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IS POLYCYSTIC OVARIAN SYNDROME PURELY AN INVENTED DIAGNOSIS AND NOTHING OTHER THAN A VARIATION OF NORMALITY?

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common cause of anovulation, infertility and hyperandrogenism, in addition to many long term unfavorable metabolic sequels in women worldwide. The question of whether the presence of polycystic ovary morphology alone, but without other diagnostic criteria of PCOS, is pathological or a normal variant of ovarian morphology is debated. Several studies have been shown abnormal hormonal responses in women who have polycystic ovary morphology alone, in absence of other features of PCOS, during ovulation induction procedures in addition to a provoked androgenic response and insulin resistance. Furthermore, there is a clear evidence of increased anti-Mullerian hormone levels, which can be considered as a surrogate marker of PCOS, in that subset of women. Based on the above, polycystic ovary morphology is obviously not a normal variant, but rather a mild phenotype of PCOS.

KEYWORDS: Polycystic ovary, anovulation, infertility, hyperandrogenism.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most prevalent condition resulting in reproductive, specifically anovulation, infertility and androgen excess; and metabolic issues in women. PCOS affects between 5 and 10% of women of reproductive age worldwide (Norman RJ 2007). PCOS is not one disease, despite its main impact on fertility, PCOS can lead to long term consequences such as cardiovascular diseases, hypertension, type 2 diabetes. Several studies have been performed to attempt to determine the prevalence of polycystic ovary (PCO) as detected by ultrasound alone in the general population and have found prevalence rates in the order of 17–33% (Balen AH 1995). In the same line, it is still a highly debatable issue whether the presence of polycystic features as detected by ultrasound, but without other relevant features of clinical or biochemical evidence of androgen excess, or chronic anovulation, is considered as a pathological condition or only represented a normal variant of ovarian morphology. For instance, a large-scale study of ovarian ageing among women enrolled in the Kaiser Permanente Health Plan in California found a high prevalence of PCO among younger women, which resolved with ageing (Johnstone, E.B 2010). Therefore, the distinction between PCO and PCOS was not clear and the available criteria defining PCOS were heterogeneous and not consensual (Catteau-Jonard S 2012).

Pathophysiology: PCOS is a real disease

The etiology of PCOS remains uncertain but intrinsic abnormalities in the synthesis and secretion of androgens are a plausible basis for the syndrome. There is clear evidence for constitutive hypersecretion of androgen by ovarian theca cells (Gilling-Smith C 1994) but abnormalities of adrenal androgen production have also been implicated in the etiology.

Moreover, increased ovarian sympathetic nerve activity might contribute to PCOS by stimulating androgen secretion (Dissen, G.A 2000). Nerve growth factor (NGF) is a strong marker for sympathetic nerve activity, and recently, it was demonstrated that women with PCOS has enhanced ovarian NGF production (Dissen, G.A 2009).

The finding that granulosa cells from anovulatory PCO responded well to follicular stimulating hormone (FSH) in culture directed initial investigations into follicular arrest towards discovery of raised levels of a locally produced inhibitors (Pasquali R (2011). Androgens are an obvious candidate, but production is raised in theca from ovulatory PCO also (Gilling-Smith, C 1997). In that line, while insulin causes premature acquisition of luteinizing hormone (LH) receptors possibly leading to early follicular luteinization(Willis, D 1996), Anti-Mullerian hormone (AMH) is raised in women with PCOS, and granulosa cell production is considerably higher in anovulatory than ovulatory women with PCOS.

Recent data indicated that it is those women in whom AMH levels fall who have the best response to methods to induce ovulation (Pasquali R 2011).

Kit ligand (KL) is an intraovarian cytokine that promotes multiple aspects of folliculogenesis in animal models may play a role in the morphogenesis of PCO such as abnormal oocyte growth, increased follicle and stromal density, thecal hypertrophy, and increased thecal cell androgen biosynthesis.

FSH refractoriness may play a key role in PCOS. Adding FSH (with clomiphene or exogenous FSH) or loss of ovarian tissue (wedge resection or laparoscopic ovarian diathermy, restores normal follicular growth, suggesting probably an ovarian endogenous inhibition of FSH action in PCOS (Elting, M.W 2003). Candidates for the source of FSH refractoriness include tissue growth factor-alpha (TGF-alpha), epidermal growth factor (EGF), follistatin and particularly the high concentrations of AMH (Pigny, P 2003).

What is the clinical significant of Polycystic ovaries in normal women?

In 2003, a joint European Society of Human Reproductive and Embryology / American Society of Reproductive Medicine (ESHRE/ASRM) consensus meeting produced a refined definition of PCOS (Rotterdam ESHRE/ASRM 2004) and the morphology of the polycystic ovary was defined as an ovary with 12 or more follicles measuring 2–9 mm in diameter and/or increased ovarian volume (>10 cm^3). A woman qualifies for the diagnosis of polycystic ovary syndrome (PCOS) if she has at least two of three items, namely polycystic ovary morphology (PCOM) , hyperandrogenism, and oligoanovulation. The inclusion of ultrasound criteria is the subject of controversy because of its apparent lack of specificity; features of PCO are also observed in normal women (Duijkers IJ 2010). Moreover, advances in ultrasound technology allowing accurate detection of small antral follicles may have contributed to an artificial increase in prevalence of polycystic ovary (PCO) (Goodman NF 2015).

While the spectrum of 'normality' might include the presence of PCOM in the absence of signs or symptoms of PCOS, women with PCO morphology alone show typical responses to stresses such as gonadotrophin stimulation during in-vitro fertilization (IVF) treatment or to weight gain, whether spontaneous or as stimulated by sodium valproate therapy (Isojarvi, JI 1993). Furthermore, It has been found that some women with hypogonadotropic hypogonadism also have PCO detected by pelvic ultrasound had significantly higher serum LH concentrations responding to GnRH for ovulation induction than women with hypogonadotropic hypogonadism without PCO(Schachter, M 1996).These results suggest that the cause of hypersecretion of LH involves a perturbation of ovarian-pituitary feedback, rather than a primary disturbance of hypothalamic pulse regulation.

Serum AMH levels in the patients with PCO are intermediate between these in the normal persons and those with PCOS, and significantly different from both. Thus, PCO is apparently not a normal variant, but rather a mild phenotype of PCOS. The clinically silent granulosa cell abnormality in women with PCO may be part of the reason for such findings (CATTEAU-JONARD S et al 2012).

PCOS: Chronic low grade inflammation &metabolic abnormalities

Women with PCOS are known to have increased risks cardiovascular disease (Wild RA 1985, Talbott E 1995, Birdsall MA 1997). It has been estimated that women with PCOS have a 7-fold relative risk for myocardial infarction. By the time women with PCOS reach perimenopause, up to 40% will have developed hypertension, and 16% will have become diabetic (Dahlgren E 1992).

In a study by Carmina E 1997, have noted that some of normal ovulatory women who have PCO have subtle metabolic abnormalities that occur in PCOS such as elevated fasting insulin, decreased insulin-like growth factor binding protein-1 similar to women with PCOS.

Furthermore, Chang PL 2000, have confirmed that up to one third of women with PCO may have subtle findings consistent with PCOS, such as high density lipoprotein (HDL) levels below 35 mg/dL, a level considered to constitute significant cardiovascular risk (National Cholesterol Education Program-NCEP 1993), and provoked ovarian androgenic responses with lower levels of Kit ligand which is inversely correlated with increased 17-hydroxyprogesterone (17-OHP) response to gonadotropin releasing hormone agonist (GnRH-agonist) suggesting a greater androgenic response with insulin resistance.

Chronic low-grade inflammation in PCOS with altered secretion of cytokines is also related to hyperandrogenism and to the hypertrophy of adipocytes, which in turn related to insulin resistance(Spritzer PM 2015). **Figure-1.**

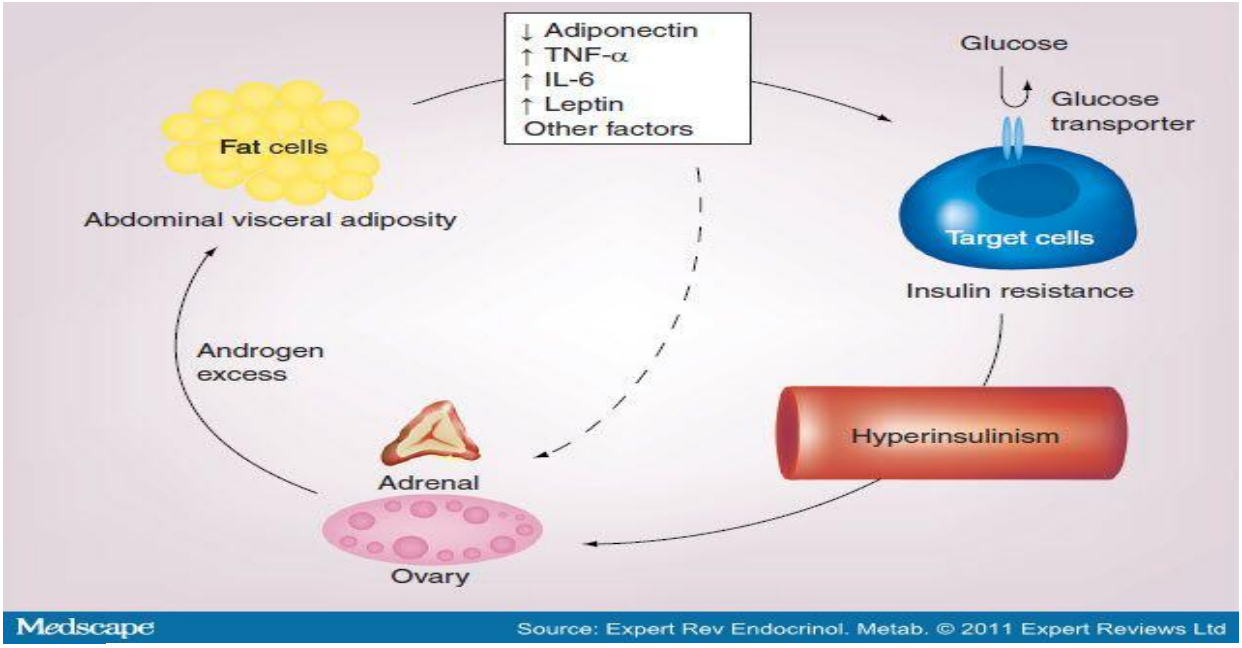

Figure-1: Unifying Hypothesis Explaining the Interplay Between the Polycystic Ovary Syndrome and Abdominal Adiposity. This interplay is the result of a vicious circle represented by the solid arrows: androgen excess favors the abdominal deposition of body fat, and visceral fat facilitates androgen excess of ovarian and/or adrenal origin by the direct effects (dashed arrow) of several autocrine, paracrine and endocrine mediators, or indirectly by the induction of insulin resistance and hyperinsulinism. Alpanes M et al (2011)// Available online:http://www.medscape.org/viewarticle/754292

CONCLUSION

PCOS status is expected to result in many long-term adverse metabolic consequences in females, specifically the increased incidence of type 2 diabetes, cardiovascular diseases and hormone-related cancers. In women with the isolated finding of polycystic ovaries on ultrasound, silent granulosa cell abnormality and subtle metabolic abnormalities are detected in those patients. Thus, polycystic ovary is an abnormal condition rather than a normal variant, and absence of hyperandrogenism in polycystic ovary does not seem linked to the metabolic condition. It is important to identify those women who are susceptible, as early as possible, which could help in adapting a proper therapeutic intervention and, probably, a successful preventive plan.

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