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REVIEW ARTICLE

Late pregnancy complications in polycystic ovarian syndrome

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Abstract

Gestational diabetes mellitus and new-onset hypertension, which includes gestational hypertension and pre-eclampsia, are common complications of pregnancy. Many features of the insulin resistance syndrome have been associated with these conditions. These include glucose intolerance, hyperinsulinemia, hypertension, obesity, and lipid abnormalities. Other accompanying abnormalities may include elevated serum levels of leptin, TNFα, plasminogen activator inhibitor-1 and testosterone. The establishment of these features before the onset of gestational diabetes mellitus and hypertension in pregnancy suggests that insulin resistance or associated abnormalities may play a role in these disorders. These observations suggest that therapeutic interventions to reduce insulin resistance may lower the risk of both gestational diabetes mellitus and hypertension in pregnancy. *Hippokratia 2006; 10 (3): 105-111*

Key words: *pregnancy, insulin resistance, gestational diabetes mellitus, hypertension in pregnancy,* pre-eclampsia

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Introduction

With a prevalence of 5%-10% the polycystic ovary syndrome (PCOS) is probably the most common endocrine abnormality in women of reproductive age[1-4]. Besides reproductive endocrine abnormalities, including amenorrhea or oligomenorrhea, hyperandrogenism and chronic anovulation, a key feature of PCOS is insulin resistance (nearly 80% of obese and 30% of lean women with PCOS demonstrate insulin resistance) with compensatory hyperinsulinemia and a β-cell dysfunction[5,6].

The presence of insulin resistance in PCOS has important later consequences upon health. Insulin resistance is associated with an increased risk for several disorders, including type 2 diabetes, hypertension, dyslipidaemia, endothelial dysfunction, elevated endothelin-1 and cardiovascular disease. This group of abnormalities coupled with insulin resistance constitutes the so-called "metabolic syndrome"[7]. Many women with PCOS show a phenotype similar to Syndrome X. Therefore, PCOS may be considered a component of the metabolic syndrome[8].

It has been demonstrated that women with PCOS present an increased risk for diabetes development and hypertension during pregnancy[9-18]. These complications might be attributed to the coexisted insulin resistance and β-cell dysfunction in a significant percentage of women with PCOS before conception[5,6].

Insulin resistance of normal pregnancy

Pregnancy is a complex metabolic entity that involves major alterations in the hormonal status as well as an increasing burden of fuel utilisation by the conceptus. In normal pregnancy, insulin resistance and compensatory hyperinsulinemia occur in the second and maximize in the third trimester of pregnancy. The insulin resistance of normal pregnancy is advantageous. It is regulated by placental hormones and is a physiological adaptation that ensures adequate amounts of maternal glucose to the increasing nutritional and growth demands of the developing fetus[17, 19-22].

The insulin resistance of normal pregnancy is probably mediated by several hormonal changes, including increases in serum levels of estradiol, progesterone, prolactin, cortisol, human chorionic gonadotropin, placental growth hormone and human placental lactogen. Human placental lactogen (hPL) has been considered as the main insulin resistance hormone of pregnancy[23]. Human placental lactogen presents its peak at thirty weeks of gestation and has been shown to have both insulin and anti-insulin effects. The major role of hPL may be the adaptive increase in insulin secretion necessary for pregnancy rather than the induction of insulin resistance. Tumour necrosis factor-alpha (TNF-α) was recently demonstrated to have a strong correlation with the insulin resistance of pregnancy but its role is not yet clear[24].

Human placental growth hormone (hPGH) is probably the main factor to mediate the insulin resistance of pregnancy, since it is known that chronically elevated levels of pituitary growth hormone have diabetogenic effects. Human placental growth hormone differs from pituitary growth hormone by 13 amino-acids[25]. It is not regulated by growth hormone releasing hormone (GH-RH) or inhibited by somatostatin analogues, but has the same affinity for the GH receptor as the pituitary growth hormone. By twenty weeks of gestation it replaces pituitary GH almost completely in the maternal

circulation. Human placental GH does not cross the placenta and appears to regulate the maternal levels of IGF-1. Maternal IGF-1 levels in plasma correlate with hPGH levels, not with hPL. Human placental growth hormone seems to be a paracrine growth factor, which through insulin growth factors may partially regulate the metabolic, and growth needs of the fetus. Barbour et al recently demonstrated in transgenic mice that hPGH, at levels similar to the third trimester of human pregnancy, causes severe insulin resistance, exhibited by both fasting and post-prandial hyperinsulinaemia; these mice require insulin levels that are five to seven times higher in order to maintain euglycaemia. They also demonstrate a marked decrease in insulin-induced GLUT-4 translocation to the plasma membrane. Additionally, Barbour et al found that the skeletal muscle tissue of these mice demonstrate abnormalities in insulin signaling which bear a remarkable similarity to that found in normal pregnant women and in pregnant women with gestational diabetes. These data suggest that human placental growth hormone may be a significant mediator of insulin resistance in normal pregnancy[26,27].

The insulin resistance of normal pregnancy has been well described. Nevertheless, the hormonal mechanisms by which insulin resistance is triggered remain a subject of debate. Normal pregnancy is characterized by a ´50% decrease in insulin-mediated glucose disposal and by a 200%-250% increase in insulin secretion in humans[20,28]. Hepatic gluconeogenesis is not normally suppressed by insulin. This procedure occurs in order to meet the metabolic demands of the fetus, of which glucose represents a 80% of the fetal energy, yet it maintains euglycaemia in the mother[29]. In normal pregnancy there is a decreased expression of the GLUT-4 glucose transporter protein in maternal adipose tissue[30] but not in skeletal muscle. Skeletal muscle is the main site of insulin-mediated glucose disposal *in vivo*, suggesting that the mechanisms behind insulin resistance in skeletal muscle lie or in the pathways for insulin signaling or in the abnormal translocation of GLUT-4 [31].

It has been demonstrated that in human incubated muscle fibres obtained at term by caesarean section from normal pregnant women with obesity, maximal insulin-stimulated 2-deoxyglucose transport was significantly reduced by 32% [31]. In these skeletal muscle fibres, normal pregnancy caused reduced insulin receptor tyrosine kinase activity toward IRS-1 as well as reduced expression of insulin receptor substrate-1 (IRS-1)[32]. Recent data in pregnancy also demonstrate increases in serine phosphorylation of the insulin receptor, which may prevent optimal binding of IRS-1 to phosphotidylinositol (PI) 3-kinase resulting in inhibition of GLUT-4 translocation[32].

Insulin resistance in gestational diabetes

In pregnancies complicated by gestational diabetes mellitus (GDM) further insulin resistance occurs and an inability to a compensatory increase in insulin secretion appears[20,28,33]. The pancreatic beta cell secretory defect is present in both obese and lean women with GDM. It has been demonstrated that overweight women who will develop GDM present insulin resistance prior to pregnancy as measured by a hyperinsulinaemic-euglycaemic clamp[20]. Insulin-mediated glucose disposal continues to decrease in the second and third trimester of pregnancy and is about two-thirds that of normal pregnant women matched for weight. Moreover, women with GDM improve their insulin resistance postpartum; however, they never achieve the same degree of insulin-mediated glucose disposal as normal pregnant women do.

Studies on muscle fibres from pregnant women undergoing caesarean section demonstrated that the mechanisms for skeletal insulin resistance in obese women with GEM involve impaired insulin receptor β-subunit tyrosine-phosphorylation and decreased IRS-1-phosphorylation and expression[31,32]. A significant decrease in maximal insulin receptor tyrosine-phosphorylation was demonstrated in muscle from obese GDM women compared to obese pregnant women[30,31]. This insulin receptor tyrosine kinase activity (IRTK) catalyses the phosphorylation of various insulin receptor substrates, particularly IRS-1, to undergo tyrosine-phosphorylation. While insulin receptor tyrosine-phosphorylation is impaired in GDM patients only, IRTK is significantly reduced by 23% in pregnancy and by 41% in the muscle fibres of GDM patients compared to obese non-pregnant controls. Conclusively, these data suggest a possible insulin receptor defect that may exacerbate the physiological effects of normal pregnancy.

Gestational diabetes mellitus in women with polycystic ovary syndrome

Gestational diabetes mellitus is detected in 3%-4% of pregnancies in women aged 15-49 years and is associated with an increased later risk for type 2 diabetes. Risk factors for gestational diabetes include obesity, age, genetic background, PCOS and ethnicity[34]. Fetal macrosomia in gestational diabetes increases the rates of birth trauma and cesarean section[35]. Diagnosis and management of gestational diabetes may reduce perinatal, neonatal, and long-term pediatric complications[34,35].

Insulin resistance and hyperinsulinemia all of which are risk factors for gestational diabetes characterize women with PCOS. These women, 46% of whom develop GDM[36], enter pregnancy with higher insulin resistance than normal women[36-41]. Women with PCOS probably develop GDM when pancreatic β-cells cannot overcome the superimposition of the physiological insulin resistance of pregnancy on their high preconception insulin resistance [9-14,36]. Women in whom gestational diabetes develops are likely to have underlying polycystic ovaries[42] and women with PCOS are likely to develop gestational diabetes[5,9,10,39].

Obesity, which characterizes a great percentage of

PCOS patients, has a deleterious additive effect on carbohydrate homeostasis and increases insulin resistance during gestation[43]. In normal women, high maternal insulin in early pregnancy promotes gestational weight gain and weight retention post-partum, increasing the risk of GDM and, later of type 2 diabetes mellitus [44]. Body mass index (BMI) >25 kg/m^2 is a major predictor of GDM[45].

Women with polycystic ovary syndrome often present with infertility [46,47]. Therefore, women with PCOS are older than the general population at conception, which is another risk factor for gestational diabetes[15].

The association among insulin resistance, metabolic syndrome, and androgen excess in PCOS has led to the use of insulin-sensitizing agent such as metformin with reported improvements in hyperinsulinemia and hyperandrogenemia. Treatment with metformin only, produced a modest reduction in weight and hirsutism in women with PCOS[48]. Metformin administration throughout pregnancy in women with PCOS reduces GDM, from 26%-31% to 3%-4% [13,49,50]. Thus, the frequency of GDM in women with PCOS on metformin does not differ from normal pregnant controls[15].

Metformin administration during pregnancy leads to a modification of the observed changes in insulin resistance during gestation. In women on metformin, serum insulin levels did not rise significantly during the first and the second trimesters of pregnancy compared to the last preconception visit. Moreover, on metformin there was no difference in fasting serum insulin levels between the third trimester (increase only 10%) and the last preconception visit on metformin, with insulin levels also lower in the third trimester than before metformin initiation[17]. Consequently, the expected changes during pregnancy, namely a significant increase in insulin and insulin resistance, were abated and blunted, by metformin, suggesting that metformin improves the "natural" insulin resistance changes during gestation in hyperinsulinemic PCOS women[10,17, 19,20,36].

A second benefit of metformin treatment in women with PCOS is weight maintenance before conception and weight loss throughout pregnancy, particularly evident in women with BMI 30-40 and ^{3}40Kg/m^2. These actions probably contribute to insulin resistance reduction and to the development of GDM[11-14].

A third effect of metformin treatment during pregnancy in women with PCOS is serum testosterone lowering, which, like the prevention of weight gain, is probably mediated through its insulin sensitizing action[51,52]. It has been proposed that high androgen levels during pregnancy in untreated women with PCOS could provide a potential source of androgen excess for the fetus, without leading to fetal virilization[53]. Metformin treatment throughout pregnancy in PCOS should reduce any putative risk of fetal virilization conferred through androgen excess[17].

Hypertensive disorders of pregnancy (HDP)

A percentage of 5%–10% of pregnancies are complicated by pregnancy-induced hypertension. This disorder is a major cause of maternal, fetal, and neonatal morbidity and mortality. Although complications of hypertensive disorders of pregnancy (HDP) have been recognized for centuries, the causes of these disorders remain poorly understood. Various data indicating associations of features of the insulin resistance syndrome and these disorders suggest that additional research is needed to elucidate the potential role of insulin resistance in the pathogenesis of pregnancy induced hypertension.

Hypertensive disorders of pregnancy include:

i) new onset of hypertension during pregnancy (gestational hypertension or preeclampsia),

ii) pre-existing hypertension, and

iii) exacerbation of pre-existing hypertension[54].

New-onset hypertension develops during the second half of pregnancy, usually in the third trimester in 3%-5% of women who were previously normotensive. Preeclampsia is a multi-system syndrome mainly characterized by proteinuria (300 mg protein or more over 24 h). Proteinuria due to glomerular endotheliosis and oedema secondary to increased vascular permeability represent only the "tip of an iceberg" of a widespread pathology arising from endothelial dysfunction and damage[18]. Other systemic manifestations include generalized intravascular coagulation, haemolysis, elevated liver function tests, and, rarely, seizures (eclampsia). Gestational hypertension, a generally more benign disorder, is diagnosed when blood pressure is elevated in the absence of the above findings. When other systemic manifestations of disease are absent, the distinction between preeclampsia and gestational hypertension is based on the presence and magnitude of proteinuria. It is not clear whether gestational hypertension and preeclampsia are different disease entities or different manifestations of the same disease process. It is possible that insulin resistance may play an important role in both of them. Twenty per cent of women with pre-existing hypertension develop superimposed preeclampsia, with its attendant risks.

The etiology of hypertensive pregnancy is uncertain and includes immune, genetic, and placental abnormalities. Three main hypotheses have been proposed regarding the metabolic alterations involved in the aetiology of hypertensive disorders in pregnancy, namely endothelial dysfunction and activation, oxidative stress and insulin resistance. All may contribute to the characteristic endothelial dysfunction of hypertensive disorders in pregnancy. Endothelial dysfunction may, in turn, underlie several critical features of preeclampsia, including vasoconstriction, hypertension, loss of the usual pregnancy-associated refractoriness to pressor effects of angiotensin II, increased platelet aggregation, and proteinuria[54].

It has been postulated that abnormalities of the placenta are the primary cause of preeclampsia. However, the observations that several metabolic abnormalities predispose to the development of preeclampsia, and that

these abnormalities are also observed in the non-pregnant state in women who have had preeclampsia, suggest that maternal features must also be considered.

All cases of new onset HDP are unlikely to be attributable to a single cause. Rather, different etiologies may lead to the same phenotype in different women.

Endothelial dysfunction and activation

Many markers of endothelial dysfunction have been observed in HDP. Coagulation activation proceeds weeks to months the clinical onset. The damaged endothelium of HDP is reflected by elevated levels of plasminogen activator inhibitor-1 (PAI-1) and von Willebrand factor[18]. Endothelial dysfunction is indicated by the elevated plasma levels of soluble adhesion molecules, which may be manifested before the clinical onset[55]. Although the increased serum levels of cytokines (TNFα, IL-6 and IL-8), observed only in the HDP group, indicated that endothelial activation is a consequence of abnormal trophoblast invasion, still additional factors are involved in its manifestation, which might be related to cytokine release.

Endothelial activation in HDP results in an enormous release of endothelin, thromboxane and superoxide, as well as an increased vascular sensitivity to the pressor effects of angiotensin II, and a decreased formation of vasodilators such as nitric oxide and prostacyclin by the damaged endothelium[56]. This may lead to an increase in total peripheral resistance, despite the increasing plasma volume of pregnancy, and thus to vasospasm and hypertension. However, a case control study, of non-pregnant, normotensive pregnant and HDP pregnant women, showed that nitric oxide (NO) and endothelin-1 production were increased in the hypertensive disorders in pregnancy group compared to the other groups[57]. The increased formation of the vasodilator NO was considered to be a compensatory response to the vasoconstriction and hypertension.

Oxidative stress

Oxidative stress is a component of HDP. The oxidative stress theory of HDP involves the hypothesis that the abnormal placentation and dyslipidaemia results in a release of free radicals, particularly superoxide anions, and lipid hydroperoxides, which damage the vascular endothelium [58]. Oxidative stress may link the decreased placental perfusion in HDP to the maternal response, via direct vascular damage and endothelial dysfunction.

Data from the literature support the view that antioxidant supplementation was associated with an improvement in biochemical indices of the disease. Evidently, these findings need further investigation via large randomised controlled trials, but raise the exciting possibility that antioxidants, either dietary or pharmaceutical, may have a role in the prevention of HDP in high-risk patients. It has been hypothesised that regular exercise enhances antioxidant enzymes in pregnant women, reduces oxidative stress and the incidence of HDP, and at the same time promotes a healthy lifestyle[59].

Insulin resistance

In women with HDP an exaggeration of insulin resistance and associated metabolic changes is noted. Although it is not clear to what extent these factors are pathogenic in hypertensive pregnancy, the available data suggest that some may play a role in the evolution of the disease, whereas others may be markers of the underlying disease process. Exaggerated hyperinsulinemia relative to normal pregnancy is well described in women with established gestational hypertension or preeclampsia. Studies upon insulin resistance have suggested differences between women with *de novo* hypertension in pregnancy and normotensive women as well.

Insulin resistance precedes the development of HDP. Various studies have documented hyperinsulinemia and/or hyperglycemia in early or midpregnancy, before the development of preeclampsia, gestational hypertension, or both[60,61]. Hyperinsulinemia may directly predispose to hypertension by increased renal sodium reabsorption and stimulation of the sympathetic nervous system[62]. Insulin resistance and/or associated hyperglycemia may impair endothelial function[63].

Two other factors, obesity and physical inactivity, are closely associated with insulin resistance, and are predictive of hypertensive pregnancy. A higher body mass index before pregnancy or early in pregnancy is associated with increased risk for both gestational hypertension and preeclampsia[60,64,65]. Moreover, increased gestational weight gain has also predicted risk for gestational hypertension[64] or preeclampsia[60], between 6 and 16 weeks. Additional factors, such as diet composition, may explain the association between gestational hypertension and gestational weight gain. Furthermore, it has been suggested that gestational diabetes, which itself is associated with underlying insulin resistance, is a risk factor for the development of hypertensive pregnancy. This association persists even after adjusting for obesity and maternal age[66].

Other putative factors associated\ with hypertensive disorders in pregnancy
Lipids

In women with established preeclampsia, serum triglyceride and free fatty acid levels have been found to be higher and high-density lipoprotein cholesterol levels lower than those in women with normotensive pregnancy [67]. Elevated total serum cholesterol, triglyceride and free fatty acid levels have been reported to antedate the development of either gestational hypertension or preeclampsia[68]. Oxidized lipids may impair endothelial function directly or indirectly by effects on prostaglandins, including increased synthesis of thromboxane and inhibited synthesis of prostacyclin[69]. Increases in small dense LDL and triglycerides may also contribute to impaired endothelial function.

Leptin

It has been reported that leptin levels as early as 20 weeks' gestation may predict the development of preeclampsia in a population of high risk[68]. Increased leptin levels may in part reflect maternal adiposity and have also been hypothesized to reflect placental insufficiency. Leptin might also contribute to endothelial dysfunction by increasing free fatty acid oxidation[70].

TNFα

It has been referred that TNFα or its receptor are elevated in women with established preeclampsia compared with normotensive controls[71]. Elevated TNFα levels in the early third trimester may predict the development of preeclampsia[72]. TNFα may promote hypercoagulability and increased lipolysis, with resulting impairment of endothelial relaxation.

PAI-1

PAI-1 is elevated in established preeclampsia and its increase is related to the severity of the disease. Among women at high risk for preeclampsia, the ratio of PAI-1 to PAI-2, the latter primarily produced by the placenta, was increased before the development of the disease. Increased PAI-1 may reflect impaired fibrinolytic function, which might predispose to the coagulopathy associated with preeclampsia[68].

Testosterone and SHBG

Total and free testosterone serum levels are higher in women with established preeclampsia compared with normotensive women. In the first trimester, lower SHBG but neither total nor free testosterone serum levels predicted the later development of preeclampsia[73].

Polycystic ovary syndrome, which is associated with insulin resistance, elevated testosterone, and low SHBG levels, has been linked to increased risk for pregnancy-induced hypertension even in the absence of associated obesity[74]. Androgens increase vasoconstriction in response to pressors[75]. Androgens also affect the prostaglandin balance, decreasing the synthesis of prostacyclin[76], and leading to increased platelet aggregation, which are both characteristics of preeclampsia.

Clinical implications and future directions

Although a cause and effect relationship between the insulin resistance syndrome and gestational diabetes mellitus and new-onset hypertension in pregnancy has not been proven, the associations between these conditions raise the possibility that interventions which improve insulin sensitivity may reduce the likelihood of these pregnancy complications. Because obesity is both a major contributor to insulin resistance and a well established risk factor for preeclampsia, interventions which are scheduled to reduce weight before pregnancy and/or to avoid excessive weight gain during pregnancy may be proved effective. Moreover, increased exercise, which improves insulin sensitivity, may also reduce risk. Given the well-recognized adverse effects of obesity on many pregnancy outcomes, including gestational diabetes and pregnancy-induced hypertension, these approaches might be worthy in women at high risk of these complications. Studies of pharmacological interventions, such as the use of metformin, may also warrant study in women at high risk for preeclampsia.

Multiple studies have demonstrated associations between markers of insulin resistance on one hand and gestational diabetes mellitus and hypertensive pregnancy on the other. Findings consistent with the insulin resistance syndrome have been observed before, during, and after these pregnancy complications. However, further work is needed in several areas. More data are needed to determine whether insulin resistance plays a causal role in the development of gestational diabetes mellitus, gestational hypertension, and preeclampsia. To improve our ability to identify women at risk for gestational diabetes mellitus and hypertensive pregnancy who might benefit from closer monitoring and intervention, large prospective longitudinal studies are needed to determine whether there are markers of insulin resistance with sufficient sensitivity and specificity to be clinically relevant. Studies should be designed to assess the effects of specific interventions directed to the insulin resistance syndrome on the risk of developing these complications in pregnancy.

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