Effect of insulin resistance in polycystic ovary syndrome and impact on pregnancy

Eric Appiah

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The University of Toledo

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Dedication

This paper is dedicated to my entire family, here in the United States of America and in Ghana, for their infinite support.

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Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder that affects body systems and leads to reproductive and metabolic complications among women of reproductive age (Kollmann et al., 2015; Fauser et al., 2012). Though the main etiology is unclear, evidence suggests that several genes are involved, as well as environmental and nutritional factors (Sedighi et al., 2015).

The clinical manifestations of PCOS are varied and include functional hyper-androgenism (clinical and biochemical), menstrual irregularities, chronic anovulation, polycystic ovaries and reduced fertility (Conway et al., 2014; Dumestic et al., 2015). In addition to reproductive complications, the majority of PCOS patients exhibit metabolic disturbances such as obesity and insulin resistance, increased risk of Type 2 diabetes mellitus (T2DM) and cardiovascular diseases (Diamanti-Kandarakis and Dunaif, 2012), along with chronic inflammation and oxidative stress (Zuo, Zhu, & Xu, 2016).

Background

PCOS affects six to fifteen percent of women depending on the diagnostic criteria used (Trikudanathan, 2015). It costs the United States healthcare system four billion dollars a year to identify and manage PCOS according to National Institute of Health (NIH); this does not include the treatment of serious conditions associated with PCOS, such as infertility, Type 2 diabetes mellitus and cardiovascular disease (NIH, 2012). An estimated 105 million women between the ages of 15 to 49 years old suffer from PCOS worldwide (Amiri et al., 2013).

The metabolic consequences of PCOS affect women's health across the lifespan, including the reproductive and post-reproductive years (Dunaif & Fauser, 2013; Orio & Palomba, 2014). According to the World Health Organization (WHO), (ESHRE Capri Workshop Group, 2012), PCOS is the most common cause of anovulatory infertility and eugo-nadotrophic hypogonadism.

According to Nandi, Chen, Patel, & Poretsky (2014), 90 to 95% of women attending infertility clinics have PCOS. Women with PCOS who achieve pregnancy have increased risk of complications such as pregnancy induced hypertension (PIH), pre-eclampsia (PE), gestational diabetes (GDM) and preterm delivery (Qin et al., 2013; Inal et al., 2015). Women with PCOS are at higher risk for preterm delivery, the neonates have increased risk for perinatal mortality, congenital abnormalities, increased hospitalization for metabolic disorders, diseases of nervous system, and asthma (Qin et al., 2013). Infants of women with PCOS are more likely to be born by Caesarean and exhibit low birth weight (Puttabyatappa, Cardoso, & Padmanabhan, 2015).

The pathophysiology of PCOS is unclear; however, there is evidence of alterations in gonadotropin secretion. Insensitivity to hypothalamic gonadotropin-releasing hormone (GnRH) secretion by the ovaries leads to increased luteinizing hormone (LH) pulse amplitude and frequency. Relative impairment in follicle-stimulating hormone (FSH) secretion creates an increased LH/follicle-stimulating hormone (FSH) ratio (Trikudanathan, 2015). LH activity, amplified by increased insulin leads to increased androgen production by the ovarian theca cells, resulting in reduced aromatase levels. Hyperinsulinemia further antagonizes sex hormone- binding protein (SHBG) in the liver, which increases the proportion of free testosterone compared with total testosterone. Between 50 to 90% of women with PCOS present with insulin resistance. Due to the role of insulin resistance in the pathogenesis of PCOS, it is hypothesized that improving insulin sensitivity, either through weight loss or drug therapy, improves reproductive, hyperandrogenic and metabolic features (Barber, Dimitriadis, Andreou, & Franks, 2015).

Women with PCOS often require assisted reproductive techniques in addition to insulin insensitivity treatment. Though women without PCOS have insulin resistance, women with PCOS often have worsened insulin resistance that leads to GDM. Women with PCOS also have low

insulin-like growth factor binding globulin-1 (IGBG-1), which may contribute to preeclampsia and growth abnormalities (Kjerulff, Sanchez-Ramos, & Duffy, 2011).

Purpose of Study

The purpose of this scholarly project is to identify specific complications of insulin resistance in women with PCOS and the impact on pregnancy outcomes.

Statement of the Problem

How does insulin resistance in PCOS affect the pregnant woman and fetus?

Definitions

Syndrome

Technical: collection of signs and features, where no single test is diagnostic (Azziz et al., 2009)

General: a group of signs and symptoms that occur together and characterize a particular condition

Polycystic Ovarian Syndrome on ultrasound (PCO)

Technical: an antral follicle count (AFC) of ≥12 in 2–9 mm diameter and/or ovarian volume of ≥10 cm3 at least in a single ovary (Yildiz, Bozdag, Yapici, Esinler, & Yarali, 2012)

General: the presence of more than 10 follicles in a single ovary

Clinical hyperandrogenism

Technical: modified Ferriman-Gallwey score (mF–G score) of ≥7 regardless of the presence or absence of acne or alopecia (Cook, Brennan, & Azziz, 2011)

General: outward presentation due to excess male hormone in females

Biochemical hyperandrogenism

Technical: any androgen including total testosterone (tT), androstenedione, (A4), dehydroepiandrosterone sulfate (DHEAS) and/or free androgen index (FAI) level exceeding the 95th percentile of healthy, non-hirsute, eumenorrheic women without PCOS; and oligo dysmenorrhea

(OD) defined as menstrual cycles ≥35 or ≤23 days; (Yildiz, Bozdag, Yapici, Esinler, & Yarali, 2012)

General: elevated levels of androgen hormone in a female

Hirsutism

Technical: presence of terminal hairs on the face and/or body of females in a male-type pattern

General: abnormal presence of hair similar to a male

Androgenic alopecia

Technical: scalp hair loss in women (Azziz et al., 2009)

General: little or no hair on head

Metabolic syndrome

Technical: presence of any three of the following traits based on ATP III criteria: serum triglycerides ≥150 mg/dl (1.7 mmol/l) or drug treatment for elevated triglycerides; abdominal obesity, defined as a waist circumference .88 cm (35 in); serum HDL cholesterol, 50 mg/dl (1.3 mmol/l) or drug treatment for low HDL-C; blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure; fasting plasma glucose (FPG) ≥100 mg/dl (5.6 mmol/l) or drug treatment for elevated blood glucose (Yildiz et al., 2012)

General: cluster of health issues related to endocrine function

Hypertension in pregnancy

Technical: blood pressure values ≥140/90mmHg on at least two occasions at >20 weeks without proteinuria (Altieri et al., 2010)

General: high blood pressure appearing in pregnancy after 20th week of gestation

Pre-eclampsia

Technical: blood pressure values ≥140/90 mmHg in at least two occasions with proteinuria >0.3 g/24h at >20 weeks (Altieri et al., 2010)

General: high blood pressure and proteinuria in pregnancy

Gestational diabetes mellitus

Technical: fasting glucose ≥5.3 mmol/L (≥95 mg/dL); 1-h ≥10.0 mmol/L (≥180 mg/dL); 2-h ≥8.6 mmol/L (≥155 mg/dL); and 3-h ≥7.8 mmol/L (≥140 mg/dL) of the 100g OGTT (American Diabetes Association, 2012)

General: elevated blood glucose because of pregnancy

Preterm birth

Technical: birth that occurs before 37 completed weeks of gestation (Boomsma, Fauser, & Macklon, 2008)

General: early birth before 40 weeks of gestation

Non-Alcoholic Fatty Liver Disease (NAFLD)

Technical: clinico-pathologic spectrum of conditions ranging from simple steatosis (simple fatty liver) to NASH, involving inflammation and some evidence of liver cell damage, and in some cases, cirrhosis, which is advanced scarring of the liver (Tominaga et al., 2009)

General: accumulation of liver fat in people who drink little or no alcohol

Methodology

Search terms

Online and in person exploration for this project included words such PCOS and pregnancy, PCOS complications, gestational diabetes, pregnancy outcomes in PCOS, diabetes mellitus and PCOS, insulin resistance and PCOS.

Databases

Sources of information for this project were gathered via Pubmed, Google Scholar, NIH, ESHRE, ASRM, AE-PCOS, Clinical Keys, and Dissertation Abstract International (DAI).

Inclusion and exclusion criteria for articles

This project utilized reports and articles available in English that are less than ten years old, except when the article was considered a classic on the topic. Articles on the psychological impact of PCOS were excluded.

Limitations

A discrepancy exists in the literature related to diagnostic criteria, partly due to differences in background study populations and difficulties in phenotypic definitions. This discrepancy may have led to biased sampling of available populations in reported research studies.

Review of Literature

History of PCOS

It is unclear when PCOS was first described, but history points as far back to Egyptian papyri that suggested the presence of PCOS-like syndrome. Hippocrates (460-377 BC) said "but those women whose menstruation is less than three days or is meager, are robust, with a healthy complexion and a masculine appearance; yet they are not concerned about bearing children nor do they become pregnant," (Nandi et al., 2014). As far back as 1771, Antonio Vallisneri described a connection between masculine features and abnormal morphology of the ovaries: "young married peasant women, moderately obese and infertile, with two larger than normal ovaries, bumpy and shiny, whitish, just like pigeon eggs". Chereau (1844) described PCOS as a change of ovarian morphology. Stein and Leventhal provided the first description of PCOS in 1935, noting varying degrees of enlarged ovaries, obesity, hirsutism, and chronic anovulation (Stein & Leventhal 1935).

NIH (1990) described PCOS as hyper-androgenism (HA) and ovulatory dysfunction and recommended these two features as diagnostic criteria (Michelmore et al., 1999). The most widely used criteria today is from the European Society for Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) from 2003. PCOS is indicated when two of the following are present: oligoamenorrhea or amenorrhea, and clinical and or biochemical signs of HA and polycystic ovarian morphology (PCOM) on ultrasound. The Androgen Excess and PCOS Society (AE-PCOS) recommended in 2006 to include the presence of HA (clinical and or biochemical) and ovarian dysfunction [oligo-anovulation (OA) and or PCO] criteria in the definition (Azziz et al., 2009).

Epidemiology

PCOS affects 6 to 15% of women depending on the diagnostic criteria used (Trikudanathan, 2015). The prevalence of PCOS using NIH criteria was 6.1%. The prevalence rate with respect to Rotterdam criteria reached 19.9% and the AE-PCOS prevalence rate was reported as 15.3% (Yildiz et al., 2012).

An estimated 105 million women worldwide between the ages of 15 to 49 years old suffer from PCOS (Amiri, 2013). Based on National Cholesterol Education Program Adult Treatment Panel III criteria, 34-46% of United States based Caucasian women with PCOS have metabolic syndrome (Barber, McCarthy, Franks, & Wass, 2007). In the United States, up to 40% of all women with PCOS have risk of type II diabetes or impaired glucose tolerance by age 40 (Boomsma et al., 2008). There may be significant ethnic differences in the presentation and spectrum of PCOS, which include variations in normal traits, risk factors for co-morbidities, response to treatment and effects of pharmacologic agents (Wijeyeratne & Balen, 2013). Fifty percent of recurrent pregnancy loss occurs in women with PCOS (Chakraborty et al., 2013).

The prevalence rate among Mexican-Americans, African-Americans and Asians are 6-13%, 3-9% and 2-9% respectively (Wang & Alvero, 2013). Mexican-Americans have the highest age-specific prevalence of the insulin resistance/metabolic syndrome compared to non-Hispanic whites and blacks, as well as a high incidence of insulin resistance and type 2 diabetes mellitus (Goodarzi et al., 2005).

Etiology of PCOS

Though the main etiology is unclear, evidence suggests that several genes are involved, as well as environmental and nutritional factors (Sedighi et al., 2015). These genetic and environmental factors can influence the PCOS phenotype, and these women constitute the most heterogeneous group of PCOS (Boomsma et al., 2008)

Environment

Placental environment is believed to play a key role in pregnancy complications, especially hypertension in pregnancy and pre-eclampsia (Redman and Sargent, 2005; Longtine and Nelson, 2011). The placenta of women with PCOS is observed to be thinner, with reduced volume and lower weight compared with women without PCOS. Chronic villitis and intervillositis is also evident (Palomba et al., 2013). Women with PCOS who are obese show an induced inflammatory response in the placenta, which leads to pathological lesions (Huang et al., 2014; Jeve et al., 2014). Environmental endocrine disrupting chemicals (EDCs) that alter ovarian and metabolic function are also being investigated as contributors in the development of PCOS phenotype (Barrett & Sobolewski, 2014).

The ‘‘intrauterine programming,’’ or fetal origins hypothesis implies that in utero factors lead to permanent changes in organ function and predispose fetal growth restriction for a variety of metabolic diseases. The increased risk for metabolic disease has been linked to increased insulin resistance in young individuals who were exposed to an adverse in utero environment and born small for gestational age (SGA). As a result, SGA infants with catch-up growth are less insulin sensitive (with higher fasting insulin and triglyceride levels) than appropriate for gestational age (AGA) infants, despite their continuing lower weight and BMI (Abbott & Bacha, 2013). In addition to in-utero environmental factors, genetic polymorphisms also modulate insulin resistance paramenters in SGA neonates; this may explain the variable degree of insulin resistance in neonates exposed to an adverse uterine environment (Appendix 1).

Nutrition

Though there is little agreement on what constitutes optimal diet for women with PCOS (Moran, Brinkworth, Noakes, & Norman, 2006), the ‘‘Atkins diet’’ has generated considerable interest.

Very low calorie diets can lead to significant decrease in body weight for PCOS patients (12% in 24 weeks) and improve reproductive outcomes ("Consensus on infertility treatment related to polycystic ovary syndrome," 2008). The report explained that in PCOS there is a close association between insulin resistance and reproductive health; reduced glycemic load (with 500 Kcal/day deficit) is suggested to alleviate hyperinsulinemia and its metabolic consequences. The 'Barker hypothesis' of fetal programming in utero suggests that fetal nutrition and endocrine environment (e.g. hyperinsulinemia) may effect neuroendocrine systems that regulate body weight, food intake and metabolism, with long-term consequences (Boomsma et al., 2006).

Genetic

Genetic factors play an important role in the etiology of PCOS, with an estimated heritability of 65% (Vink et al., 2006). The mode of inheritance remains unclear; both dominant and multigenic modes of transmission have been proposed (Kosova & Urbanek, 2013). Evidence of genetic contribution includes familial clustering of PCOS, increased prevalence of hyperandrogenemia and type 2 diabetes mellitus in first-degree relatives of women with PCOS (Ehrmann, Kasza, Azziz, Legro, & Ghazzi, 2005). High heritability was reported in Dutch twin studies (Puttabyatappa et al., 2015). Approximately 35% of mothers and 40% of sisters of women with PCOS were affected (Azziz et al., 2009). Genetic polymorphism is suggested to modulate insulin resistance parameters in small for gestational age (SGA) individuals; this may explain the variable degree of insulin resistance in women with PCOS exposed to an adverse in utero environment (Abbott & Bacha, 2013).

Even though there is no consensus in literature regarding a specific PCOS candidate gene, a region surrounding D19S884, a microsatellite marker in intron 55 of fibrillin 3 (FBN3), located on chromosome 19p13.2 about 800 kb centromeric to the insulin receptor (INSR) gene has been identified (Ewens et al., 2010). Although the role of FBN3 in PCOS remains unclear, FBN3

expression is demonstrated in the human ovary (Prodoehl et al., 2009). Other members of the fibrillin family of proteins are known to bind members of the transforming growth factor-beta (TGFβ) family, which plays a significant role in controlling ovarian follicular development (Rosairo, Kuyznierewicz, Findlay, & Drummond, 2008), as well as muscle and adipocyte development and differentiation (Allen et al., 2008). The role of more than 70 candidate genes have been evaluated: CYP11A (encoding cytochrome P450, family 11, subfamily A polypeptides); CAPN10 (encoding calpain 10); and the insulin gene VNTR (variable number of tandem repeats), have all been implicated in PCOS (Urbanek, 2007). Replication studies indicate that FBN3, hydroxysteroid dehydrogenase (HSD) 17B6, POMC, ACRR2A, FEM1B, SGTA, LHCGR, and DENNDIA show positive association for PCOS and variants of these genes. This association was not evident with other gene loci, due to either small sample size, varied diagnostic criteria, or phenotypic heterogeneity (Goodarzi et al., 2011).

Ovarian luteinizing hormone receptor (LHR) variants may diminish or enhance pituitary LH stimulation of ovarian theca and stroma cell T production, ovarian follicle development, LH surge induced ovulation, and corpus luteum function (Dickinson, Stewart, Myers, Millar, & Duncan, 2009). In adipocytes, LHR variants may alter LH stimulation of adipogenesis (Dos Santos et al., 2007); variants in these multiorgan system genes could contribute to genetic determination of PCOS phenotypes for reproductive and metabolic pathophysiology.

Interaction of genetic and environmental factors shape the intrauterine environment, leading to epigenetic changes and alteration of organ function at several levels. Childhood obesity and associated insulin resistance promote the manifestation of genetic/epigenetic traits predisposing to hyperandrogenism, including effects on steroidogenesis and hypothalamic/pituitary function (Abbott & Bacha, 2013) as shown in appendix 2.

Genetics, in combination with risk-increasing lifestyle such as over-nutrition and increased sedentary time, in conjunction with environmental factors might drive the development and manifestation of PCOS traits (Franks et al., 2006).

Risk Factors Associated with PCOS

Gestational Diabetes Mellitus

GDM is defined as hyperglycemia first detected during pregnancy; it is less severe than diabetes mellitus in non-pregnant adults (WHO, 2014). GDM frequently precedes type 2 diabetes mellitus in midlife; it is recommended that women with increased risk be tested early and often for hyperglycemia (Odsaeter, Asberg, Vanky, & Carlsen, 2015).

GDM is the most frequent pregnancy complication in women with PCOS (deWilde et al., 2014). The risk of GDM is nearly three times higher than in the general pregnant population (Boomsman et al., 2006; Toulis et al., 2009; Kjerulff et al., 2011; Qin et al., 2013) and increases with each subsequent pregnancy (Ashrafi et al., 2014). The prevalence rate of GDM ranges from 0.2-8% of all pregnancies and shows variation depending on ethnic and racial backgrounds, as well as diagnostic criteria. Common risk factors include ethnicity such as non-white race, obesity, older age and previous GDM history (Lo et al., 2006). Though PCOS itself is a risk factor for GDM, Wang et al., (2013) determined PCOS to be independent of obesity.

The underlying pathogenesis mechanism of GDM is an imbalance between the capacity of pancreatic beta cells and increased demands for insulin due to decreased insulin sensitivity during pregnancy (Ashrafi et al., 2014). Women with PCOS are predisposed to develop a degree of insulin resistance that manifests clinically as GDM. Women with PCOS who develop GDM have significantly increased placental villous immaturity, villous necrosis, chorangiosis, ischemia and nucleated red blood cells (nRBCs) compared with women without GDM (Daskalakis et al., 2008).

Long-term consequences of GDM on infant development include adverse effects on attention span and motor functions (Boomsma et al., 2008), along with macrosomia, childhood obesity and risk for metabolic syndrome (Reece et al., 2009). Short and long-term effects on the woman include metabolic syndrome and T2DM (Reece et al., 2009). Early diagnosis of GDM is

crucial and careful treatment significantly reduces the incidence of related maternal and neonatal complications (Ngai et al., 2014; Poolsup et al., 2014).

Cardiovascular Complications

The association between PCOS and cardiovascular comorbidities is well-recognized (Wild et al., 2010). Women with PCOS demonstrate increased classic risk factors for cardiovascular disease (CVD) such as hypertension, dyslipidemia, diabetes, and obesity and non-classic risk factors such as elevated C-reactive protein (CRP), homocysteine, and tumor necrosis factor-α (Toulis et al., 2011). Despite the higher prevalence of CVD risk markers in women with PCOS than in healthy controls, association of these markers with cardiovascular events remains unclear (Palomba, Santagni, Falbo, & La Sala, 2015).

Metabolic syndrome (MetSyn) is one of the strongest predictors of cardiovascular disease (Hillman et al., 2014). Women with PCOS have increased risk for subclinical atherosclerosis (Dokras, 2013) and there is higher prevalence of coronary artery calcium in African American women with PCOS compared with Caucasian women with PCOS (Hillman et al., 2014). Adolescents with PCOS also have increased cardio metabolic risk factors compared with age-matched controls (Roe, Prochaska, Smith, Sammel, & Dokras, 2013).

Obesity

Women with PCOS represent a cohort with a high prevalence of overweight (BMI .25kg/m2) and obesity (BMI .30 kg/m2), up to 61% prevalence when compared to healthy women without PCOS (Lim, Davies, Norman, & Moran, 2012). Women with PCOS in Australia, United States, and United Kingdom have the highest prevalence of overweight and obesity (Conway et al., 2014), compared to Chinese women with PCOS where only 20% have a BMI of 25 kg/m2 greater (Chen, Ni, Mo, Li, & Yang, 2010).

The causal role of association between obesity and PCOS has yet to be determined but cultural, lifestyle, and ethnic factors contribute to these conditions. Obesity worsens the presentation of PCOS in adolescence and adulthood; weight gain after adolescence is a predictor for development of hirsutism and menstrual disturbances in PCOS (Moran et al., 2006). Women with PCOS are more likely to have increased upper body fat distribution, even in the absence of an obesity condition and independent of BMI levels (Palomba, Santagni, et al., 2015).

The greatest health consequences of PCOS are associated with excess weight and abdominal circumference (Bates & Legro, 2013). Increased visceral adiposity is associated with greater intrinsic resistance (IR), (Carmina et al., 2007), one of the most important metabolic pathophysiologic features of the syndrome. Obesity and overweight increase the risk of developing T2DM in women with PCOS, even though PCOS represents an independent risk factor for T2DM (Alberti, Zimmet, & Shaw, 2007).

Hypertension in pregnancy

The prevalence of hypertension in pregnancy in PCOS is 19.20% (Shi et al., 2014) and 18.6% (Azevedo et al., 2011) compared with controls. Three meta-analyses (Boomsma et al., 2006; Kjerulff et al., 2011; Qin et al., 2013) reported a three to four times increase in risk of pregnancy-induced hypertension (PIH) in women with PCOS. Women with PCOS also present a three to four-fold increased risk of developing pre-eclampsia (PE) during pregnancy (Boomsma et al., 2006; Kjerulff et al., 2011; Qin et al., 2013). A quadruple increase in the risk of hypertension during pregnancy has been linked to arterial wall stiffness in women with PCOS. The risk of pre-eclampsia, the most severe of all pregnancy complications, is four times higher in women with PCOS (Katulski, Czyzyk, Podfigurna-Stopa, Genazzani, & Meczekalski, 2015).

Preterm delivery and PCOS

Two cohort studies (Roos et al., 2011; Naver et al., 2014) demonstrated that neonates born to women with PCOS have higher risk for preterm delivery and an increased risk of meconium aspiration. Two meta-analyses (Boomsma et al., 2006; Kjerulff et al., 2011) noted that women with PCOS have a two-fold increased risk of preterm delivery. In contrast, a recent meta-analysis by Qin et al. (2013) indicates no effect for women with PCOS. A 2015 population-based cohort study (Lovvik et al.) focused on twin pregnancies; outcomes indicate that women with a previous diagnosis of PCOS have a higher risk preterm delivery and neonates with low birth weight. Precise risk is uncertain when research findings do not elaborate on whether preterm delivery was due to induction of labor because of placental insufficiency or for other reasons (Palomba, de Wilde, et al., 2015).

Perinatal mortality is higher for neonates born to women with PCOS (Boomsma et al., 2006). There is a 2-fold increased risk for admission to a neonatal intensive care unit (Boomsma et al., 2006; Kjerulff et al., 2011; Qin et al., 2013) and low Apgar scores are more frequent (Roos et al., 2011).

Infertility and PCOS

Although women with PCOS may achieve pregnancy without intervention (Hudecova, Holte, Olovsson, & Sundstrom Poromaa, 2009), the great majority of women with PCOS experience anovulatory infertility. A Finnish study showed that while women with PCOS may take longer to become pregnant, their lifetime fertility is not impaired (Koivunen et al., 2008) and they may display sustained fertility with advancing age (Mellembakken et al., 2011). Ovulation induction is the initial treatment for non-obese women and for women for which a non-pharmacological approach has failed. Live birth is achieved in 80% in women with PCOS undergoing treatment within two years (Veltman-Verhulst, Fauser, & Eijkemans, 2012).

Although there is a lack of evidence-based data, infertility treatments are considered a potential risk for women with PCOS because multiple fetuses may result instead of singleton pregnancy (Fauser, Devroey, & Macklon, 2005; Pinborg et al., 2012).

Effect of insulin resistance on polycystic ovary syndrome

Insulin resistance (IR) is observed in about 50% to 80% of women with PCOS (Baranova, Tran, Birerdinc, & Younossi, 2011). Insulin resistance, with compensatory hyperinsulinemia, is one of the cornerstones in the pathogenesis of PCOS and in development of short and long-term complications related to PCOS (Diamanti-Kandarakis & Dunaif, 2012). Insulin resistance and compensatory hyperinsulinemia have been shown to independently contribute to the obesity prevalent among women with PCOS (Kamalanathan, Sahoo, & Sathyapalan, 2013). Abnormalities in insulin action have been noted in a variety of tissues from women with PCOS, which may explain the pleiotropic presentation and multi-organ involvement of the syndrome. Insulin resistance has also been implicated in infertility and increased risk of pregnancy complications, as well as the elevated lifetime risk of developing type 2 diabetes (Pauli, Raja-Khan, Wu, & Legro, 2011). Euglycemic studies indicate there is insulin resistance in both obese and lean women with PCOS (Trikudanathan, 2015).

A similar profile is present in adolescent girls with PCOS, who express approximately 50% lower insulin sensitivity compared with obese control subjects of similar age, body composition and abdominal adiposity (Abbott & Bacha, 2013). The origin of childhood insulin resistance and adolescent predisposition to PCOS may be linked to in utero adverse events (Davies, March, Willson, Giles, & Moore, 2012); premature adrenarche (Maliqueo et al., 2009 & MacCartney et al., 2007); along with family history and obesity (Littlejohn, Weiss, Deplewski, Edidin, & Rosenfield, 2007). The increased risk for metabolic diseases has been linked to increased insulin resistance.

The gold standard for assessing metabolic insulin resistance in vivo is the hyperinsulinemic, euglycemic glucose clamp technique (Diamanti-Kandarakis & Dunaif, 2012). The homeostatic model assessment value for IR (HOMA-IR) after adjustment for age, BMI, and race (DeUgarte, Bartolucci, & Azziz, 2005) and fasting glucose: insulin ratio and quantitative insulin sensitivity check index (QUICKI) are easier and are routinely used in clinical practice for IR evaluation (Peigne & Dewailly, 2014).

Cellular Mechanism of Insulin Resistance in PCOS

The defect in the insulin signal pathway results in a trianglulation of factors: insulin resistance, hyperinsulinemia and glucose intolerance, all of which are implicated in the pathophysiologic mechanisms of metabolic syndrome (Baranova et al., 2011).

Insulin binds to its membrane receptor and leads to certain intracellular cascades. The phosphoinoditide 3-kinase (PI3K) pathway mediates insulin's metabolic actions on glucsoe uptake and utilization. The mitogen-activated protein kinase (MAPK) signal transduction pathway controls mitogenic, proliferative and anti-apoptotic actions of insulin. The cellular mechanism underlying insulin resistance is an imbalance between the two insulin signalling pathways, namely metabolic versus mitogenic pathways (Pauli et al., 2011). Impaired glucose uptake caused by downregulation of Insulin-like growth factor (IGF-1) receptor can result in blastocyst apoptosis and hyperglycemia; hyperinsulinemic insulin resistance can induce the expression of caspase, an enzyme triggering apoptosis of blastocyst (Kamalanathan, Sahoo, & Sathyapalan, 2013).

Insulin resistance in adipose tissue

Key molecules throughout the insulin-signaling pathway are altered in adipose tissue of women with PCOS. Ciaraldi et al. (2009) documented tissue-specific differences in insulin action and decreased insulin sensitivity in women with PCOS. Alteration in phosphorylation in adipocytes has been noted for women with PCOS. Abnormal regulation of glycogen synthase kinase 3β

(GSK3β) is a potential mechanism for the insulin resistance, as GSK3β levels are restored in adipocytes after insulin stimulation (Chang et al., 2008). Glucose transporter 4 (GLUT4) expression has also been implicated for reduced adipocytes (Corbould et al., 2005). The adipose tissue in women with PCOS is often excessive, central in distribution, has aberrant morphology and function; with enlarged adipocyte size and reduced adiponectin level (Manneras-Holm et al., 2011).

Skeletal muscle and insulin resistance (IR)

Insulin resistance involves both intrinsic and acquired defects in insulin signaling in skeletal muscle of women with PCOS (Pauli et al., 2011). The cause of IR in skeletal muscle might be due to low levels of Insulin receptor substrate 1 (IRS-1) expression, impaired IRS-1 phosphorylation, reduced activity of the serine/threonine kinase AKT2, and altered glucose transporter GLUT4 translocation to the plasma membrane (Mukherjee & Maitra, 2010).

Insulin resistance and non-alcoholic fatty liver disease (NAFLD)

NAFLD occurs in approximately 25% to 30% of the United States general population; the potentially progressive form or non-alcoholic steatohepatitis (NASH) is reported in 2–3% of the population (Baranova et al., 2011). The prevalence of NAFLD in women with PCOS rises proportionally to the severity of insulin resistance (Pauli et al., 2011). IR is the key event linking NAFLD to metabolic syndrome. The association of decreased SHBG levels with NAFLD probably reflects the known abnormalities associated with NAFLD that influence SHBG secretion by the liver, such as obesity, central adiposity and insulin resistance (Vassilatou et al., 2010). Type 2 diabetes mellitus, obesity and dyslipidemia are the principal factors associated with NAFLD (Marchesini, Marzocchi, Agostini, & Bugianesi, 2005).

Although PCOS and NAFLD share a common attribute in regards to pathogenesis, insulin resistance as the link between the two diseases was not obvious until the first case was described in 2005 (Brown, Tendler, McMurray, & Setji). Elevated alanine aminotransferase (ALT) serum levels

are also a common finding in PCOS (Vassilatou et al., 2010). Ultrasonography is widely accepted as a surrogate method of liver biopsy in obese populations (Tominaga et al., 2009) and is widely used as a tool for grading NAFLD (Fenkci, Rota, Sabir, & Akdag, 2007; Sagi et al., 2007).

Insulin resistance in the reproductive cells of women with PCOS

Studies suggest the paradox of insulin activity is not only present in the macro-environment but also in the micro-environment within the ovary (Rice et al., 2005). Ovarian insulin resistance is associated with mitogenic signaling amplification and ovarian hyper-function, including excess androgen production by the theca cells and granulosa cell proliferation (Franks, Stark, & Hardy, 2008). The abnormal environment of decreased follicle apoptosis, increased follicle numbers, and increased estrogen production related to suppression of FSH by strict negative feedback of hyperestrogenism results in suspension of normal follicle growth. Ovarian insulin resistance is a key pathological mechanism in PCOS and peripheral insulin resistance plays an important auxiliary role in stimulating PCOS (Pauli et al., 2011). Hence, the insulin-signaling pathway is impaired in the endometrium for women with PCOS (Rosas, Gabler, Vantman, Romero, & Vega, 2010).

Laboratory, biomarkers and diagnostic tests

Serum advanced glycation end product (AGE) concentrations are elevated in lean and obese women with PCOS (Diamanti-Kandarakis et al., 2008), with localization of AGE and their receptors to both theca and granulosa cells (Diamanti-Kandarakis et al., 2007). A fuller understanding of the role of AGE concentrations in ovarian follicular development may assist in predicting the outcome of infertility treatments for women with PCOS (Merhi, Irani, Doswell, & Ambroggio, 2014).

Testosterone is the primary circulating active androgen; obtaining a total serum testosterone concentration is the initial recommendation for assessing androgen excess (Stanczyk, 2006). Measurement of total testosterone at any time during the menstrual cycle is adequate, since

variations are marginally significant (Conway et al., 2014). Most immunoassays yield higher values than those obtained using gas chromatography coupled with mass spectrometry or liquid chromatography coupled with tandem mass spectrometry (Haring et al., 2012; Janse et al., 2011). Isotope-dilution gas chromatography-mass spectrometry is considered the gold standard method for evaluating steroid hormones (Moal, Mathieu, Reynier, Malthiery, & Gallois, 2007; Vicente, Smith, Sierra, & Wang, 2006).

The free androgen index (FAI), calculated as the ratio between total testosterone and sex hormone-binding globulin (SHBG), is the most sensitive measurement for the evaluation of hyperandrogenemia (Azziz et al., 2009). Low SHBG has excellent diagnostic accuracy for diagnosis of PCOS in epidemiological studies, even superior to measurements of serum androgen concentrations (Bhasin et al., 2011). Low SHBG is a surrogate marker of insulin resistance and androgen excess that predicts the susceptibility to develop metabolic syndrome and gestational diabetes in women with PCOS (Glueck, Morrison, Daniels, Wang, & Stroop, 2011; L. Moran et al., 2013; Pasquali, 2006; Veltman-Verhulst et al., 2010).

Anti-Mullerian hormone (AMH) is recognized as an important marker of the number of small antral follicles. AMH is used to measure ovarian reserve, but also reflects the greater number of follicles present in ovaries with polycystic morphology (Conway et al., 2014; Dumont, Robin, Catteau-Jonard, & Dewailly, 2015). Serum concentrations of AMH correlate with the antral follicle counts and degree of menstrual disturbances (Homburg et al., 2013; Pawelczak, Kenigsberg, Milla, Liu, & Shah, 2012; Pellatt, Rice, & Mason, 2010). Serum AMH correlates with the severity of both hyperandrogenism (Piouka et al., 2009) and oligo-anovulation in women with PCOS (Catteau-Jonard et al., 2012).

According to AE-PCOS, an oral glucose tolerance test should be performed for all obese women, as well as for lean women with PCOS of advanced age (>40years), in the presence of a

personal history of gestational diabetes or family history of T2DM (Salley et al., 2007; Wild et al., 2010).

Hypersecretion of LH, resulting from increased pulsatility of GNRH is a common feature of lean women with PCOS who report oligo-menorrhea (Hendriks, Brouwer, Hompes, Homburg, & Lambalk, 2008).

The current AE-PCOS Consensus Report (2004) does not support use of a single LH measurement due to intrinsic variability; LH should be measured in the follicular phase of the menstrual cycle or at random in the presence of amenorrhea (Conway et al., 2014).

Sonographic assessment of ovaries is an obligatory criteria for the diagnosis of PCOS according to the Rotterdam consensus (2003) and AE-PCOS (2006) (Bachanek, Abdalla, Cendrowski, & Sawicki, 2015). Ultrasound is a practical approach to investigate the pelvic space, uterus, ovaries and other adnexal mass and can be utilized to evaluate pelvic masses as to risk for malignancy (Lee, Park, Lee, Jeong, & Chung, 2015). Transvaginal ultrasound is a noninvasive technique for assessing ovarian morphology and the most commonly used method for identification of polycystic ovaries. Polycystic ovaries are common in young healthy women under 36 years of age, with a prevalence of 20-30% (Zhu, Wong, & Yong, 2016).

The AE-PCOS guidelines from 2014 recommend using follicle number per ovary (FNPO) >25 to designate PCOM when using newer technology that affords maximal resolution of ovarian follicles (i.e., transducer frequency >8 MHz). If such technology is not available, ovarian volume is recommended for the diagnosis of PCOM (Zhu et al., 2016).

Treatment of infertility

Clomiphene citrate remains the treatment of first choice for induction of ovulation in most anovulatory women with PCOS. Selection of patients for clomiphene citrate treatment should take into account body weight/BMI, age, and the presence of other infertility factors. The starting dose

of clomiphene citrate should be 50mg/day (for five days), and the recommended maximum dose is 150 mg/day ("Consensus on infertility treatment," 2008).

A systematic review of four crossover random controlled trials that compared clomiphene citrate with placebo in patients with amenorrhea/oligo-amenorrhea (Brown et al., 2009), demonstrated that all doses of clomiphene citrate were associated with increased pregnancy rates per treatment cycle. Furthermore, it was demonstrated that the ovulation rate was 70-85% per cycle and a cumulative pregnancy rate was 60-70% after six cycles of treatment (Brown et al., 2009).

At present, the use of metformin in PCOS should be restricted to those patients with glucose intolerance. In women with PCOS, metformin appears to lower the fasting insulin level, but it does not appear to result in consistent significant changes in BMI or waist-to-hip ratio ("Consensus on infertility treatment," 2008).

The latest version of the Cochrane Review on oral agents for ovulation induction concluded that the use of metformin and other insulin sensitizing agents as an adjunct is limited and might be favorable only in patients that are resistant to clomiphene citrate alone (Franik et al., 2014).

Gonadotropins could be second-line pharmacological therapy in women with PCOS who have clomiphene citrate resistance and/or failure, or are anovulatory and infertile with no other infertility factors (Balen et al., 2013).

Lifestyle modification programs are considered a valid alternative to drug therapy for obese women with anovulatory infertility (Pasquali et al., 2006; Palomba et al., 2008). Many clinicians and recent guidelines regard lifestyle management as the primary therapy in overweight and obese women with PCOS (Moran et al., 2006).

Discussion and Recommendations

PCOS is a worldwide health concern. Research indicates that PCOS has existed for centuries, yet remains a mystery to researchers and healthcare practitioners even though a lot is known about the syndrome. PCOS poses a challenge for patients and family members especially in the areas of care, treatment and cost. Numerous phenotypes of PCOS are identified: hyperandrogenism, oligo-amenorrhea, hirsutism, chronic anovulation, polycystic ovaries and obesity with insulin resistance as the main mechanism of PCOS.

Currently, four diagnostic criteria exist for diagnosing PCOS. The 2003 ESHRE/ASRM criteria remains the most widely used tool in practice, but adds complexity to diagnosis when women present with some symptoms of PCOS, but do not meet all of the criteria.

Implications for Patient

Nutrition, as a contributing factor, can be easily modified to reduce risk of poor pregnancy and neonatal outcomes. Research indicates that reduced caloric intake and balanced nutrient food sources should be encouraged and enforced in pregnant women with PCOS to reduce insulin resistance and hyperinsulinemia. Past studies have demonstrated that decreased weight in women with PCOS improves health outcomes.

Hypertension and GDM are frequent comorbidities for pregnant women with PCOS. Hypertension during pregnancy increases the risk of pre-eclampsia and eclampsia, which escalates the risk of preterm delivery. GDM can result in fetal macrosomia and lead to cesarean delivery. Not all women with PCOS are affected, but those who are require closer monitoring during pregnancy.

Implications for Family

A woman with PCOS is designated as a high-risk pregnancy, which requires more frequent prenatal assessment and increases cost for transportation and care. Loss of income from missed

work is a significant financial burden for the family; this occurs when the women is confined to bedrest for a long duration or needs to remain home to care for a preterm neonate.

Preterm delivery also predisposes the neonate to illness and presents challenges with "growth and developmental catch-up" with peers. Preterm delivery usually necessitates the neonate to experience a prolonged stay in neonatal intensive care and step-down units. Separation generates pressure for parents to participate in care and for extended family to provide care for siblings at home. There is no accurate measure for emotional costs.

Implications for Society

It has been estimated that every $1.00 invested in prenatal care and poor outcome prevention results in $4.00 of savings in care in the United States. Women with PCOS experience financial burden from medications and therapies to manage hypertension and altered glucose; the burden escalates even more during pregnancy. Facilitation of early recognition, diagnosis and management of comorbidities related to pregnancy can reduce downstream pressure on reimbursement systems such as private and employer insurance, publicly funded programs or federal mandates.

Implications for Healthcare Practitioners

Young female adolescents whose first-degree women relatives have PCOS should have early monitoring as the rate of familiar occurrence and heritability is high. Early detection can lead to prompt management, which reduces the consequences of uncontrolled hyperandrogenemia and T2DM. Early detection of pregnancy in women with PCOS is vital to moderating the fetal consequences, as well as minimizing risk for litigation when perinatal outcomes are poor.

Healthcare providers need to negotiate with payment systems for expanded laboratory test panels and to join forces with outpatient services that provide advanced perinatal surveillance. Healthcare providers need to serve as case managers when bedrest is necessary or intensive insulin

therapy is warranted. Individual healthcare providers must collaborate with peers, incorporating the full range of specialties such as endocrinology, cardiology, and perinatology so that family medicine and internal medicine practices can provide the best standards of care.

Implications for physician assistants (PAs)

PAs should understand the symptoms, causes and risk factors of PCOS in order to identify and assist in accurate diagnosis of women with PCOS. PAs should access reviews and criteria available through NIH, ESHRE/ASRM and WHO in order to avoid mistakenly ruling "in or out" of PCOS. PAs should know the diagnostic procedures available and select tests that are effective in diagnosing PCOS based on current WHO recommendations. PAs should be aware of the treatment guidelines available for PCOS such as the current WHO recommendations. PAs should be aware of the challenges that women with PCOS face in achieving pregnancy and having a healthy baby.

Finally, yet importantly, PAs must have the requisite skills to counsel patients and family members accurately and compassionately. Trust is foundational to quality care.

Implications for future research

Although there exists a sizeable body of knowledge regarding women with PCOS, further methodologically rigorous trials are important to address the following:

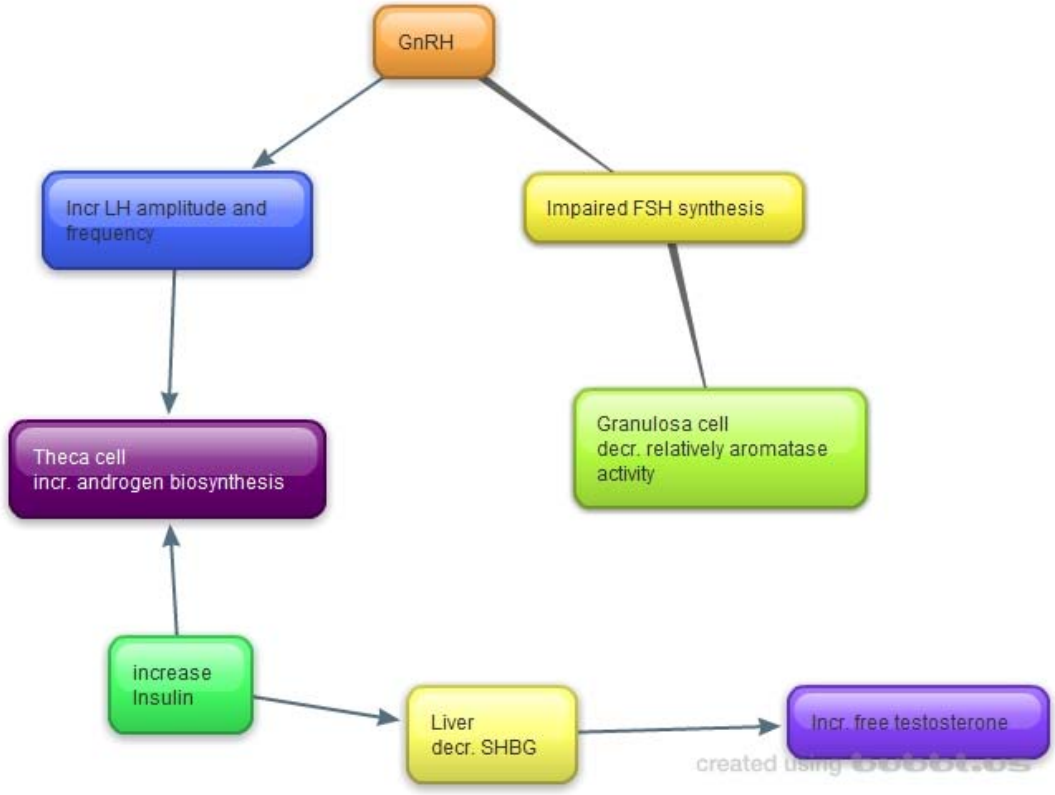
1. The extent of benefits of lifestyle management compared with no or minimal therapy for all clinically relevant PCOS outcomes.
2. The efficacy of different modes of lifestyle management in PCOS such diet, exercise, behavioral modification or combinations.
3. The effect of lifestyle management for overweight and non-overweight women with PCOS and specific reproductive outcomes such as menstrual regularity, ovulation, fertility, pregnancy complications and offspring outcomes.
4. Development of highly accurate, simple, and cost effective screening assays

Conclusion

PCOS is a major health concern for affected women, their families, healthcare practitioners, and general society. Insulin resistance and hyperinsulinemia, both implicated in the mechanisms of PCOS, should be monitored in all affected women. The necessary lifestyle adjustments and therapeutic medical regimen are well supported as means to reduce the risks associated with the PCOS.

APPENDIX 1

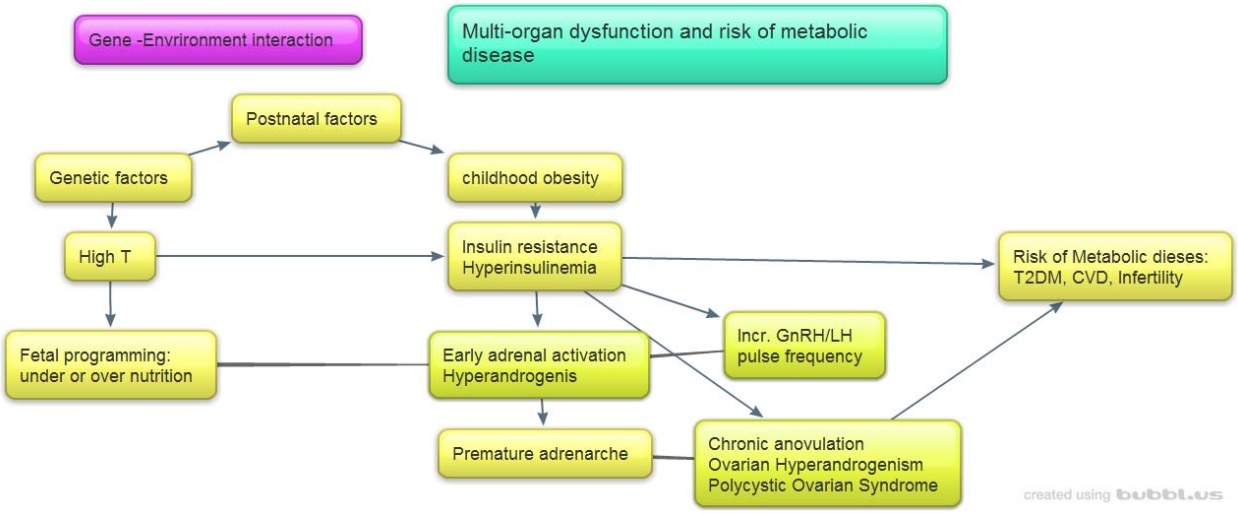
Pathophysiology of PCOS



(Courtesy of Dr. Diane E. Woodford, Clinical Assistant professor, Reproductive Endocrinology and Infertility, University of Washington Medical Center, Seattle).

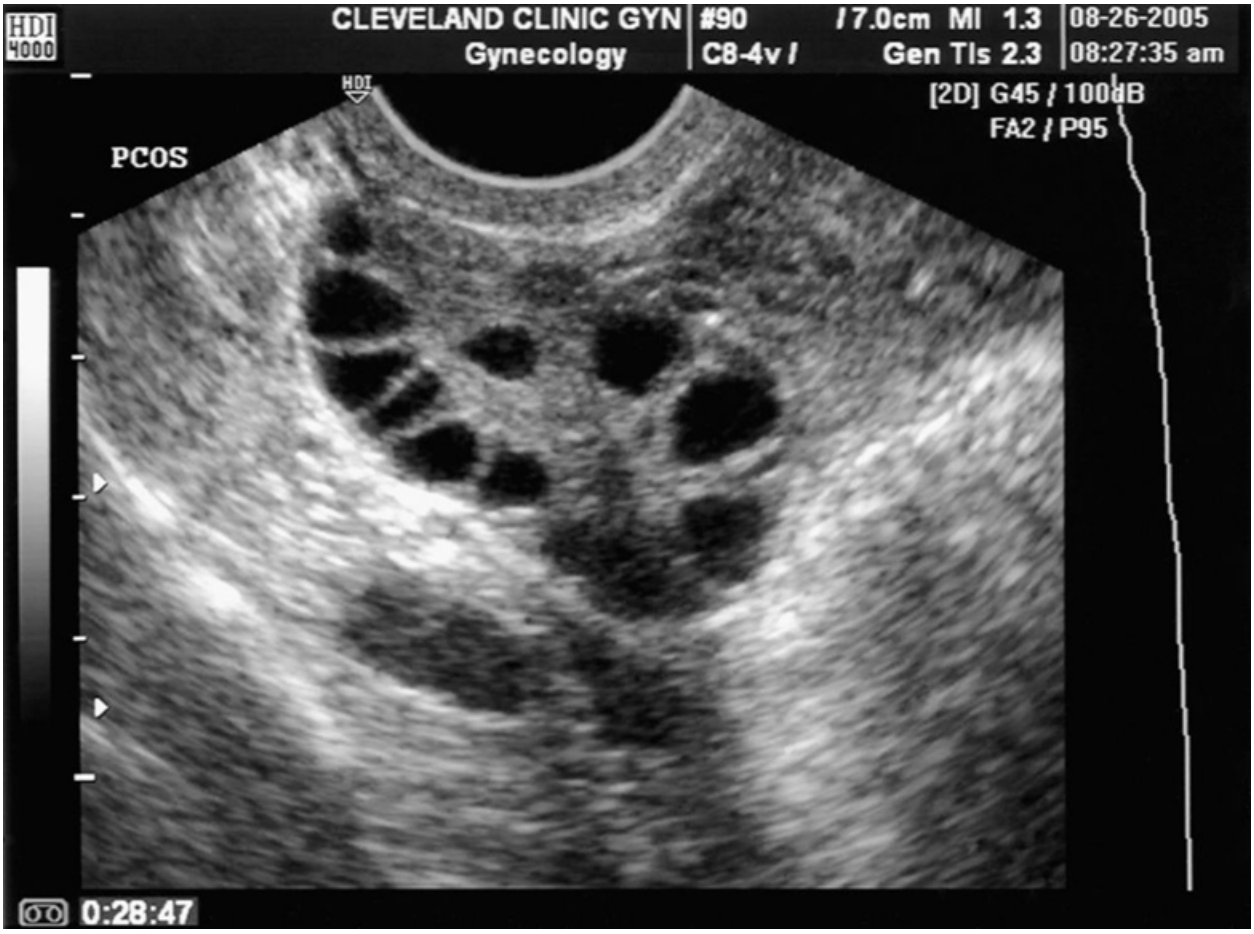
APPENDIX 2

Proposed ontogeny of polycystic ovary syndrome with manifestations starting in childhood (Abbott & Bacha, 2013). Straight lines conncection, relationship has not been clearly established.



APPENDIX 3

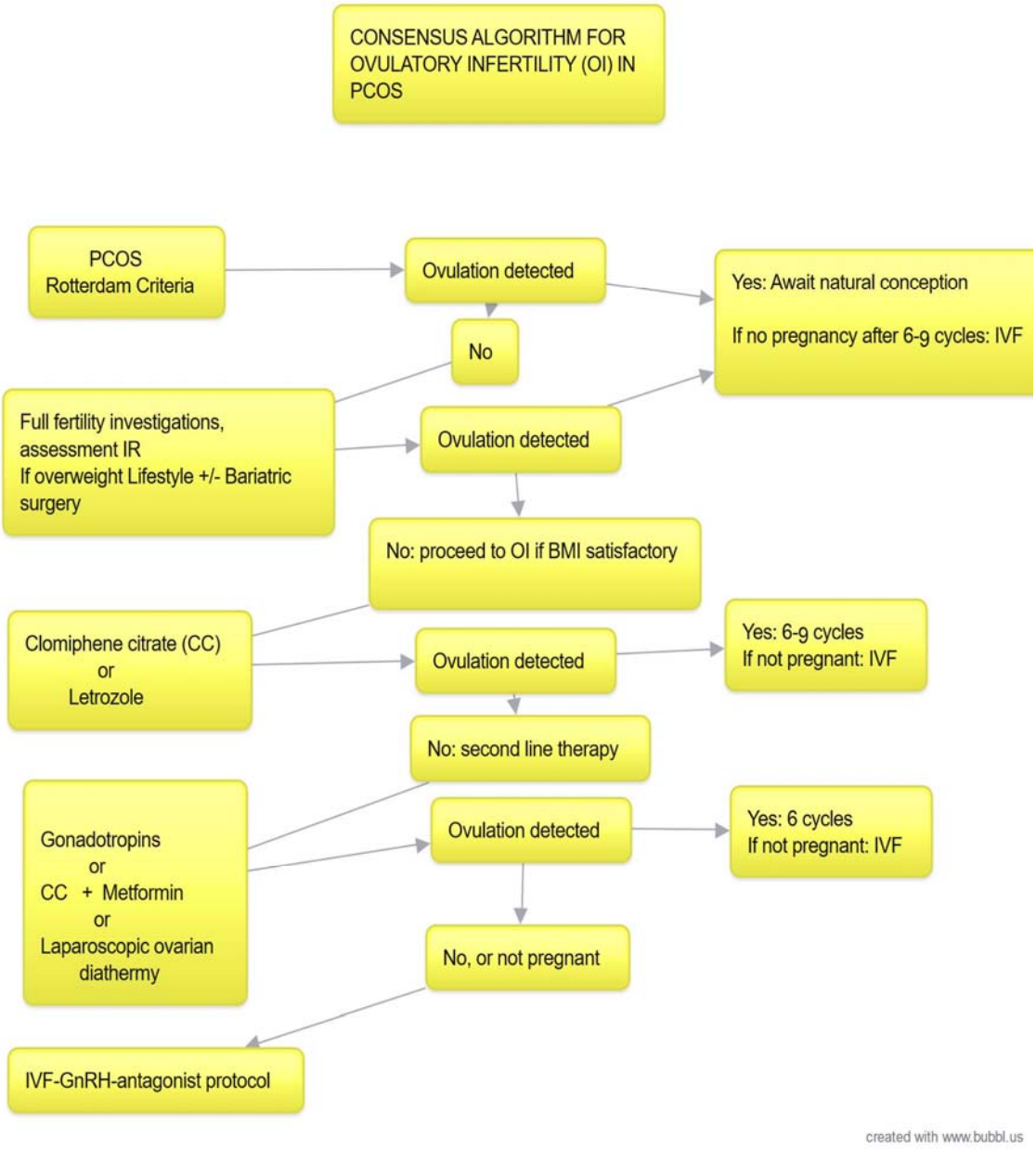
Ultrasound capture displaying a “String of Pearls”



http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/womens-health/infertility/

APPENDIX 4

Consensus Algorithm to guide clinicians when managing women with anovulatory infertility in PCOS (Balen et al., 2016).



APPENDIX 5

WHO Recommendations (2014)

It is our strong recommendation, based on high quality evidence, that either clinical evidence of HA or biochemical assessment should suffice to define HA in PCOS. Dermatological manifestations of PCOS (acne, hirsutism and alopecia) should be assessed but vary widely between different ethnic groups and correlate poorly with biochemical HA (WHO, 2014).

(i) The measurement of total testosterone is a good screening tool for the exclusion of other causes of androgen excess and will suffice when other testosterone assays are not available.

(ii) Calculated bioavailable testosterone, free testosterone or FAI should be considered the best test at this time for biochemical diagnosis of HA and may be elevated even in the presence of normal total testosterone in PCOS.

(iii) The assay for SHBG is expensive and, in low resource settings, the measurement of total testosterone will suffice.

(iv) If androgen levels are markedly above laboratory reference ranges, or there is rapid onset or progression of signs of HA, secondary causes should be considered such as non-classical CAH and further investigations should be implemented.

(v) Reference ranges for different assays and laboratories vary widely and clinical decisions should be guided by the reference ranges of the laboratory used.

We suggest that the following practice points be strongly recommended, despite being based upon ungraded evidence.

(i) FSH, LH and estradiol should be measured on days 1–5 of the cycle, or at random in a woman with amenorrhea or oligo-amenorrhea.

(ii) Assessing ovulation in oligo-amernorrheic or amenorrheic women with PCOS is difficult.

(iii) A luteal-phase progesterone measurement can be used to assess ovulation.

(iv) Ultrasound monitoring of ovarian activity combined with biochemical assessment of ovulation should be administered to provide more information about timing of ovulation and ovarian function.

(v) AMH may be a biochemical marker for polycystic ovaries, although normative ranges are yet to be agreed and therefore this is a weak recommendation.

It is our strong recommendation, based on high quality evidence, that ultrasound of the pelvis should be performed to assess ovarian morphology. The polycystic ovary should contain at least 12 follicles in at least one ovary, 2–9mm in diameter. With modern-day high resolution scanning, it is appropriate to consider a polycystic ovary to have more than 12 follicles but there is no consensus on the precise number.

It is our strong recommendation, based on ungraded evidence that women with PCOS at high risk of diabetes or prediabetes, i.e. women with a BMI > 30 kg/m², and high-risk ethnic groups including South Asian, Hispanic and Polynesian women with BMI > 25 kg/m², or with a family history of DM2 should be screened with an OGTT prior to fertility treatment. Furthermore, HbA1c is an alternative marker for metabolic disease.

It is strongly recommended based on high-quality evidence that practitioners must consider the ethnicity of the woman when diagnosing and managing PCOS. We suggest the following practice points be strongly recommended based upon high quality evidence.
(i) Ethnic-specific BMI cut-off points should include waist circumference measurement to identify those at risk and apply secondary prevention despite a 'lower' BMI in high-risk groups.

(ii) Family history (of diabetes/PCOS) should be reviewed and baseline 75 g OGTT or measurement of HbA1C should be carried out at initial evaluation of high-risk ethnic groups e.g. South Asian, Hispanic and Polynesian women.

In addition, we suggest the following practice points be strongly recommended based upon ungraded evidence.

(i) Greater awareness is required about the variation in PCOS phenotype linked to IR related to ethnicity e.g. South Asian, Hispanic, Polynesian women.

(ii) A policy of training primary healthcare givers in resource-limited countries with high-risk populations should be adopted and should include evaluating women of reproductive age with PCOS using simple low-cost methods, such as measuring BMI, waist circumference, blood pressure and acanthosis nigricans.

We strongly recommend the following based upon moderate quality evidence:

(i) Lifestyle management (single or combined approaches of diet, exercise and/or behavioral interventions) for weight loss or prevention of weight gain, or for general health benefits, should be recommended in all women with PCOS.

(ii) Lifestyle management targeting weight loss in overweight women and prevention of weight gain in lean women should include exercise and reduced dietary energy (caloric) intake and should be first-line therapy for all women with PCOS.

(iii) To optimize adherence with lifestyle interventions, psychosocial factors should be considered and support should be provided to infertile women with PCOS, although the evidence for this is weak.

We suggest a weak recommendation based upon low quality evidence that bariatric surgery could be considered to improve fertility outcomes in women with PCOS who are anovulatory, have a BMI ≥ 35 kg/m2, and who remain infertile despite undertaking an intensive structured lifestyle management program involving reducing dietary energy intake, exercise and behavioral interventions preferably for a minimum of 6 months.

We strongly recommend the following treatment guidelines:

(i) Ovulation induction should be carefully monitored by practitioners with appropriate training and expertise to ensure effectiveness and safety, with respect to reducing risk of multiple pregnancy and OHSS (high-quality evidence).

(ii) CC or letrozole (when available and permissible) should be first-line pharmacological therapy to improve fertility outcomes in women with PCOS and anovulatory infertility, with no other infertility factors (high-quality evidence).

(iii) CC-resistant patients could be offered low dose gonadotropin therapy, CC with metformin or laparoscopic ovarian diathermy (LOD) (low quality evidence).

In addition, we suggest a weak recommendation based upon high-quality evidence, that letrozole can be used as second-line pharmacological therapy in women with PCOS who have CC resistance and/or failure, and are anovulatory, and infertile, with no other infertility factors.

We suggest as the following weak recommendations:

(i) Metformin could be used alone to improve ovulation rate and pregnancy rate in women with PCOS who are anovulatory and are infertile with no other infertility factors, if facilities are not available for monitoring of CC or letrozole, which are more effective (high-quality evidence).

(ii) Metformin could be combined with CC to improve fertility outcomes rather than persisting with further treatment with CC alone in women with PCOS who are CC resistant, anovulatory and infertile with no other infertility factors effective (high-quality evidence).

(iii) There is insufficient evidence to recommend the use of other insulin sensitizers such as thiazolidionediones, d-chiro-inositol and myo-inositol in the treatment of anovulatory PCOS (ungraded evidence).

Furthermore, we strongly recommended the following:

(i) Gonadotropins 'could' be second-line pharmacological therapy in women with PCOS who have CC resistance and/or failure, are anovulatory and infertile, with no other infertility factors (moderate quality evidence).

(ii) In women with PCOS who are anovulatory and infertile, with no other infertility factors, where appropriate to use gonadotropins, consideration should be taken to provide a low-dose protocol and appropriate monitoring that minimizes the risk of multiple pregnancy (high-quality evidence).
We strongly recommend based upon moderate quality evidence that laparoscopic ovarian surgery could be second-line therapy in women with PCOS who are CC resistant, anovulatory, and infertile, with no other infertility factors (WHO, 2014).

We strongly recommend the following based upon good quality evidence:

(i) In women with PCOS, IVF is indicated in those who have not responded to first or second-line ovulation induction therapies or those who require IVF for other indications.

(ii) Women with PCOS undergoing IVF are at an increased risk of OHSS and should be monitored carefully.

(iii) In women with PCOS undergoing IVF, the GnRH antagonist protocol should be preferred as a safer alternative to the traditional GnRH-agonist protocols because of the reduced risk of OHSS.

(iv) If a long GnRH-agonist protocol is to be used, the addition of metformin reduces the risk of OHSS (high-quality evidence).

We strongly recommend the following based upon high-quality evidence.

(i) Women with PCOS should be fully informed that the risks of pregnancy are increased; e.g. GDM, pre-eclampsia and hypertension.

(ii) Women with PCOS should be fully informed that obesity both exacerbates the risks outlined above and is associated with an increased risk of miscarriage.

In addition, women with PCOS should be fully informed that the risks for the child are increased; e.g. prematurity, SGA and metabolic dysfunction in later life (high-quality of evidence, weak recommendation) (Balen et al., 2016)

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Abstract

Objective: Identify specific features of insulin resistance in women with PCOS and impact on pregnancy outcomes.

Study design: More than 150 articles about PCOS from 2005-2016 were reviewed. Classic articles older than ten years were incorporated as background. Articles related to psychological effect of PCOS and non-English articles were excluded.

Database: PubMed, Google Scholar, NIH, ESHRE, ASRM, AE-PCOS, Clinical Key, Dissertation Abstract International (DAI).

Conclusion: PCOS is a major health concern for parents, family, healthcare practitioners, and society. Insulin resistance and hyperinsulinemia, which are involved in the mechanism of PCOS, should be monitored in all women with PCOS. The necessary medical interventions and lifestyle modifications should be encouraged in order to reduce the risks associated with PCOS syndrome for women and future progeny.

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Complete Title: Effect of Insulin Resistance in PCOS and impact on pregnancy

Date Completed: 12/12/16 Date Approved: 12/14/16

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