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ARE WOMEN WITH POLYCYSTIC OVARY SYNDROME AT AN INCREASED RISK OF PREGNANCY-INDUCED HYPERTENSION AND/OR PRE-ECLAMPSIA?

T E S I S

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DEDICATORIA

Pocas cosas son tan satisfactorias,
como dejar una evidencia tangible de tu paso por la vida.

A Pedro Jáidar,
por su apoyo, amor y paciencia.

A mis hijos Yareli, Omar y Valeria,
ya que juntos son mi fuente
de inspiración eterna y de amor incondicional.

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Are women with polycystic ovary syndrome at an increased risk of pregnancy-induced hypertension and/or preeclampsia?

Dra. María del Socorro Benavides Salazar

Summary

The Polycystic Ovary Syndrome (PCOS) is a common condition characterized by menstrual abnormalities and clinical or biochemical features of hyperandrogenism. These features of PCOS may be manifested at any age, ranging from childhood (premature puberty), teenage years (hirsutism, menstrual abnormalities), middle life (infertility, glucose intolerance) to later life (diabetes mellitus and cardiovascular diseases). Androgen excess and insulin resistance are common in women with PCOS. Insulin resistance (IR) and compensatory hyperinsulinemia appear to impart an increased risk of glucose intolerance, and lipid abnormalities that are recognized not only in type 2 diabetes mellitus, but also in patients with essential hypertension, hyperlipidemia and obesity. These risks are known as the components of the metabolic syndrome and their accumulation, increases the risk of developing macrovascular disease, and cardiovascular diseases, that are present in some patients with PCOS.[1]

On the other hand, hypertensive disorders of pregnancy affect approximately 3 – 8 % of pregnancies and are a mayor cause of maternal, fetal and neonatal morbidity and mortality. Despite the frequency of these disorders, their cause is unknown. In the present chapter we review the risk factors present in PCOS, that increase the risk of developing pregnancy-induced hypertension and/or pre-eclampsia.

Rationale

Although the literature directly linking PCOS with pre-eclampsia or pregnancy induced hypertension is scarce, there is a clear correlation between PCOS and several conditions, such as obesity and insulin resistance, which are known to increase the risk of cardiovascular disease, particularly during pregnancy. In this chapter, we will cover the subject of these conditions as they relate to PCOS and pre-eclampsia.

Introduction

The first recognition of an association between glucose intolerance and hyperandrogenism was made by Achard & Thiers in 1921 and was called the “diabetes of bearded women”. The association between increased insulin resistance and PCOS is now well recognized.

Polycystic ovary syndrome remains as one of the most common hormonal disorders in women, with an estimated prevalence between 5 - 10% .[2,3]

The Polycystic ovary syndrome, has multiple components: reproductive, metabolic, and cardiovascular, with health implications in women affected with it.[4] The consequences of PCOS extend beyond the reproductive axis; women with the disorder are at substantial risk for developing metabolic and cardiovascular abnormalities similar to those that make up the metabolic syndrome.[5]

The metabolic syndrome is one of the major public-health challenges worldwide,[6] and is closely related with both type 2 diabetes and cardiovascular disease (CVD). These factors have been know for more than 80 years. In l988, Reaven described “syndrome X”: insulin resistance, hyperglycemia, hypertension, low high density lipoprotein (HDL)-cholesterol, and raised VLDL-triglycerides.[7] Surprisingly he omitted obesity, now seen by many as an essential component (visceral obesity).[6] Reaven proposed that insulin resistance played a causative role. Both, the PCOS and the metabolic syndrome share insulin resistance as a central pathogenic feature, and are viewed as a sex-specific form of the metabolic syndrome, called “syndrome XX”.[8] There is a considerable overlap between PCOS and the metabolic syndrome; 46% of women with PCOS also have metabolic syndrome, compared with 23% in the general female population above the age of 20 years.[5]

The idea of fetal programming has been linked to the development of CVD.[9] Interestingly, a link between low birth weight and PCOS has been found in precocious puberty. Young girls with precocious puberty are at an increased risk of developing PCOS, particularly if they had low birth weight. It has been proposed that this is the result of *in utero* fetal adaptation to undernutrition, resulting in permanent metabolic changes. The malnourished newborn is prone to develop obesity, IR, and type-2 diabetes, or else the underlying lesion of IR predisposes them to a defective insulin-affected growth. Weight gain can be rapid during adrenarche at 8 -9 years of age and associated with premature pubarche. An early biochemical lesion is low HDL levels with a rise in trygliceride levels when approaching puberty, after which hypertension becomes more common.

Young women with PCOS generally have blood pressure within the normal range.[10] However, they have an increased prevalence of labile day-time blood pressure, which might predispose them to sustained hypertension later in life.[11] Adolescents with PCOS fail to exhibit the fall in blood pressure that usually occurs at night, which is regarded as an early risk factor for developing hypertension.[12]

Hypertension develops in some women with PCOS during their reproductive years, [5,10] and sustained hypertension may develop in later life in women with the disorder.[13] Reduced vascular compliance [14] and vascular endothelial dysfunction were noted in most,[13,14] but not all, [15] studies of women with PCOS. Furthermore, the degree of impairment in vascular reactivity is significantly greater than can be explained by obesity alone.[13]

The association of essential hypertension with insulin resistance and hyperinsulinemia has been well described.[16,17] However, it was not until recent years that more widespread interest developed in the possible role of insulin resistance in the pathogenesis of pregnancy-induced hypertension (PIH).

Around the time of menopause, women with PCOS are 2.5 times more likely to have hypertension than their age-matched controls, which has been attributed to their associated obesity.[18]

Clinical Discussion

As different etiologies may lead to the same phenotype in different women, we focus on the potential role of insulin resistance and associated abnormalities as pathogenic factors for the development of PIH. Insulin resistance and elevated androgens provide a plausible link between PIH and PCOS.

Insulin is the most potent anabolic hormone known and is essential for appropriate tissue development, growth, and maintenance of whole-body glucose homeostasis. This hormone is secreted by the β cells of the pancreatic islets of Langerhans in response to increased circulating levels of glucose and amino acids after a meal. Insulin regulates glucose homeostasis at many sites, reducing hepatic glucose output (via decreased gluconeogenesis and glycogenolisis) and increasing the rate of glucose uptake, primarily into striated muscle and adipose tissue. In muscle and fat cells, the clearance of circulating glucose depends on the insulin-stimulated translocation of glucose transporter GLUT 4 isoform to the cell surface[19] and the essential phosphoinositol 3-kinase (PI3) activation. Insulin also profoundly affects lipid metabolism, increasing lipid synthesis in liver and fat cells, and attenuating fatty acid release from triglycerides in fat and muscle. Insulin resistance occurs when normal circulating concentrations of the hormone are insufficient to regulate these processes appropriately. Thus, by definition, IR is a defect in signal transduction.

It must be considered that there may be no single or common defect that underlies peripheral IR. Insulin resistance is most likely, a complex phenomenon with several genetic defects combined with environmental stress, such as obesity and infections, to generate the phenotype.

The cause(s) of PIH are unknown and include immune, genetic, and placental abnormalities. All may contribute to the endothelial dysfunction characteristic of pre-eclampsia.

Insulin resistance and normal pregnancy

In normal pregnancy, plasma volume increases by 40%,[20] associated with a reduction in peripheral vascular resistance (40 to 80%), and a rise in cardiac output, renal blood flow, and glomerular filtration rate.[21] The rennin-angiotensin-aldosterone system is activated despite the increase in plasma volume.[22] This activation is believed to be related to prostanoids, for example prostacyclin and prostaglandin E_2, direct effects of estrogen, or an antinatruretic action of progesterone.

Blood pressure generally falls in the first and second trimesters therefore, women with high blood pressure before the 20th week of gestation are assumed to have pre-existing hypertension. The frequency of superimposed pre-eclampsia is between 15 and 25 %, increasing maternal and fetal risk.

Insulin resistance and hyperinsulinemia are characteristic of normal pregnancies, are maximal in the third trimester, and rapidly return to normal after delivery. This is probably mediated by several hormonal changes, including elevation in levels of human placental lactogen, progesterone, cortisol and estradiol. The basis of the insulin resistance seen in normal pregnancy is not well understood. Increased risk for preeclampsia and/or gestational hypertension has been reported in several conditions associated with insulin resistance. These include gestational diabetes, polycystic ovary syndrome, obesity and increased

weight gain.[3] Both PCOS and metabolic syndrome have been associated with an increased risk of cardiovascular disease,[23,24] and both have hypertension, dyslipidemia, elevated serum glucose and central obesity in common. Insulin resistance is secondary to abnormalities at the insulin receptor, which may then result in a breakdown of glucose homeostasis mechanism.

Etiology

Hypertension during pregnancy can be classified into two main groups: women who are hypertensive when they become pregnant, and those who are hypertensive for the first time in the second half of pregnancy. (Table 1)

Table 1 Classification is based on the National High Blood Pressure Education Working Group Report on High Blood Pressure in Pregnancy.

New onset in pregnancy (after 20 week of gestation in a previously normotensive woman):
1. Preeclampsia: blood pressure al least 140 mm Hg systolic or 90 mm Hg diastolic, with urine protein al least 300 mg in 24 hrs.
2. Gestational Hypertension: Blood pressure at least 140 mm Hg systolic or 90 mm Hg diastolic, without proteinuria or other signs of pre-eclampsia.
3.Preexisting hypertension:
a. Without exacerbation
b. with superimposed pre-eclampsia.

Current hypotheses include: inflammatory disease, vascular-mediated factors, placental ischemia, genetic predisposition, immunologic derangements (a maternal immune reaction to a paternal antigen in the placenta), increased insulin resistance (associated elevations in the levels of insulin, free fatty acids, and triglycerides), dietary calcium deficiency, increased oxidative stress, and prostaglandin imbalance (an increased ratio of thromboxane to prostacyclin levels).

Preeclampsia is likely to be multifactorial in origin, and characteristics of the mother and the placenta may interact to lead to its development.

Pathophysiology

Pre-eclampsia typically manifests in the third trimester of a first pregnancy and resolves in the immediate puerperium. Rarely do “early” (<20 weeks gestation) forms of the disorder occur. It is multisystemic, primarily affecting the vasculature, kidneys, liver and brain. Pre-eclampsia is diagnosed in a woman with new onset of hypertension (> 140/90 mmHg), usually after gestational week 20 accompanied by proteinuria 300 mg/dL. Other common clinical and laboratory manifestations include facial and distal extremity edema, hemoconcentration, thrombocitopenia, hypoalbuminemia, elevated uric acid levels, liver enzyme abnormalities and hypocalciuria. The diagnosis is more difficult in women with preexisting chronic hypertension, but it is prudent to consider “superimposed preeclampsia” when systolic or diastolic blood pressure (BP) levels increase more than 30 and 15 mmHg respectively, proteinuria >300mg/dL appears and protein excretion increases dramatically.

Pre-eclampsia may progress to a life-threatening convulsive phase called *eclampsia,* when there is evidence of "**HELLP"** syndrome (hemolysis, elevated liver function test and low platelets).[25]

Polycystic ovary syndrome, which is associated with insulin resistance, elevated testosterone, and low SHBG levels, has been linked to an increased risk for pregnancy-induced hypertension even in the absence of associated obesity. Elevated androgen levels may be explained, at least in part, by increases in inhibin A,[26] which have also been described in women with pre-eclampsia. Elevated testosterone levels were found 17 years after a pre-eclamptic pregnancy, suggesting that endothelial dysfunction in pre-eclampsia is an underlying characteristic of affected women.[27]

Evaluation of long likelihood ratios in multivariable modeling indicates that first trimester SHBG has the strongest association with future gestational diabetes. Owing to its sensitivity and positive predictive value, SHBG may be a useful marker in the evaluation for the prediction of gestational diabetes mellitus (GDM).

The presence of hyperinsulinemia in non-pregnant women, years after a diagnosis of preeclampsia, indicates that these women may be at increased risk, although the observed association between insulin resistance and PIH *does not prove a causal relation***.** This observation, nonetheless, raises the possibility of potential preventive strategies before and during pregnancy. Management of obesity and excessive weight gain before pregnancy (risk of GDM and macrosomia), are among potential measures to decrease the risk of PIH. Excessive weight gain during pregnancy is another risk factor for pregnancy–induced hypertension. The recommendations we make in the diagnosis of patients with PCOS before pregnancy are presented in Table 2.

Table 2. Mnemonic Table listing the steps that can be carried out in order to avoid pregnancy complications in women with PCOS.

PCOS is confirmed with any 2 of the following 3 disorders: Oligomenorrhea or amenorrhea, Hiperandrogenism (hirsutism, acne, alopecia) or Hyperandrogenemia (elevated levels of total or free testosterone). PCOS on ultrasonography.
Risk factors are: increased body weight, (particularly if body fat is distributed in an android pattern), history of gestational diabetes type 2 diabetes in a first-degree relative, and Caribbean-Hispanic, Mexican-American or African-American heritage.
Early recognition of insulin resistance provides a unique opportunity to prevent or delay development of type 2 diabetes and the sequelae of CVDs.
Vascular disease in PCOS is higher if hypertriglyceridemia, increased levels of VLDL, LDL-C, cholesterol and decreased levels of HDL-C are presents, with predisposition to macrovascular disease and thrombosis, PCOS and metabolic syndrome share insulin resistance as a central pathogenetic feature.
Exercise or physical activity, changes in diet, changes in life style, attenuate insulin resistance, ameliorate (but not necessarily normalize) many of the metabolic aberrations in women with PCOS
Normal BMI (Body Mass Index): If women with PCOS are overweight and need fertility treatment such as, ovulation induction, this need must be deferred until BIM is preferably less than 30 Kg/m^2 .
Treatment with metformin has been reported to improve miscarriage rates and reduce the incidence of gestational diabetes, SHBG and LH concentrations.
Increased adiposity, increased particularly visceral adiposity reflected by an increased waist Circumference (> 35 in or 88 cm) or waist-to-hip ratio has been associated with hyperandrogenemia, insulin resistance, glucose intolerance and dyslipidemia.
Obesity is a key factor in determining cardiovascular risk particularly in older PCOS women.
No Smoking, in the Lipid research Clinics Prevalence Study. Smoking ≥ 20 cigarettes/day was shown to decrease HDL-C levels by 11-14% in a dose-dependent manner.[47]

Lipids

Abnormal lipid profiles have been demonstrated in adolecents with PCOS.[28] In these teenagers, elevated triglycerides and low high density lipoprotein (HDL) are more consistently observed in obese PCOS patients.[28] Often, the only abnormality in lean PCOS women is a reduced HDL-2 a sub-fraction of HDL.

Although, low density lipoprotein (LDL) levels are often only modestly elevated in PCOS, the percentage of the more atherogenic small dense LDL component (LDL III) is higher.[29] Insulin and body fat distribution play an important role in regulating lipid levels.[30]

In women with established pre-eclampsia, cholesterol, triglyceride,[28] and free fatty acid levels have been reported to be higher and HDL-C levels lower.[24] A potential mechanism through which hyperlipidemia may predispose to hypertension is by altering the prostaglandin balance and causing of vasoconstriction.

Alterations in blood vessel function

Decrease antioxidant capacity has been demonstrated in women with PCOS and oxidative stress has been implicated in the pathogenesis of atherosclerosis. [31]

Coagulopathy is a feature of the metabolic syndrome with reduced fibrinolysis, increased plasma viscosity and platelet dysfunction being observed in women with PCOS. The long term increase in risk of CVD with PCOS may arise as result of changes in blood vessel physiology or abnormal coagulation.[32]

Obesity

Obesity is defined as a body mass index (BMI) ≥ 30.4 Kg/m^2, but we must also consider body fat distribution. Visceral fat deposition is associated more closely with dyslipidemia and hyperinsulinemia than subcutaneous fat. Around 50% of patients with PCOS are obese. 70% of lean PCOS women have this pattern of fat deposition, and have been found to be hyperinsulinemic with reduced serum HDL levels compared to normal women,[33] the obese patient being at a higher risk.

Weight loss in obese or overweight women with PCOS prior to conception may be the most effective primary intervention for short and long term health (reduced risk of diabetes and impaired glucose tolerance, increased regularity of ovulatory cycles and spontaneous conception, improved hirsutism and reduced early pregnancy loss).

The metabolic syndrome and PCOS

The metabolic syndrome is diagnosed when three or more of the following criteria according to the National Institutes for Health (NIH) are present:

a) Fasting serum triglycerides ≥ 1.70 mmol/l.

b) High-density lipoprotein (HDL)-cholesterol < 1.30mmol/l.

c) Blood pressure ≥ 130/85 mmHg.

d) Serum glucose ≥6.0 mmol/l or

e) Waist circumference > 88 cm.[34]

Recently, the International Diabetes Federation has redefined the concept of metabolic syndrome (MS). The new concept will help identify people at increased risk (for more information see reference.[35]) The consensus group also recommended additional criteria including, tomographic assessment of visceral adiposity and liver fat, biomarkers for adipose tissue (adiponectin, leptin), apolipoprotein B, LDL particle size, formal measurement of insulin resistance and an oral glucose-tolerance test, endothelial dysfunction, urinary albumin, inflammatory markers (C-reactive protein, tumour necrosis α, interleukin 6), and thrombotic markers (plasminogen activator-inhibitor type 1, fibirinogen), that should be a part of further research into the metabolic syndrome. These factors should be combined with an assessment of CVD outcome and development of diabetes (Table 3). Researchers and clinicians should use the new criteria for the identification of high- risk individuals and for research studies.

Treatment

It is not clear if PCOS represents an independent risk factor for CVD, other than that of the metabolic syndrome. The identification and treatment of the features that these two conditions have in common (hypertension, dyslipidemia, elevated serum glucose, hyperinsulinemia and central obesity), have been shown to reduce the risk. The diagnosis of PCOS during adolescence provides an excellent opportunity to begin primary intervention. (see Questions and Table 2).

Strategies to improve sensitivity to insulin are required, for example diet, exercise and the use of insulin-sensitizing drugs, such as metformin and the thiazolidinediones.

Table 3. Features metabolic syndrome and PCOS, associated with Preeclampsia

Biomarkers	Metabolic syndrome	PCOS
1. Hypertension	+	+ or -
2. Hyperinsulinemia	+	+ or -
3. G.I.	+	+ or -
4. Central Obesity	+	+ or -
5. Lipid abnormalities		
a. ↑ tryglycerides	+	+ or -
b. ↓ HDL	+	+ or -
c. ↑ LDL	+	+ or -
6. ↑ Leptin	+ or -	+ or -
7. ↑ TNF α	+ or -	+ or -
8. ↑ PAI-1 and ↑ TPA Ag	+ or -	+ or -
9. ↑ testosterone	+ or -	+
10 ↓ SHBG	+ or -	+
11. Family history of DM.	+ or -	+or-

Case Studies

Due to the heterogeneity of the clinical manifestations of PCOS, the diagnosis of this condition is carrier out when the patient seeks help in achieving a pregnancy. Frequently the patient is treated with low complexity schemes for induction of ovulation, without being studied thoroughly. The following is a sample case study.

Case Study

A 32 year old patient presented with a maternal family history of diabetes mellitus type 2, positive tobacco use, and a diagnosis of PCOS. Pregnancy was achieved by a private practice physician with the use of clomifen citrate. The patient's BMI was 30Kg/m^2 prior to conception, with irregular follow up during the pregnancy.

The first visit to the emergency ward was made at 33 weeks of pregnancy according to reliable last menstrual period (LMP), and a syndrome characterized by cephalea, scotomata and edema of inferior extremities. During the examination, she had BP of 150/120 mmHg, was conscious, well hydrated but disoriented . Her fundal height was 28 cm and fetal heart rate frecuency (FHR) was 148 beats/min. There was no uterine activity. Vaginal examination revealed a formed posterior cervix with a 2 cm dilation, intact membranes, with cephalic presentation. Edema level of the lower extremities was +++ and deep tendon reflexes (DTR) were +++.

The emergency lab results were as follows: Hb 15.8 g/dl, haematocrit 44.7%, platelets 118 000 prothrombin time (PT): 14.3/12sec, partial thromboplastin time (PTT): 36/33 sec, creatinine: 1.07 mg/dl, uric acid: 8.9 mg/dl, total bilirubin: 0.65mg/dl, (indirect 0.4 mg/dl, direct 0.23mg/dl), lactate dehydrogenase (LDH): 485 U/L, aspartate aminotransferase (AST): 90 U/L, alanine aminotransferase (ALT): 37U/L, electrolytes: (Na: 138mEq/L; Cl: 107 mEq/L, K: 4.6 mEq/L; Ca: 10.20 mEq/L; Mg: 3.29 mEq/L).

Urine dustier was diagnosed with more than 30 mg of protein. At the emergency room, she was diagnosed as severe PHI-HELLP. The recommended treatment was parenteral hydratation and single dose 30 mg oral hydrazine, and transfer to the intensive care unit (ICU).

At the ICU, an antihypertensive treatment was recommended with oral alfamethyldopa (AMD), 500 mg every 8 hours, and hydralazine 50 mg every 6 hours, Magnesium Sulphate (MgSO4) 4g, I.V. loading dose followed by 1 g/h for 24 hours. Dexametazone 16 mg I.V. and 40% dextran 300 ml was given every three hours. Monitoring for BP curve, hourly diuresis (by a Foley probe) and CVP was performed.

Evolution: At 12 hours, the patient was drowsy, with intermittent cephalea without other signs of vasospasms. BP was 130/80 to 85 mmHg, normal PVC, 80 ml/h diuresis, FHR 142 beats/min, exalted DTR +. It was decided to end the pregnancy by cesarean section.

A female baby weighing 2,175 gms with an APGAR score 7 and 8 was delivered and transferred to intermediate care nursery. Her subsequent evolution was satisfactory.

The patient was returned to the ICU with an estimated blood loss of 500 ml and the double hypertensive treatment with MgSO4 and dexamethazone was continued. Her evolution was satisfactory; she was discharged from the ICU after 2 days, and stayed in a regular room.

Recently, the Norway group, conducted a prospective cohort study comprising of 29 non-insulin-resistant PCOS women, 23 insulin resistant PCOS women and a control group of 355 women who had conceived after assisted reproduction. The frequency of hypertension was significantly elevated in PCOS women (11.5%) compared to controls (0.3%), $P< 0.01$. However, the frequency of pre-eclampsia was significantly elevated only in the insulin resistant PCOS women (13.5%) compared to controls (7.0%), $P < 0.02$, and GDM was significantly more frequent in PCOS women than controls.[36]

Fridstrom et al.[37] reported a trend for higher blood pressure in PCOS women in the third trimester and during labor, However, the PCOS women did not have their insulin sensitivity tested.

Endothelial dysfunction is an early abnormality in insulin-resistant states that might contribute to premature atherosclerosis. Sub-clinical chronic low-grade inflammation may be an important factor in the pathogenesis of insulin resistance and type 2 diabetes.[38] C-reactive protein (CRP) promotes atherosclerotic processes and endothelial cell inflammation. Population studies show strong correlation between proinflammatory biomarkers (such as CRP, interleukin 6, and TNF α) and perturbations in glucose homeostasis, obesity and atherosclerosis. CRP levels may be independently related to the degree of insulin resistance, independent of obesity.

Several prospective epidemiological studies have tested the hypothesis that the circulating insulin concentrations are a cardiovascular risk factor.[39] None of these studies, however, distinguished between insulin and insulin resistance as the possible atherogenic factor. It might be the other way around – that the insulin resistance itself, by the production of pro-inflammatory cytokines, induces atherogenesis, and that, hyperinsulinemia could be the body's compensatory attempt to suppress inflammation and overcome insulin resistance.[40] Eventually, however, the total amount of insulin secreted by the pancreas is also decreased after several years of insulin resistance-i.e., beta cells become exhausted implying that, eventually prevailing insulin concentration will not be sufficient to counter the overwhelmingly strong insulin resistance.

Recent Advances

The protein product of the ob gene (obesity mice) named Leptine ("leptos" meaning thin), is produced by differentiated adipocytes, although production has been demonstrated in other tissues, such as the fundus of stomach, the skeletal muscle, the liver, and the placenta.[41] Leptin acts on the central nervous system, in particular, the hypothalamus, suppressing food intake and stimulating energy expenditure.[42]

Leptin, a satiety hormone, regulates appetite and energy balance of the body. Adiponectin could suppress the development of atherosclerosis and liver fibrosis, and might play a role as an anti-inflammatory hormone. Increased resistin concentrations may cause insulin resistance and thus, could link obesity with type 2 diabetes. These hormones have important roles in energy homeostasis, glucose and lipid metabolism, reproduction, cardiovascular function, and immunity. They directly influence other organ systems, including the brain, liver and skeletal muscle, and are significantly regulated by the nutritional status. This newly discovered secretory function has extended the biological relevance of adipose tissue, which is no longer considered as only an energy storage site. The pathophysiology that links maternal obesity and pregnancy-induced hypertension is a subject of intensive research.[43,44] The main hypothesis involves an endothelial dysfunction caused by obesity, which predisposes the patient to pre-eclampsia. However, obesity is associated with increased insulin resistance, which is thought to play a critical role in the predisposition for pre-eclampsia as well.[45]

Non-pregnant obese adults have an increased secretion of leptin and resistin, as well as decreased secretion of adiponectin.[46] The changes in these hormone levels, are known to increase insulin resistance and atherosclerosis. Leptin is heavily secreted by the placenta during pregnancy, and increased leptin is thought to play a role in the pathophysiology of pre-eclampsia.[47]

In very recent study, Hendler and colleagues[48], compared adipokine levels between women with and without pre-eclampsia based on maternal BMI, normal weight, overweight and obese women. They concluded that the increase in adiponectin in normal weight women with pre-eclampsia may represent the normal physiologic feedback response. This mechanism may not function properly in the overweight and obese gravida with pre-eclampsia because of increased adiponectin and IR.[48]

Conclusions

The possibility that a young woman with PCOS who is asymptomatic, may progress to a PCOS patient with obesity, hyperandrogynism, hyperinunsulinemia, altered menstrual cycle, and infertility, may be a function of time. It is important that PCOS patient be treated as soon as the diagnosis of PCOS is made.

Metabolic abnormalities and obesity have long been associated with the development of cardiovascular disease in the general population. These same outcomes are also associated with PCOS. An increased prevalence of hypertension, dyslipidemia, obesity and hyperinsulinemia, as well as changes in coagulation and blood vessel function, provide an explanation as to why women with PCOS are at an increased risk of developing cardiovascular disease over the years. The risk of CVD is uncertain at present, but two factors need to be borne in mind; the young age of the cohorts studied so far (~55 years) and the possibility that unknown factor(s) may be present in PCOS, which protect the heart in the face of other risk factors.

Although current practice does not recommend aggressive treatment of individuals who exhibit impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both, these high risk individuals represent an attractive target for slowing or reversing the progression to diabetes and reducing CVD too.

Lack of knowledge regarding the etiology of pre-eclampsia limits the understanding of the disorder, however, if the risk factors present in PCOS like impaired fasting glucose (IFG) or IGT are decreased, insulin resistance, obesity and lipid abnormalities, the morbidity and mortality of this disease may be decreased. With the application of modern technologies in molecular and cell biology, the cause of pre-eclampsia may be discovered in the first decade of this millennium.

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Frequently Asked Questions

1. Do therapeutic lifestyle changes improve the risk of coronary heart disease (CHD) in patients with PCOS?

Lifestyle changes include smoking cessation, weight loss, exercise and diet. The Lipid Research Clinics Prevalence Study[49] reported an inverse relationship between body mass index and HDL-C, and an increase in HDL-C of approximately 2 mg/dl. for every 4.5 Kg weight reduction, and a direct relationship between exercise and HDL-C. Smoking was shown to decrease HDL-C.

2. What is the contraceptive of choice in a woman with PCOS in her reproductive age?

The best pharmacological treatment of proven effectiveness is a combination of the synthetic progestogen, cyproterone acetate with ethinyl estradiol. Cyproterone acetate is antigonadotrophic and antiandrogenic, while estrogen increases the hepatic production of SHBG, resulting in lower free testosterone.

3. Weight loss in obese women with PCOS may be difficult. What other treatments, other than metformin that are useful?

The FDA-approved obesity drugs of Xenical (gastrointestinal lipase inhibitor) and Meridia, may soon be joined by a promising canabinoid receptor blocker named Accomplia (Rimonabat in Europe).

4. Should metformin be stopped immediately after pregnancy is diagnosed?

There is presently no evidence to suggest that metformin is teratogenic. On the contrary, metformin has been reported to reduce miscarriage rates and reduce the incidence of gestational diabetes.

5. Should a patient with eclampsia, with blood pressure at 200/120 mm Hg. with evidence of a generalized seizure, first be given diazepan or $MgSO_4$?

The Eclampsia Trial established $MgSO_4$ as the most effective therapy for eclampsia, both to treat active seizures and to prevent further seizures. The regimen should be 4 g IV loading dose followed by 1g/h for 24 hours.

6. Compared to singleton pregnancies, what can be expected for women with twin gestations and hypertension?

Compared to singleton pregnancies, women with twin gestations have higher rates of gestational hypertension and pre-eclampsia.

7. A 34 year old G3 P2 at 6 weeks gestation presents for evaluation. She has a history of chronic hypertension that developed two years after her last pregnancy. She has been taking Enelapril 10 mg, PO daily, her pre-pregnancy blood pressure measurements were 120-130/70-80 mmHg. She is otherwise completely healthy. What would you advice be done about her antihypertensive medication?

The Enalapril should be stopped and blood pressure followed to see whether or nor it raises.

8. How should hypertension in pregnancy be managed?

The initial aim of treatment is to reduce the systolic blood pressure by approximately 10 mmHg in a controlled manner. This can be effectively archived with oral Labetalol or Nifedipine. There is now some evidence to suggest that early treatment reduces the incidence of respiratory distress syndrome as well as hypertensive crisis in the mother. The use of ACE-inhibitors is not indicated during pregnancy.

9. In the assessment of severe pre-eclampsia, we recommended in the following considerations.

Uric acid is a better indicator of fetal morbidity than blood pressure. If the platelet count is greater than 100 000/mm^3, there is no need to carry out coagulation screening, since it is unlikely to be abnormal. The urine stick testing tends to over-estimate the presence of proteinuria and this should be quantified by 24-hour urine collection.

Abbreviations

HDL = High Density Lipoprotein

LDL = low Density Lipoprotein

TNF α = Tumor Necrosis Factor α

TPA Ag = Tissue Plasminogen Activator antigen

PAI-1 = Plasminogen Activator-Inhibitor-1

SHBG = Sex Hormone Binding Globulin.

DM = Diabetes Mellitus

PAI-1 = Plasmininogen Activator-Inhibitor-1 may reflect impaired fibrinolysis, which might predispose to the coagulopathy associated with pre-eclampsia.

PAI – 2, Primarily Produced by the Placenta, is increased before the development of disease.

TPA Ag: Higher levels and elevations are proportional to the magnitude of proteinuria.

TNF α levels, in the early third trimester, may predict the development of pre-eclampsia.

CRP: is not predictive of pre-eclampsia.

SHBG: lower levels are predictive of the development of pre-eclampsia.

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