

Review Article

PATHOGENESIS OF REPEATED ABORTION IN POLYCYSTIC OVARIAN SYNDROME (PCOS)

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ABSTRACT

Early abortion occurs in approximately 15% of all detected pregnancy. However, the actual incidence rate of early abortion is 2-4 times higher in whole pregnancies, either detected or undetected. The causing factors of repeated abortion were uterine anatomy abnormalities (12%-16%), endocrine abnormalities (17%-20%), infection (0.5%-5%), immunological problems (20%-25%), and others (about 10%). Endocrine factor related to the incidence of repeated abortion are luteal phase insufficiency, diabetes mellitus, thyroid disease, and polycystic ovarian syndrome (PCOS). An epidemiological study reported the incidence of repeated abortion among women with PCOS was about 82%. Such higher incidence is related to high level of luteinizing hormone (LH). Another study showed that the pathogenesis of repeated abortion in PCOS was highly complex, not only involving one factor, but it had mutual correlation among several factors. It was suggested that those factors were hyperinsulin, hyperandrogen, and uterine factors.

Keywords: repeated abortion, polycystic ovarian syndrome, luteinizing hormone, hyperinsulin, hyperandrogen, uterine factors

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INTRODUCTION

Abortion can be viewed as natural selection process to control the quality of conception outcome. Early abortion occurs in approximately 15% of all detected pregnancy. However, the actual incidence of early abortion is 2 to 4 times higher in whole pregnancies, either detected or undetected. Although 30-50% of the conceptions result in abortion, only 1% had repeated abortion (Speroff 2005). The factors of repeated abortion are uterine anatomy abnormalities (12%-16%), endocrine abnormalities (17%-20%), infection (0.5%-5%), immunological problems (20%-25%), and others (about 10%). Endocrine factor related to the incidence of repeated abortion are luteal phase insufficiency, diabetes mellitus, thyroid disease, and polycystic ovarian syndrome (PCOS). An epidemiological study reported the incidence of repeated abortion among women with PCOS was about 82%. Such higher incidence is related to high level of luteinizing hormone (LH), so the objective of the therapy is directed toward the reduction of LH serum level. Not all PCOS women with increasing LH level are successfully treated with such strategy (Schusct 2002; Speroff 2005). Another study showed that the pathogenesis of repeated abortion in PCOS was highly complex, not only involving one factor, but it also had mutual correlation among several factors. It was suggested that those factors were

hyperinsulin, hyperandrogen, and uterine factors (Balen 2001, 2005; Spuy 2004).

In view of the uterine factor, there are two proteins that play an important role, the glycodeilin and the insulin growth factor binding protein-1 (IGFBP-1). It is suggested that these proteins play vital role during implantation process. Glycodeilin is a glycoprotein produced by decidualized endometrial gland. The function of the protein was to maintain implantation by suppressing endometrial immune response against the embryo. The reduction of glycodeilin level may impair endometrial growth, resulting in increasing incidence of repeated abortion (Jacubowicz et al. 2004). IGFBP-1 is a protein that facilitates adhesion process of the embryo with endometrium during preimplantation. In non-pregnant women IGFBP-1 is produced by the liver and its production is suppressed by the insulin. During pregnancy, IGFBP-1 is produced by endometrium. It remains unclear how hyperinsulin mechanism is able to induce repeated abortion. It is suggested, however, that the reduction of endometrial glycodeilin and IGFBP-1 levels may result in disordered endometrial receptivity (inhospitable). This paper discusses the pathogenetic possibility of repeated abortion in polycystic ovarian syndrome (Jacubowicz et al. 2004).

PATHOGENESIS OF REPEATED ABORTION IN PCOS

LH Hypersecretion

In follicular phase, there is an increase of LH tonic secretion in PCOS women, which is expected to affect her fertility and the outcome of pregnancy. Such condition is secondary to the increase of estrogen level or results from amplitude pulse disorder and LH frequency. Hyperinsulinemia may also affect gonadotropic cells, which results in the increase of LH secretion (Balen 2005; Spuy 2004). This study investigated the effect of LH in follicular phase in relations with successful pregnancy, and was performed to infertile couples with normally menstrual cycle who wanted to have children. Those with high LH level who had successful pregnancy were 67% and those who ended with abortion were 65%. In contrast, if LH level is normal, the pregnancy successful rate will be 88% and abortion incidence is 12%. The conclusion of this study was that the increasing LH secretion resulted in fertilization disorder and embryonal survival (Spuy 2004).

Watson (2004) conducted a retrospective study in patients with repeated abortion. In 81% of these patients he found polycystic appearance in their ovary. Increasing LH level in serum and urine was also found in 75% of the patients. Watson and Sagle suggested serial LH examinations, which is in accordance to the pulsatile-secreted LH characteristics (Balen 2005; Spuy 2004). There are several reasons to explain why the increase of LH level may cause early abortion. Uncorresponding LH level in follicular phase may result in early oocyte maturation whose mechanism is through the action inhibition by oocyte maturation inhibitor (OMI) (Balen 2005; Speroff 2005).

The increase of LH level results in secondary hyperandrogen. This condition impairs folliculogenetic process, resulting in incomplete granulotic cell function, which finally leads to the atresia of the follicle. The subsequent sequelae is the endometrial function disorder (endometrial non-receptivity) that leads to early abortion (Balen 2001, 2005; Spuy 2004). Other authors who supported this finding were the ones who provided therapy to infertile couples with high LH level. They found that the success of ovulation induction with clomiphene citrate was low, and, when the pregnancy was successful, the incidence of abortion was high. Homborg (1993) and Balen (1993) reported the result of retrospective study on the administration of gonadotropin-releasing hormone agonist (GnRH agonist) as compared to control before ovulatory induction with gonadotropin. It was found that the incidence of

abortion was reduced with GnRH agonist administration (Balen 2005). Clifford (1996), however, found different result. It was no use to conduct LH level suppression in order to reduce repeated abortion in PCOS. Both studies had principal difference. The Body Mass Index (BMI) in Homburg's study was 28.3 ± 5.9 while that in Clifford's was 19 - 25. This might have effect on the outcome of the conception (Spuy 2004). A study conducted in St. Mary's Hospital, London, by Regan's group revised the effect of increased LH concentration on repeated abortion and PCOS and also compared the final pregnancy outcome with that in normal women. There was no effect of the increase of LH concentration and testosterone level in the incidence of abortion. The patient was limited to women with natural pregnancy and BMI was within normal limit, so that it did not reflect the general characteristics of PCOS (Spuy 2004).

Hyperandrogen

Hyperandrogen is common in PCOS. Obesity amplifies the effect of androgen increase due to the reduction of sex hormone binding globulin (SHBG), resulting in the increase of free circulating bioactive androgens. The level of progesterone and androgen serum in early pregnancy can be used to predict pregnancy success. Increased ratio of free testosterone was found in patients who had abortion (Jacubowicz et al. 2004). Tulpalla et al. reported that PCOS with history of repeated abortion had higher androgen level as compared to that in women with successful pregnancy. In their study gonadotropine level was found normal, but the measurement was conducted only once, not reflecting, therefore, the actual endocrine disorder (Spuy 2004).

Higher testosterone concentration in repeated abortion was found as compared to normal. Okon et al. suggested that androgen is able to impair endometrial function, as well as prevent endometrial development during follicular and luteal phase. An in vitro study by the same group confirmed the inhibitory effect of androgen on cell growth and endometrial activity (Spuy 2004). There was an increase of androgenic change into estrogen within granulosa cells, resulting in the increase of estron and estradiol concentrations. This may result in the increase of LH level through positive feedback mechanism in the pituitary. Androgen may result in disordered fertility and impaired pregnancy success at ovarian, endometrial, and hypophysial levels (Jacubowicz et al. 2004; Speroff 2005).

Hyperinsulin

Along with LH hypersecretion, hyperinsulin results in the increase of ovarian androgenic production in the patients. Insulin resistance may occur in either in obese

or lean individuals. It has been reported that insulin resistance is related with the increased prevalence of repeated abortion. Change in lifestyle and diet modification that results in intraabdominal fat reduction and increased insulin sensitivity may relieve reproductive capability (Speroff 2005; Spuy 2004). Hypersinsulin may affect the success of pregnancy through its interaction with LH and androgen synthesis. Obesity itself may also affect the reproductive capability. Metformin increases insulin sensitivity and used in hyperinsulin PCOS individuals (Spuy 2004).

Several studies have been undertaken on the use of metformin in early abortion with PCOS. Retrospective study in women with metformin therapy by Jakubowicz et al. found an improvement in early abortion as compared to control (Jakubowicz et al. 2004). Glueck and his colleagues investigated post-gestational continuous administration of metformin, and they found the decrease of abortion incidence. Abortion incidence decreases from 62% to 26%. However, the direct effect of metformin remains unclear (Spuy 2004). Both studies revealed promising results, but the methodology employed in those studies was not randomized controlled trial (RCT). Although there is confirming evidence that the use of metformin will improve insulin sensitivity in the management of anovulation in PCOS, the evidence has not been sufficient to conclude the reduction of early abortion incidence (Spuy 2004).

Uterine Factor

Jakubowicz (2002) found that in pregnancy with PCOS at the first trimester, there was a decrease of glycodeilin level and IGFBP-1. Particularly in the first 2 months of pregnancy, glycodeilin serum and IGFBP-1 are very low as compared to that in normal pregnancy. However, IGFBP-1 serum remains low at the end of the first semester, while glycodeilin serum becomes equal to that in normal pregnancy (Jakubowicz et al. 2004). Glycodeilin has a role in maternal immune response mechanism by suppressing the reaction of lymphocytes and the activity of natural killer cells. Low glycodeilin level may reduce endometrial receptivity to maintain implantation and pregnancy. IGFBP-1 has a role as paracrine in maintaining fetal-maternal adhesion process. Low IGFBP-1 level in the endometrium may impair implantation process. This was suggested as having a role in the abortion mechanism among PCOS patients (Jakubowicz et al. 2004). The primary source of IGFBP-1 in the circulation is the liver. Insulin is able to inhibit IGFBP-1 production in the liver and endometrium. Low IGFBP-1 concentration in PCOS indicates its low production in the liver and endometrium (Jakubowicz et al. 2004).

The result of this study was consistent to other studies that also found glycodeilin level reduction in luteal phase among women with unexplained infertility and repeated abortion. These characteristics are also consistent to the results of studies on the effect of insulin sensitizing drug (metformin) on the increase of glycodeilin serum and IGFBP-1 in unpregnant PCOS women. The incidence of early abortion was also found to decrease after the woman was pregnant. There was positive correlation between IGFBP-1 serum level and glycodeilin and insulin sensitivity (Jakubowicz et al. 2004). Glycodeilin is synthesized by epithelial cells and IGFBP-1 by endometrial stromal cells. IGFBP-1 synthesis and secretion are regulated by serum insulin level. Insulin may affect directly or indirectly to endometrial layer. Epithelial function is often regulated by stromal factor, so that hyperinsulinemia is able to block stromal cell signal to the epithelium and, subsequently, the reduction of glycodeilin level ensues (Jakubowicz et al. 2004). The limitation of the study is that, instead of cohort, it used cross-sectional design, so that the rank and the causal relationship were difficult to establish. This study, for example, could not determine the reduction of glycodeilin level as the predictive marker of early abortion due to other causes or that glycodeilin deficiency itself triggers the pathologic process of abortion (Jakubowicz et al. 2004).

Other Factors

In order to identify pathogenesis that underlies early abortion in PCOS, several factors and causes, regardless of the PCOS endocrinopathy, have been investigated. The activity of abnormal plasminogen activator inhibitor (PAI) was suggested as the cause of repeated abortion due to abnormal placentation (Spuy 2004). Glueck et al. found an increase of PAI activity in PCOS and abortion. The author wrote that hypofibrinolysis mediated by the increase of PAI function in PCOS women may hold an important role in the high incidence of abortion and other pregnancy complications (Spuy 2004). Hyperinsulinemia affects PAI activity, so that it is believed that by restoring the patient's metabolic profile, such as the administration of metformin, PAI activity can be reduced and pregnancy complications can be decreased as well. Endothelial dysfunction has been found in PCOS, resulting in vascular reactivity disorder. Such condition is related with hyperandrogenemia and insulin resistance (Spuy 2004).

As has been previously explained, uterus is also a target of PCOS abnormal condition, such as high LH level (LH receptor also exists in the uterus) and hyperandrogenemia, which affects the increase of EGF receptor concentration (Spuy 2004). HOXA 10 is a vital

gene to regulate endometrial receptivity. In vitro studies found that HOXA 10 expression can be suppressed by testosterone, and testosterone can prevent the increase of HOXA 10. In normal condition, estrogen and progesterone are able to increase HOXA 10 gene expression. In PCOS cases, the reduction of HOXA 10 gene expression has been proved by endometrial biopsy. This may explain the effect of hyperandrogenemia on the occurrence of early abortion (Spuy 2004).

CONCLUSION

PCOS is related with anovulation and results in early abortion. Its definite diagnosis remains unclear, although several authors report the occurrence of disordered folliculogenesis and steroidogenesis processes, as well as gonadotrophin, androgen, and insulin secretion. The function of granulosa and thecal cells is also impaired, such as the inhibition of apoptotic process and local regulative mechanism (autocrine and paracrine). The underlying mechanism of abortion is the LH hypersecretion, which has been widely reported by many authors. Hyperinsulin and hyperandrogen are also regarded as central factors through the change that occurs in endometrial layer. Other suspected factors are the abnormalities in PAI activity and growth factor that confuse steroidogenetic process. Today, the possibility widely accepted by the experts is that hyperinsulin and hyperandrogen may result in disordered ovulatory process and the survival of the embryo. This effect occurs in the oocyte, endometrium, local factors (autocrine and paracrine) and the growth factor. Several therapies have been developed in the last decade, but the results remain controversial.

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