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Polycystic Ovarian Syndrome

Research Project

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By

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DEDICATION

To:

My lovely mother

My sweet father

My lovely family

Azhin

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I would like to thank Allah for his blessing virtues to implant the Soul of endurance and faith in myself for completing this study. Also, I have no appropriate words that fully express the immense indebtedness and deep gratitude I own to my worthy learned research assistant lecturer **Dr. Sarhang Hasan Azeez** for him keen interest admirable guidance constructive suggestions, affectionate supervision inspiring behavior and valuable knowledge which she contributed in this work in multitude ways whenever I needed, she was there near me and always strayed me out from the disaster. I would like to dedicate this work to all staff of biology department, my family and our friends.

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Abstract

Polycystic ovary syndrome (PCOS) is a chronic, complex and the most common endocrine disorder observed in women of reproductive age. This syndrome is heterogeneous by nature and is characterized by a combination of signs and symptoms of androgen excess and ovarian dysfunction. It is a significant public health issue. PCOS is associated with many comorbidities and also has a number of long term metabolic and other consequences. The prevalence is quite high and is increasing day by day. It is a syndrome to be prevented by awakening awareness both in health workers and patients. There are many areas of controversies starting from its diagnosis, pathogenesis, consequences and treatment modalities. This review is an attempt to summarize the evolution of the diagnosis and current management guidelines and also to look into the future approaches. An extensive search was made through the Cochrane database, available systematic reviews and meta-analyses and recent international guidelines for providing an updated scientific overview of PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a female endocrine disorder characterized by elevated androgen levels, ovulatory dysfunction, and polycystic ovarian morphology, as well as a constellation of classic clinical features that may include obesity, hirsutism, alopecia, acne, irregular menses, infertility and high blood pressure [Rotterdam 2004,Bulletin 2018]. Stein and Leventhal first described PCOS in 1935 when they reported on a series of seven female patients who presented with cystic ovaries amenorrhea, and abnormal terminal hair growth [Stein etal.,1935]. Since that time, the diagnosis of PCOS, among reproductive-aged women has become commonplace, with up to 10 percent of women presenting to gynecology clinic visits meeting criteria for diagnosis [Cahill etal.,March2015]. The diagnosis of PCOS has varied over the years and has included requirements of oligo/anovulation or polycys- tic ovaries, with androgen excess [Azziz etal.,2006., Zawadski etal., 1992]. However, recent consensus and current international guidelines affirm the European Society for Human Reproduction and Embryol- ogy (ESHRE)/American Society for Reproductive Medicine (ASRM) Rotterdam criteria of androgen excess, oligoovu- lation or anovulation, and polycystic ovaries on ultrasound (two of three requirements met) [Rotterdam ,2004., Sirmans etal.,2013.] as the most inclusive diagnostic criteria for PCOS and the most commonly used internationally [Mortada etal.,2015.., ccessed, 2018]. There is evidence that women with PCOS may be at greater risk for various obstetric complications, including gestational hypertension and preeclampsia [Vries etal.,1998, Palomba etal.,2015.], ges- tational diabetes mellitus (GDM), premature birth, and cesarean delivery [Qin etal., 2013.]. Gestational hypertensive disorders are the leading causes of maternal morbidity

and mortality affecting 3-10% of all pregnancies including a subset of pregnancies resulting in preeclampsia [Duley,2009., Wallis etal.,2004 “2008.], and contribute up to 16% of maternal deaths in developed nations [Khan etal.,2006]. Two large meta-analyses found a two- to four-fold increased rate of pregnancy-induced hypertension (PIH) as well as preeclampsia in women with PCOS [Qin etal.,2013., Boomsma etal.,2006], and a large nationwide study conducted in Sweden found that PCOS was associated with a 1.5-fold increased odds of preeclampsia, even after adjusting for body mass index (BMI), parity, and use of reproductive technology [Roos etal., ,2011]. The primary objective of this study was to investigate hypertension in pregnancy and the incidence of gestational hyper tension and preeclampsia in a racially and ethnically diverse cohort of pregnant women with and without PCOS and examine the independent association of maternal PCOS and gestational hypertensive disorders among women with- out preexisting hypertension. A secondary aim was to exam- ine the clinical and demo graphic predictors of gestational hypertensive disorders among the subset of women with PCOS.

Literature review

1-Definitions

While there are a number of definitions of PCOS, the Rotterdam consensus is the most widely accepted across Europe, Asia and Australia and was the definition used for the guideline. It encompasses the National Institutes of Health definition, which generally describes women with a more severe form of PCOS and requires the presence of both hyperandrogenism and oligo/anovulation. The Rotterdam Criteria require the presence of two of the following: oligo/anovulation, hyperandrogenism or polycystic ovaries on hyperandrogenism or polycystic ovaries on ultrasound.

2-Risk factor

2.1 Obesity:

Obesity is a key contributor to the clinical and metabolic manifestations of PCOS patients. The prevalence of obesity in women with PCOS was assessed in two systematic reviews and a greater risk of obesity was reported. 49,50 Observation in a meta-analysis was that PCOS women are at two and three-fold higher risk of being overweight or obese, respectively, compared with their non-PCOS counterparts and this prevalence is also affected by ethnicity; higher in Caucasian than in Asian women. The body's distribution of adipose tissue is of utmost importance as abdominal obesity is an independent risk factor for CVD. The prevalence of overweight and obesity in PCOS is about 80%, with a higher BMI and waist-hip ratio. 51 The key role of excess weight in worsening reproductive, metabolic and psychological outcomes in PCOS has also been recognized in all the

researches and analyses. 37 The international guideline in PCOS recommends that BMI be assessed in all women with PCOS and that prevention of excess weight gain is vital and weight loss is recommended as the first-line treatment for overweight or obese women. 17,52).

2.2 Insulin Resistance and Hyperinsulinemia

The majority of women with PCOS exhibit insulin resistance. This symptom is further exacerbated in obese PCOS patients as a result of their excess adiposity. The forthcoming consequence of the insulin resistance is hyperinsulinemia, which stems in part from excess release of insulin in the pancreas to compensate for insulin resistance. In turn, biosynthesis of sex steroids is modulated by insulin and insulin-like growth factor-1 (IGF-1), which are considered as most notable extra-ovarian factors stimulating androgen production. Both substances support ovarian and adrenal steroidogenesis (by increasing the activity of CYP type 17A1, or activating steroidogenic factor (SF-1) and its steroidogenic target genes, respectively) [Rosenfield etal., 2016, Kinyua etal.,2018]. Additionally, insulin also modulates LH pulse amplitude [Van rtal.,2016], and suppresses hepatic SHBG production [Yki rtal.,1995]. From this perspective, insulin resistance and hyperinsulinemia seem to be the most prominent extra-ovarian factors imposing symptoms of PCOS [Barberetal.,2016], as presented in Figure 1.:

An interesting question is whether insulin is directly involved in the arrest of preantral andantral follicle development, and another is what the underlying molecular mechanism is. The local expressions of IGFs, their receptors, IGF binding proteins (IGFBPs) and IGFBP proteases are undoubtedly important in normal and abnormal ovarian follicle development, as confirmed by the animal models [Monte etal.,2019 ,Campbell, 2018] However, unraveling the exact

molecular mechanism indicating how insulin can interfere with the growing follicle, along with its role in ovulation, still remains a task for future research.

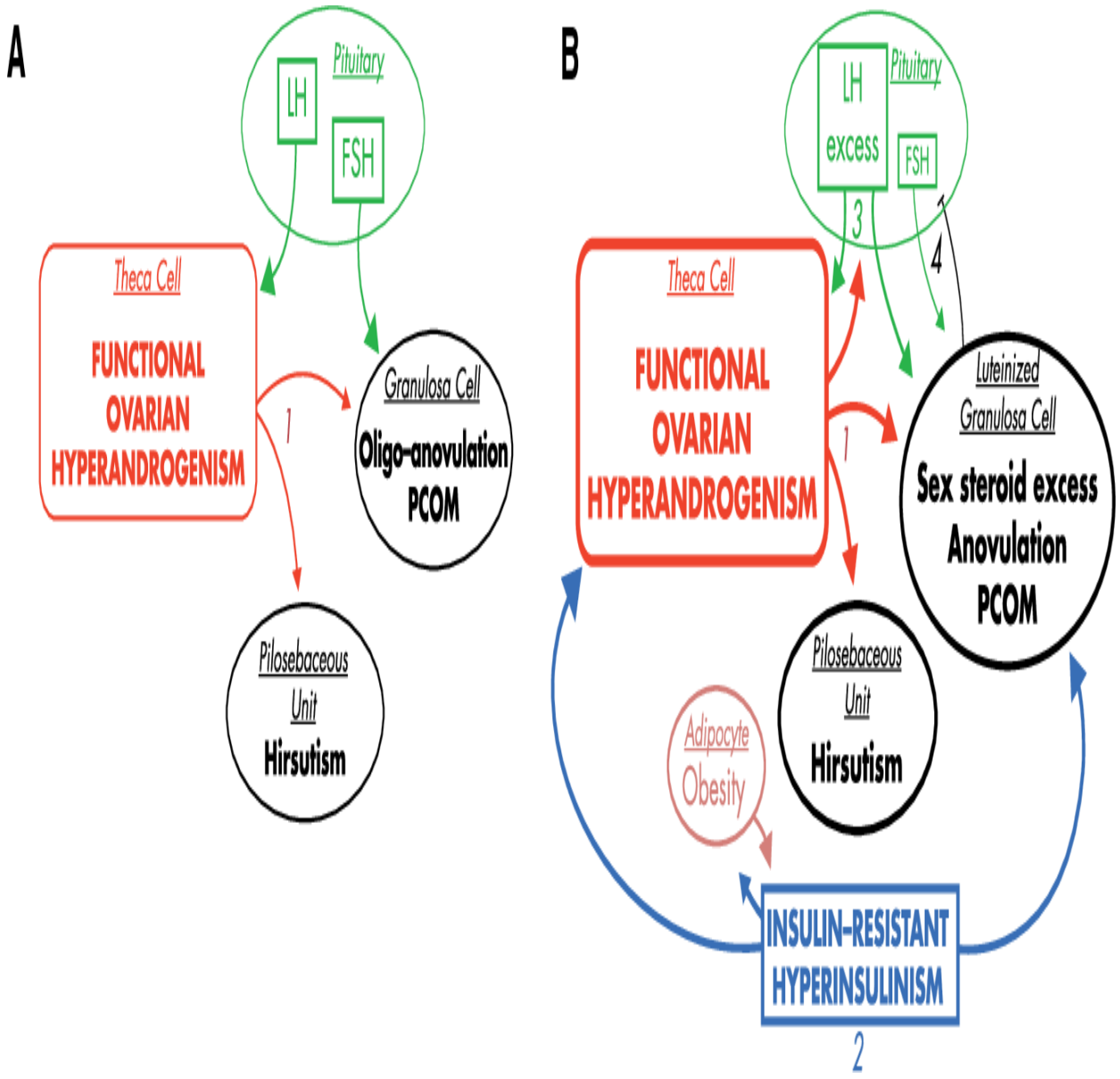

Figure 1 :

The effects of hyper insulinemia in the context of PCOS pathogenesis, reprinted and captioned from [Rosenfield etal.,2016] with permission of the Oxford University Press. Ovarian hyperandrogenism is nearly universal in PCOS and can account for all the cardinal clinical features of the syndrome: hyperandrogenemia, oligo-anovulation and polycystic ovaries (1). About half of patients with functional ovarian hyperandrogenism have insulin-resistant

hyperinsulinism (2). Insulin- resistant hyperinsulinism acts on theca cells to aggravate hyper androgenism, synergizes with androgen to prematurely luteinize granulosa cells and stimulates adipogenesis. The increased hyperandrogenemia provokes LH excess (3), which then acts on both theca and luteinized granulosa cells to worsen hyperandrogenism. LH also stimulates luteinized granulosa cells to secrete estradiol (4), which suppresses FSH secretion. These hyperinsulinism-initiated changes in granulosa cell function further exacerbate PCOS and further hinder ovulation. Obesity increases insulin resistance, and the resultantly increased hyperinsulinism further aggravates hyperandrogenism. Heaviness of lines and fonts represents severity. Both functional ovarian hyperandrogenism and insulin resistance typically have an intrinsic basis. This model does not exclude the possibility that the unknown intrinsic ovarian defects that underpin the ovarian steroidogenic dysfunction also involve granulosa cell folliculogenesis. The figure also does not depict other associated defects, such as the functional adrenal hyperandrogenism that often accompanies the ovarian hyperandrogenism and the contribution of excess adiposity to peripheral androgen production and gonadotropin suppression.

2.3. Family factors:

The rate of PCOS in mother and sister of patients with PCOS were 24% and 32%, respectively, although the risk was higher when considering untreated premenopausal women only. Our data demonstrated a high degree of familial aggregation of PCOS. Overall, we have observed a 5- to 6-fold increase in the incidence of among first-degree female relatives of affected patients when compared with the prevalence of PCOS in our general population (i.e,4%) [Melissa D 2010].

How is PCOS diagnosed?

Having polycystic ovaries does not mean you have PCOS. Women with PCOS often have symptoms that come and go, particularly if their weight goes up and down. This can make it a difficult condition to diagnose, which means it may take a while to get a diagnosis

A diagnosis is made when you have any two of the following:

• irregular, infrequent periods or no periods at all

• an increase in facial or body hair and/or blood tests that show higher testosterone levels than normal

• an ultrasound scan that shows polycystic ovaries.

When a diagnosis is made, you may be referred to a gynaecologist (a doctor who specializes in caring for a woman's reproductive system) or an endocrinologist (a doctor who specializes in the hormonal system).

TREATMENT

- PCOS treatment focuses on managing for individual concerns, such as
- Infertility , hirsutism, acne or obesity. Specific treatment might involve lifestyle changes or medication.

Lifestyle changes

Recommend weight loss through a low-calorie diet combined with moderate exercise activities.

Medications:

(a)To regulate menstrual cycle:

Combination birth control pills:

- Pills that contain estrogen and progestin decrease androgen production and regulate estrogen.
- Which regulating hormones can lower the risk of endometrial cancer and correct abnormal bleeding, excess hair growth and acne. Instead of pills.
- Use a skin patch or vaginal ring that contains a combination of estrogen and progestin.
- Progestin the rapy: Taking progestin for 10 to 14 days every one to two months can regulate periods and protect against endometrial cancer. Progestin therapy doesn't improve androgen levels and won't prevent pregnancy. The progestin-only minipill or progestin- containing intrauterine device is a better choice if you
- also wish to avoid pregnancy.

(b)To help for ovulation:

- ♣**Clomiphene:**This oral anti-estrogen medication is taken during the first part of menstrual cycle.
- ♣**Letrozole:**This breast cancer treatment can work to stimulate the ovaries.
- ♣**Metformin:**This oral medication for type 2 diabetes improves insulin resistance and lowers insulin levels.
- ♣**Gonadotropins:** These hormone medications are given by injection.

(c)To reduce excessive hair growth:

♣**Birth control pills:** These pills decrease androgen production that can cause excessive hair growth.

♣**Spironolactone:**This medication blocks the effects of androgen on the skin. Spironolactone can cause birth defect, so effective contraception is required while taking this medication. It isn't recommended during pregnancy or planning to become pregnant.

♣**Eflornithine:**This cream can slow facial hair growth in women.

♣**Electrolysis:**A tiny needle is inserted into each hair follicle. The needle emits apulse of electric current to damage and eventually destroy the follicle. So might need multiple treatments.

Lifestyle and home remedies

♣**Maintain a healthy weight:** Weight loss can reduce insulin and androgen levels and may restore ovulation.

♣**Limit carbohydrates Diet:** Low-fat, high-carbohydrate diets might increase insulin levels. Choose complex carbohydrates, which raise blood sugar levels more slowly. Exercise helps lower blood sugar levels

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