOS. *In vitro* and *in vivo* evidence offer support that high LH and hyperinsulinemia work synergistically, causing ovarian growth, androgen production and ovarian cyst formation. Obesity, which is seen in 50-65% of PCOS patients, may increase the insulin resistance and hyperinsulinemia. One important caveat is that the correlation between hyperandrogenism and insulin resistance has been recognized in both obese and non-obese anovulatory women. Thus, it is important to realize that a non-obese patient may also have insulin resistance. However, the insulin levels in obese women are higher than their non-obese counterparts.[22,23]

Insulin resistance can be characterized as impaired action of insulin in the uptake and metabolism of glucose. Impaired insulin action leads to elevated insulin levels, which causes a decrease in the synthesis of two important binding proteins: Insulin-like growth factor-binding protein (IGFBP-I) and sex hormone-binding globulin (SHBG). IGFBP-I binds to IGFBP-II and SHBG binds to sex steroids, especially androgens.

A recent meta-analyses of pregnancy outcomes in women with PCOS demonstrated a significantly higher chance of developing GDM for PCOS women (odds ratios of about 2.90).[24,25] But, the difference was not statistically significant when PCOS and non-PCOS groups were compared when they underwent IVF–ET. Similar results were re-inforced by another study, in which there was no difference between the two groups in the results of modified OGTT at 20 weeks of gestation (85 mg/dL vs. 77 mg/dL).[26]

However, when analyzing the available evidence separately, there were largely conflicting results: While most of the studies demonstrated an increased risk for GDM in PCOS women (odds ratios ranging from 1.15 to 22.15),[27,28] a few found odds ratios from 0.31 to 0.96.[29,30]

A comparison between the study designs revealed that the increased risks were predominantly found in cohort

studies rather than in case-control studies. In addition, meta-analyses revealed a significant heterogeneity between the analyzed studies.

Conversely, some studies did not seem to support a higher prevalence and previous history of PCOS in women diagnosed with GDM when compared with pregnancies in women with normal glucose homeostasis.[31,32]

Obesity, PCOS and diabetes in first-degree relatives have been described as risk factors for developing GDM and gestational impaired glucose tolerance, especially in young women and teenage pregnancies (<20 years).[33]

All in all, there is no solid evidence proving the increased risk for GDM in PCOS patients, but a trend assuming that the risk is, indeed, increased in women with PCOS is recognizable. Confronted with the wide clinical and pathophysiological spectrum associated with the syndrome, further studies are warranted to validate the existing data.

PRE-ECLAMPSIA

In spite of the noted characteristics that typically accompany PCOS (e.g., insulin resistance, obesity, etc.), the exact mechanisms responsible for hypertension in women with PCOS are yet to be clarified. Insulin resistance causes secondary hyperinsulinemia. Hyperinsulinemia may produce enhanced sodium retention,[34] increasing intracellular sodium and calcium and augmenting sympathetic activity, which may have a role in the development of hypertension.[35] Insulin also stimulates the release of insulin-like growth factor (IGF-1), which may contribute to the development of hypertension by determining vascular smooth muscle hypertrophy.[36] Furthermore, the obesity that is common in PCOS adds to the risk of hypertension. The higher level of androgens seems to be strongly related to blood pressure (BP) in women with PCOS who are not obese.

Although the mechanisms by which hyperandrogenemia mediate the higher BP in women with PCOS remain to be determined, it is possible that androgens may directly stimulate endothelin-1 or may stimulate the rennin–angiotensin system (RAS) to increase endothelin-1 thus leading to the expression of two powerful vasoconstrictors that could impact BP in these women.[37]

A recent meta-analysis observed a strong association between PCOS and pre-eclampsia.[38] Some studies have supported this finding[24,39] and others not.[40] It is well stated that women undergoing assisted reproductive technology are at an increased risk of hypertensive disease during pregnancy,[41,42] which has been attributed to the underlying cause of infertility.

SMALL FOR GESTATIONAL AGE/LARGE FOR GESTATIONAL AGE FETUSES

Pregnancy in a woman with PCOS does not give smaller babies, but they may result secondary to pre-eclampsia. On the contrary, even in the absence of GDM, pregnancy in a PCOS woman is more likely to give a large for gestation baby as compared with the non-PCOS cohort.

In one study,[43] the risk of being born small for gestational age in the offspring of women with PCOS was increased, whereas this could not be confirmed in other studies.[30,40,44]

Maternal glucose levels correlate with fetal birth weight, development of fetal macrosomia, fetal hyperinsulinemia and fetal body-fat percentage.[45] Cesarean section is performed more frequently in women with GDM, as the diagnosis "large for gestational age" due to elevated maternal glucose levels is associated with a higher incidence of adverse pregnancy outcomes in spontaneous delivery (e.g., shoulder dystocia). PCOS also seems to correlate with a lower rate of vaginal delivery compared with healthy controls,[46] although the higher incidence of cesarean sections correlates with the occurrence of obesity, as women with a normal body mass index (BMI) and PCOS have an incidence of cesarean section equal to that of age-matched controls.[24]

PERINATAL OUTCOME

A lot of focus has been given on the antenatal complications of women who have PCOS. Relatively lower attention has been given on the intra-partum and post-natal complications.

Recently, the first study was conducted to analyze the effect of PCOS on perinatal and neonatal outcomes. Infants born to mothers with PCOS were more likely to have low Apgar scores at 5 min and to experience meconium aspiration. These infants may be more susceptible to fetal distress during labor. However, there was no association with stillbirth, and the increased risk for neonatal death was not statistically significant.[38] These findings need to be confirmed in future studies.

SUMMARY – POSSIBLE PATHOPHYSIOLOGY FOR ADVERSE OUTCOMES IN PCOS

The pathophysiological mechanisms behind the increased risk of adverse pregnancy outcomes among women with PCOS are not fully known. In most large clinical trials,

PCOS was associated with being overweight and obese, with an increased risk of macrosomia and large for gestational age infants, even after adjustments for BMI. A higher prevalence of pre-eclampsia and gestational diabetes may account for increased fetal stress, leading to pre-term birth, low Apgar scores at 5 min and meconium aspiration. Women with PCOS have increased levels of androgens, which have been associated with the development of pre-eclampsia.[47] Metformin treatment during pregnancy does not seem to lower maternal androgen levels but has been shown to decrease severe pregnancy and post-partum complications, which may be mediated by reduced uterine artery impedance.[48,49]

Most of the studies do not support the notion that assisted reproductive technology mediates adverse pregnancy outcomes among women with PCOS.[12,24] This finding is supported by another study, which reported that adverse outcomes are attributable to the factors leading to infertility rather than to factors related to reproductive technology.[50]

WHAT WAS ALREADY KNOWN

PCOS is associated with increased obstetric adverse outcomes.

Women with PCOS undergoing assisted reproductive technology have increased risks of gestational diabetes, pre-eclampsia, etc.

WHAT THIS REVIEW ADDS

PCOS is often accompanied by infertility that necessitates ovulation induction, using clomiphene citrate, gonadotropins or even IVF.[24] These treatment methods are known to increase the incidence of multiple pregnancies as well as some negative consequences, including a rise in the risk for GDM, pre-eclampsia, etc.[51] Furthermore, pregnancies established after IVF carry an increased risk for maternal complications.[52,53] However, the increased risk of developing adverse obstetric complications has been suggested to occur independently of obesity as well as in populations without assisted reproductive techniques.[24,25]Irrespective of the use of assisted reproduction, PCOS is associated with adverse obstetric outcomes.

In conclusion, women with PCOS are at an increased risk of adverse pregnancy and perinatal outcomes, which could not be explained by assisted reproductive technology. These women may need increased surveillance during pregnancy and parturition. Future research would benefit from focusing on glucose control, medical treatment and hormonal status among women with PCOS during pregnancy.

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