

Short Commentary

Polycystic ovarian syndrome (PCOS) this mysterious disease

Eissa MK*

*Cyberjaya University College of Medical Sciences, Malaysia

***Corresponding author:** Eissa MK, Cyberjaya University College of Medical Sciences, Malaysia, Tel:+60 3-8313 7000; E-mail: mosteissa@hotmail.com

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PCOS is more than a reproductive pathology. It is a systemic syndrome. This syndrome affects 5-10% of females at reproductive age. It does not only disfigure the woman by trunk obesity and hirsutism but induces her infertile with oligo/amenorrhea. The diagnosis of PCOS depends on the consensus of ESHRE/ASRM meeting in Rotterdam (2003) [1]. This means the presence of two of three criteria; clinical as obesity, infertility, hirsutism, and oligo/amenorrhea, ultrasound finding of polycystic ovaries and endocrinological as increased level of LH/FSH ratio and increased levels of androgens. It is widely believed to be a multifactorial disease. It affects women at various stages of their life. It may start in-utero in genetically predisposed fetus. At reproductive age, it causes infertility, oligo/amenorrhea, and type II Diabetes Mellitus. During pregnancy, there is an increased incidence of miscarriages, gestational diabetes, hypertension and preeclampsia. Later in life may increase the risk of cardiovascular accidents, hypertension, diabetes and other metabolic disorders.

Franks et al in 2006 [2], hypothesized, that syndrome starts in utero in genetically predisposed fetus and continue in prepubertal life depending on endocrinological and environmental factors. The disorder is diagnosed in prepubertal girls [3]. The characteristic insulin resistance is recognized not only in obese PCOS patients but also in lean ones. This insulin resistance plays a major role in hyperandrogenic status with the increased level of LH. Both, affect the steroidogenesis of the ovaries and the production of the sex hormones binding globulin produced by the liver.

The exposure of the female fetus, in utero, to excessive production of androgens may alter the ovarian activity later on and explain some of the endocrinological abnormalities [4]. The source of androgens excess is more likely to be the fetal ovary, which is normally quiescent, but it could produce an excess of androgens in response to maternal hCG in subjects genetically predisposed to PCOS [4]. There are controversial results regarding the level of testosterone (T) in the umbilical cord of the female fetus [5,6]. By the time of delivery, the high level of T may be abolished. Measuring T at mid-term pregnancy may be more appropriate. The hypothesized increased T at mid-term pregnancy was found to be associated with high level of anti-mullerian hormone (AMH) which

is characteristic of PCOS patients [7]. In adolescence, when the hypothalamic pituitary ovarian axis is activated the insulin level is increased which may result in increased level of circulating androgens and reduction of sex hormone binding globulin. Both result in stimulating steroidogenesis of the ovaries.

Malequo et al (2009) [8] studied girls at age 4-8 and 9-13 of PCOS mothers and found exaggerated adrenarche in comparison with daughters of nonPCOS mothers. This obesity caused by insulin resistance may result in hyperandrogenaemia through an effect of insulin on adrenal and ovarian steroidogenesis [9]. This may result in modifications of LH pulse and magnitude, increased LH frequency but low LH amplitude, and diminished overnight LH pulse amplitude compared with normal-weight girls [10]. Subsequently, hyperandrogenaemia reduces the inhibition of GnRH pulse frequency by progesterone, causing rapid LH pulse secretion and a further increase in ovarian androgen production [11,12].

Since Barker advertised his theory in 1979 [13] about that some diseases in adulthood may result from epigenetic mechanisms developed under hormonal or nutritional status in-utero, the PCOS may have the same origin. Exposure of the female fetus to the environment of excessive androgens may epigenetically alter fetal reproductive tissue leading to the appearance of phenotype PCOS in adulthood. Other, genetic factors as insulin resistance and environmental factors as nutrition in adulthood may contribute to the development of PCOS phenotype in association with the epigenetic anomalies. If further research verifies this hypothesis, new prospects for preventive treatment during the critical prenatal period will be mandatory.

PCOS run in families which suggest genetic predisposition [14]. The mechanism of inheritance is not clear. Some researchers suggested an autosomal dominant transmission linked to a single genetic defect but most authors define PCOS as a polygenic disorder. An association has also been found between "pro-inflammatory" genotypes and PCOS, linked to polymorphism of genes coding for TNF-alfa, IL-6 and IL-6 receptor [14].

Environmental factors in PCOS are important. Although PCOS appear more common in Asian and mediterranean women,

other observations suggest the existence of different environmental factors, such as diet, physical activity and lifestyle in general.

Many factors affect the folliculogenesis. Deficiency of FSH, excessive LH, hyperandrogenemia and excessive insulin level and insulin resistance [15]. Follicular fluid plays a role in the development of PCOS [15]. Vitamin D is implicated in the pathogenesis of PCOS. Deficiency of Vitamin D is noticed in obese patients with PCOS. Hypo-vitaminosis D may play a role in the development of insulin resistance and impaired glucose tolerance [16].

Gonadotropin-releasing hormone (GnRH), LH and FSH play an important role in the pathogenesis of PCOS. Excessive secretion of LH which may be affected by high frequency or amplitude of GnRH impulse may result in abnormal folliculogenesis. Excessive LH may result in premature luteinization of primordial follicles and later on degeneration. LH may also activate premature meiotic processes that damage oocyte quality and contribute to the formation of embryonic aneuploidies [17].

Hyperandrogenaemia is characteristic to PCOS. In PCOS there is increased the level of total T, free T, SHBG, androstenedione (A), 17-hydroxy progesterone (17-OHP) and dehydroepiandrosteronesulfate. Aromatase is a granulosa cell enzyme that converts androgens into estrogens. It may be partly responsible for hypoandrogenism in this syndrome [18].

Insulin resistance is defined as tissues and cells needs more insulin level to function normally. There is a hyperinsulinemia status while glucose level remains normal. When pancreatic cells fail to secrete enough insulin, glucose level increase and Diabetes type 2 are diagnosed [19]. Many PCOS women have insulin resistance and hyperinsulinemia. This results in excessive androgen production by direct stimulation of ovaries and by inhibiting SHBG production by the liver. Insulin increases ACTH-mediated androgen production and increases LH-stimulated follicular steroidogenesis [20]. About two-thirds of PCOS women are obese and have insulin resistance. However, many studies showed hyperinsulinemia in lean ones [19]. These findings proved by cell cultures in a bovine model. These studies showed that insulin has receptors on the hypothalamus and pituitary glands that contribute to LH and FSH secretion [19].

AMH is expressed by granulosa cells of women at the reproductive age to control the formation of primary follicles and recruitment by FSH [21]. PCOS women have a high concentration of AMH in serum and follicular fluid. This results in increased number of antral follicles and failure of further growth [22]. This high AMH level in follicular fluid is associated with the development of immature follicles and low fertilization rate [22].

An increased Follistatin/activin ratio and elevated concentrations of inhibin B have been found in PCOS patients [23]. Follistatin (FS) has been associated with the arrest of follicle growth and reduced oocyte development. Activin promotes follicular growth by increasing granulosa cell response to FSH. It decreases androgen synthesis and stimulates oocyte maturation. Inhibin-B inhibits FSH production and stimulated thecal cells to produce androgens [21].

Vascular endothelial growth factor (VEGF) is expressed in granulosa cell, theca cells and follicular fluid (Qiao and Feng 2011, Dumesic and Abbott 2008). It plays a role in follicular maturation, oocyte quality, fertilization and embryos development. In PCOS [15,21,23]. VEGF is low in PCOS which means oocyte immaturity, low fertilization rate and bad quality of embryos, which may lead to a high incidence of miscarriages [23].

Interleukins (IL) is a group of cytokines released by leucocytes. IL1, IL2, IL6, IL8, IL11 and IL12 play a role in follicular maturation. Deficiency of IL12 and increased level of IL13 in PCOS mean immaturity and bad quality of oocytes, low rate of fertilization and pregnancy [15,21,23].

Tumours necrosis factor alpha (TNF alpha) plays a role in regulating follicular growth, steroidogenesis and apoptosis. High concentration of TNF alpha is inversely proportion to oestradiol concentrations in follicular fluid and indicated bad quality ovum and embryo [23]

Fas and Fas legend (FASL) are members of TNF-alpha. Fas has an anti-apoptotic activity while FASL has an apoptotic effect. In PCOS patients, treated by metformin, FASL concentration drops which mean a better quality of follicles and embryos pregnancy [15,21,23].

Typical PCOS patients are obese, hirsute, amenorrhea or hypomenorrhea, infertile and have ultrasonic polycystic ovaries. During pregnancy, there is increased the incidence of miscarriage, gestational Diabetes, and hypertension. This cycle irregularates are usually associated with anovulation. This cycle irregularity begins after menarche and decreases towards menopause. This indicated a drop of androgen in PCOS patients with the advancement of age [24]. In adult women with PCOS, 95% have amenorrhea while during adolescence, 21% have amenorrhea while 43% have oligomenorrhea, 21% have a regular menstrual cycle and 7% have polymenorrhea [19,25]. Although ultrasonographic polycystic features are characteristic of PCOS, this feature may be found in healthy fertile women. During adolescence, the ovaries are polycystic with hypothalamic amenorrhea and hyperprolactinemia [26].

Hirsutism is present in 60% of PCOS patients but ethnicity has a role. The best scoring system to evaluate hirsutism is the Ferriman-Gallwey score. The score is 0 (no hair present) to 4(maximum) in 10 assessed areas of the body, the chin, upper lip, peri areolar and intermammary areas, upper and lower back upper and lower abdomen, upper and lower limbs. The score of each area (0-4) is summed. If the total score is 7-9 (slight), 10-14 (moderate) and >15 (severe), [27]. 12-14% of PCOS patients have acne. This has ethnicity effect, being highest in endo-Asian women and least in Pacific islanders. 50% of women with acne has no PCOS. Many hirsute women have no acne. These differences may be due to the different peripheral sensitivity of androgen receptors [28].

PCOS patients have a high incidence of certain diseases as Diabetes mellitus, metabolic syndrome, cardiovascular accidents, endometrial carcinoma and others. In adolescence, obesity, hirsutism, and acne have an influence on self-acceptance and personality development. Early diagnosis and treatment of PCOS in adolescence is, therefore, fundamental because it can slow down or prevent the appearance of these pathologies in adulthood. However, Diagnosis of PCOS in such age may be problematic. Some authors advise having the three criteria of Rotterdam. If the case is not confirmed, the patient should be monitored to adulthood [29]. In pre-menopause, studies showed a higher concentration of primordial follicles and better ovarian reserve in comparison with healthy women. They have better-controlled cycles during that period and goes to menopause two years later [30].

High insulin resistance and hyperandrogenic, in PCOS patients, increase the risk of developing morbid diseases as Diabetes mellitus, metabolic syndrome, hyperlipidemia, hypertension, vascular accidents, myocardial infarction [19,31]. Such women are more vulnerable to endometrial hyperplasia and carcinoma. Predisposing factors include obesity, hyperandrogenic and infertility, all present in PCOS patients. Prophylactic measures should be taken in PCOS patients to guard against this development as giving progestogens to compact hyperandrogenic status, ultrasound examination to detect endometrial hyperplasia and endometrial biopsy. Induction of menstruation, at least, every three months is recommended [32].

PCOS patients have 50% chance to miscarry. This is three times the non-PCOS patients [33]. Mechanisms of miscarriage include overexpression of androgen and steroid receptors and simultaneously reduced expression of molecules of implantation, such as α vs β 3 integrins and glycodeclin. hyperinsulinemia which inhibits endometrial and stromal differentiation in vitro (decidualisation) and locally down-regulates IGFBP-1. Hypofibrinolysis mediated by high levels of plasminogen activator inhibitor (PAI).

increased resistance to the uterine arteries blood flow leading to reduced sub-endometrial and endometrial vascularisation [33].

PCOS patients have 20-30% incidence of Diabetes mellitus and 10-15% incidence of preeclampsia and pregnancy induced hypertension. The mechanism behind that may be related to obesity, alterations of glucose metabolism and uterine vascularization (Denison et al 2010). Obesity in pregnancy is, in fact, associated with various complications, such as miscarriage, pre-eclampsia, gestational diabetes, fetal macrosomia and cesarean section [34]. Fat tissue produces adipokines, including leptin, adiponectin, TNF- α , IL-6, resistin and visfatin, which could be involved in activation of insulin resistance in pregnancy. Adipokines can also produce an excessive local and systemic inflammatory reaction, which would play a key role in the pathophysiology of PE/PIH and the birth of SGA babies. It is also possible that placental macrophages contribute to inflammation within the placenta by secretion of pro-inflammatory cytokines such as IL-1, TNF- α and IL-6 in cytotrophoblast and syncytiotrophoblast cells [35]. Physiologically, pregnancy is associated with insulin resistance because of human placental lactogen (HPL), human placental growth hormone (hPGH) and progesterone. PCOS are more likely to have higher insulin resistance and a higher risk of developing gestational Diabetes. Alterations of uterine vascularization may interfere with trophoblastic invasion resulting in the development of hypertension and intrauterine growth restriction [34].

Assessment of neonates of PCOS patients showed a higher incidence of neonatal morbidity and mortality in addition to a higher admission rate to intensive care units [36]. This may be due to higher incidences of maternal and fetal complications as gestational diabetes and hypertension, prematurity, small for gestational age and multiple pregnancies. This multiple pregnancy is due to a higher incidence of induction of ovulation in PCOS anovulatory patients.

In conclusion, the pathophysiology of PCOS is not completely understood. PCOS is not a reproductive pathology but a systemic disease that starts early in intrauterine life. There is a great advancement in diagnosis and prevention of PCOS including hormonal contraceptives, antiandrogen drugs, metformin and inositols. Hyperinsulinaemia and insulin resistance are as important as obesity and hirsutism. Research in this field may shed more light on this condition.

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