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Review Article

Polycystic Ovarian Syndrome Overview

Nabeel Abdullah Yamany[1]*, Amani Nabil Yamani[2], Reham Othman Althomali[3], Rawan Abdullah Alhamyani[3], Maram Mohammed Alwagdani[3], Ahmad Ateeq A Alseraihi[4], Najoud Marzooq Alotaibi[5], Ali Bakir Alsharif[6], Fatima Habib Mohammed Lajami[7], Shahad Sami Alansari[8] and Ghadeer Ghalib Basakran[8]

[1]Head of Ob/Gyn Department, Senior of Surgery Obstetrics, Gynecology and Infertility, Ohud Hospital, Medina, Saudi Arabia

[2]Prince Mohammad Bin Abdulaziz Hospital Medina, National Guard Health Affairs, Saudi Arabia

[3]Taif University, Taif, Saudi Arabia

[4]Taibah University, Medina, Saudi Arabia

[5]King Saud University, Riyadh, Saudi Arabia

[6]King Fahad General Hospital, Jeddah, Saudi Arabia

[7]Qatif Central Hospital, Qatif, Eastern Province, Saudi Arabia

[8]Umm Al-Qura University, Mecca, Saudi Arabia

***Corresponding Author:** Nabeel Abdullah Yamany, Head of Ob/Gyn Department, Senior of Surgery Obstetrics, Gynecology and Infertility, Ohud Hospital, Medina, Saudi Arabia.

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Abstract

Introduction: Polycystic ovarian syndrome (PCOS) is considered to be the commonest endocrine medical conditions in females in the reproductive-age. The most common definition for Polycystic ovarian syndrome originated from Stein and Leventhal in the year 1935, who defined overweight females who had amenorrhea, hirsutism, and infertility with cystic and enlarged ovaries. Polycystic ovarian syndrome is a heterogeneous medical pathology with several phenotypic expressions causing significant debates on the specific diagnostic criteria. The frequency of this medical condition varies between six percent and fifteen percent based on the used diagnostic criteria used.1 each individual can develop a ranging severity of the components of Polycystic ovarian syndrome and, thus, the treatment should be modified based on each patient's preferences and clinical manifestations.

Aim of Work: In this review, we will discuss Polycystic ovarian syndrome.

Methodology: We did a systematic search for Polycystic ovarian syndrome using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

Conclusions: Females who have Polycystic ovarian syndrome manifest with several signs and symptoms of chronic anovulation, hyperandrogenism, and metabolic dysfunctions. The NIH recently recommended the use of Rotterdam criteria to broadly detect all the subtype of Polycystic ovarian syndrome. Females who have Polycystic ovarian syndrome are usually overweight and have insulin resistance and thus have a higher risk of developing glucose intolerance and type 2 diabetes mellitus. Future studies must focus on the genetic, epigenetic, and environmental predisposing factors of Polycystic ovarian syndrome to develop new treatment modalities to address the prevention of this medical conditions and its chronic associated adverse events.

Keywords: *Polycystic Ovarian Syndrome; Anovulation; Hyperandrogenism; Insulin Resistance*

Introduction

Polycystic ovarian syndrome (PCOS) is considered to be the commonest endocrine medical conditions in females in the reproductive-age. The most common definition for Polycystic ovarian syndrome originated from Stein and Leventhal in the year 1935, who defined overweight females who had amenorrhea, hirsutism, and infertility with cystic and enlarged ovaries. Polycystic ovarian syndrome is a heterogeneous medical pathology with several phenotypic expressions causing significant debates on the specific diagnostic criteria. The frequency of this medical condition varies between six percent and fifteen percent based on the used diagnostic criteria used. Each individual can develop a ranging severity of the components of Polycystic ovarian syndrome and, thus, the treatment should be modified based on each patient's preferences and clinical manifestations.

In this review, we will discuss the most recent evidence regarding Polycystic ovarian syndrome.

Methodology

We did a systematic search for Polycystic ovarian syndrome using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Polycystic ovarian syndrome, Anovulation, Hyperandrogenism, Insulin resistance.

Clinical presentation

Key clinical manifestations of Polycystic ovarian syndrome include anovulation with irregularities in the menstrual period, the development of hyperandrogenism, infertility, and abnormalities in the metabolic state.

Menstrual abnormalities

Oligo-anovulation classically manifests as the development of a case of oligomenorrhea (defined by less than nine cycles a year) or amenorrhea (complete absence of menstrual cycles). Dysfunctional bleeding of the uterus is frequently found from the presence of unopposed estrogen stimulation with the absence of progesterone secretion due to anovulation. These irregularities in the menstrual cycle will develop peri-pubertally and are usually noticed following periods of increased weight. It is found that females who have Polycystic ovarian syndrome might spontaneously ovulate, despite that the prevalence of this is not known [1]. Menstrual cycles in females with Polycystic ovarian syndrome usually become more regular as the female enters menopause.

Infertility

Females who have Polycystic ovarian syndrome have been found to have an increased risk for developing infertility due to oligo-anovulation. Other pathological mechanisms that leads to the development of infertility include decreased oocyte competence [2], undesirable endometrial changes, and overweight.

Endometrial cancer risk

Females who have Polycystic ovarian syndrome develop are exposed long-term unopposed estrogen which results in the development of endometrial hyperplasia due to anovulation. This might elevate the risk of developing endometrial cancer. Other predisposing factors that might cause this risk include chronic hyperinsulinemia, hyperandrogenemia, and obesity.

Hyperandrogenism

Hyperandrogenism usually presents clinically with the development of hirsutism, acne, and/or androgenic alopecia. Hirsutism is generally known as the occurrence of increased terminal, coarse, and pigmented hair that has a male pattern distribution in the areas of the upper lip, the chin, the shoulders, the chest, the peri-areolar areas, along the linea alba of the abdomen, the thighs' inner aspects, and the midline lower back area. The hirsutism degree could be gauged by the Ferriman-Gallwey score [3], which is a semi-objective quantitative

score used for recording the severity and distribution of excess body hair in nine skin areas. Recording these scores objectively aids in assessing the degree of response of hirsutism to management and interventions.

Pictures prior to shaving might aid in documenting the status of hirsutism accurately. Other hyperandrogenic clinical manifestations in females who have alopecia include acne and androgenic alopecia. Signs of virilization like deepening of the voice, clitoromegaly, reduced size of the breasts, and higher muscle mass must raise the concerns of the clinician to the presence of more severe cases of androgen excess (which we will discuss later, with examples).

Metabolic components

Females who have Polycystic ovarian syndrome are usually obese or overweight, specifically with visceral adiposity [4]. It has also been well documented that most females who have Polycystic ovarian syndrome also have hyperinsulinemia and insulin resistance, regardless of obesity [5]. Females who have Polycystic ovarian syndrome must be assessed for the presence of clinical manifestations of insulin resistance including the development of acanthosis nigricans, multiple skin tags [6] and/or keratosis pilaris. A two-fold elevation in the frequency of metabolic syndrome has been noticed in female who have Polycystic ovarian syndrome in previous retrospective studies [7]. Females who have Polycystic ovarian syndrome have a significant elevation in the risk of developing dysfunctional glucose tolerance and type two diabetes. Previous large cross-sectional studies have concluded that twenty-three to thirty-five percent of females with Polycystic ovarian syndrome will have impaired glucose tolerance and up to ten percent will have diabetes mellitus. These findings account for a three-fold more prevalence rate of impaired glucose tolerance in women with Polycystic ovarian syndrome when compared to age-matched females using data from the National Health and Nutrition Survey (NHANES) II [8]. Approximately a seven-fold to ten-fold increase in prevalence rates was noticed for undiagnosed type two diabetes mellitus in females with Polycystic ovarian syndrome when compared to NHANES II females of similar age. The risk of developing type two diabetes mellitus was found to be higher in females with Polycystic ovarian syndrome where a family history of diabetes mellitus was present [9].

Females who have Polycystic ovarian syndrome are generally predisposed to developing increased blood pressure and vascular endothelial dysfunction [10], which puts them at an elevated risk for the development of macrovascular diseases. Several studies have demonstrated that dyslipidemia, specifically increases in small dense low-density lipoprotein cholesterol particles and triglyceride concentrations with lower high-density lipoprotein cholesterol. despite that accurate cardiovascular-related morbidity and mortality have not been assessed in long-term studies, the clustering of cardiometabolic predisposing factors predisposes female who have Polycystic ovarian syndrome to coronary heart disease.

Other components

Sleep apnea is considered to be a relatively common finding in females who have Polycystic ovarian syndrome. Insulin resistance also looks as an important predictor of the severity of obstructive sleep apnea than overweight. The frequency of non-alcoholic fatty liver disease has also been found to be higher in females who have Polycystic ovarian syndrome with higher serum alanine aminotransferase levels in up to thirty percent of females who have Polycystic ovarian syndrome. Females who have Polycystic ovarian syndrome are usually at an increased risk to develop mood disorders, specifically depression and anxiety [11].

Pathophysiology

Multiple pathophysiological mechanisms have been suggested in the etiology of Polycystic ovarian syndrome. It is not clear which of these mechanisms actually trigger the vicious cycle of developing anovulation, androgen excess, and hyperinsulinemia which are seen in females with Polycystic ovarian syndrome. One of the main neuroendocrine dysfunctions which are described is the presence of alterations in the secretion of gonadotropins. There is underlying insensitivity of the hypothalamic gonadotropin-releasing hormone (GnRH) secretion to ovarian steroids causing elevated luteinizing hormone (LH) pulse frequency and amplitude [12]. Low progesterone concentrations have also been postulated to increase the pulsatility of the hypothalamic gonadotropin-releasing hormone, causing an increase in

the LH/follicle-stimulating hormone (FSH) ratio. This relative elevation in LH concentrations stimulates the ovarian theca cells to release more androgenic precursors and androgens. The follicle-stimulating hormone maintains the aromatase activity of the ovarian granulosa cells. Impaired follicle-stimulating hormone production and secretion causes insufficient follicle development and decreased aromatase concentrations. Therefore, there is a relative inability to aromatize androgenic precursors to estrogen, which in turn causes preferential elevation of ovarian androgens levels [13].

Females who have Polycystic ovarian syndrome tend to have intrinsic dysfunctions in ovarian theca cell steroidogenesis which causes the development of hyperandrogenemia. In the ovarian theca cells, androgen biosynthesis is regulated by cytochrome P-450c enzymes to produce androstenedione. Androstenedione is then turned into testosterone by 17b-hydroxysteroid enzyme or aromatized to produce estrone. In vivo and in vitro studies have demonstrated that Polycystic ovarian syndrome ovaries have higher cytochrome P-450c17 enzymatic activity causing increased production of androgenic precursors, and thus, testosterone.

Euglycemic clamp studies have demonstrated insulin resistance in both overweight and thin females with Polycystic ovarian syndrome. Hyperinsulinemia increases androgen synthesis in females who have Polycystic ovarian syndrome. Insulin has both a direct activity on the ovaries by increasing LH activity to produce more androgens and an indirect activity in enhancing the amplitude of LH pulses. moreover, insulin also inhibits hepatic production of sex hormone-binding protein (SHBG), that binds to testosterone. thus, females who have Polycystic ovarian syndrome tend to have an elevated proportion of free or biologically active testosterone when compared to total testosterone.

Genetics of polycystic ovarian syndrome

Familial patterns of Polycystic ovarian syndrome indicate the presence of an underlying genetic basis for the disease. Several susceptibility genes have been demonstrated, specifically in the region of the insulin receptor gene, insulin gene, follistatin, fibrillin-3, and other members of the transforming growth factor beta signaling group [14]. Reproductive phenotype of hyperandrogenism and metabolic dysfunctions accumulate in families where Polycystic ovarian syndrome runs. Some sisters develop hyperandrogenism with regular menstrual cycles and insulin resistance, while other sisters have irregularities in their menstrual cycles. Mothers of females who have Polycystic ovarian syndrome and menstrual irregularities were found to have increase testosterone concentrations, dyslipidemia, and markers indicating insulin resistance [15]. Brothers of females who have Polycystic ovarian syndrome had elevated levels of dehydroepiandrosterone sulfate (DHEAS), indicating abnormalities in androgen steroidogenesis similar to their sisters who have Polycystic ovarian syndrome. In other studies, brothers of females who have Polycystic ovarian syndrome demonstrated abnormalities in the functions of pancreatic beta-cell that was associated with higher risk for developing type 2 diabetes mellitus.

Diagnosis of polycystic ovarian syndrome

There have been significant debates over the three separate definitions that have been proposed by professional organizations for the diagnosis Polycystic ovarian syndrome. The National Institutes of Health (NIH) in the year 1990 suggested the following diagnostic criteria for diagnosing Polycystic ovarian syndrome:

- The presence of chronic anovulation.
- The presence of clinical and/or biochemical manifestations of hyperandrogenism.
- Ruling out of other causes of hyperandrogenism, including congenital adrenal hyperplasia, androgen-secreting tumors, and/or hyperprolactinemia.

The European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine, on the other hand, has held a consensus meeting at Rotterdam in the year 2003 and developed revised criteria incorporating a wider spectrum of phenotypes

in Polycystic ovarian syndrome. Two out of three criteria would be required to establish the diagnosis after ruling out other etiologies for hyperandrogenism. These three criteria are:

- The presence of Oligo-anovulation and/or anovulation.
- The presence of clinical and/or biochemical manifestations of hyperandrogenism.
- The detection of polycystic ovarian morphology using ultrasonography.

The Androgen Excess Society (2006) also proposed diagnosing Polycystic ovarian syndrome following the presence of three characteristics:

- Clinical and/or biochemical manifestations of hyperandrogenism.
- the presence of Ovarian abnormalities (oligo-anovulation and/or polycystic ovarian morphology).
- Ruling out other etiologies of hyperandrogenism.

These three diagnostic criteria are usually used to determine different phenotypes of females with Polycystic ovarian syndrome. Despite that the NIH criteria detected hyperandrogenic females who are at an increased metabolic risk, the Rotterdam criteria also detected females who had ovulatory dysfunction and polycystic ovarian morphology. Most recently, in December 2012, the NIH sponsored an expert panel that suggested the acceptance of the Rotterdam criteria as they encompass a broad spectrum of subtypes representing Polycystic ovarian syndrome.

Evaluation

Serum total testosterone gives the best estimate of the androgen levels status as direct assays for free testosterone could sometimes be inaccurate if the equilibrium dialysis method was not used. Serum total testosterone levels could be measured at any point throughout the menstrual cycle. Liquid chromatography-tandem mass spectrometry precisely measures the testosterone concentrations in women with Polycystic ovarian syndrome. On the other hand, several clinical laboratories use direct immunoassays to decrease the costs and increase throughput. As the direct immunoassays skip the extraction steps, there is significant cross reactivity from other steroids, causing inaccuracies [16]. Another important factor to consider is the presence of low circulating concentrations of testosterone in females (about fifteen to twenty times less than in males). Other measurements to evaluate androgen excess in females who have Polycystic ovarian syndrome include the measurement of free androgen index (FAI), androstenedione, and DHEAS. free androgen index is generally defined as the ratio between total testosterone and sex hormone-binding protein and might also be used to assess hyperandrogenemia. Androstenedione, which is an immediate precursor of testosterone, is synthesized by the ovaries, adrenals, and peripheral tissues. A recent study documented that the measurement of both androstenedione and total testosterone better predicted metabolic risks in females who have Polycystic ovarian syndrome. This study also concluded that that androstenedione concentrations could be elevated when total testosterone concentrations are normal in females who have Polycystic ovarian syndrome. The utility of androstenedione merits further investigation in longitudinal studies.

Other biochemical features

Anti-mullerian hormone (AMH) which is produced by the granulosa cells of small antral follicles has been suggested as a possible marker for Polycystic ovarian syndrome. Elevated Anti-mullerian hormone concentrations has been suggested as a potential substitute for polycystic ovarian morphology. Until there is a standard assay techniques and larger evidence, the diagnostic cutoff for Anti-mullerian hormone in Polycystic ovarian syndrome will remain a research tool. Low sex hormone-binding protein concentrations indicate the presence of insulin resistance and predicts the susceptibility for later developing metabolic syndrome. Low sex hormone-binding protein also lead to elevations in the free testosterone concentrations in target tissues.

Previously, elevated LH/FSH ratio has been used to diagnose of Polycystic ovarian syndrome. However, LH secretion is pulsatile and one single measurement of LH concentrations could miss the intrinsic variability. Therefore, an elevated LH/FSH ratio contributes to the diagnosis of Polycystic ovarian syndrome, but its absence does not necessarily exclude Polycystic ovarian syndrome.

Screening for cardiometabolic risks

All females who have Polycystic ovarian syndrome should get a 75-g oral glucose tolerance test with evaluating fasting and two-hour glucose concentrations at the time of initial diagnosis of their disease. If doing oral glucose tolerance test is not possible, then fasting glucose and hemoglobin A1c must be tested. If oral glucose tolerance test is found to be normal, rescreening every three-to-five years, or earlier in cases of excessive weight gain, is recommended [17]. The gold standard for evaluating insulin resistance is a euglycemic hyper-insulinemic clamp, which could be done only in a research setting. Routine evaluation for insulin resistance in clinical settings with calculated indices such as homeostasis model assessment of insulin resistance is not generally advised because it has many limitations. Fasting lipid profile must also be assessed at the time of initial diagnosis of Polycystic ovarian syndrome.

Ultrasonography assessment of polycystic ovarian morphology

The 2003 Rotterdam criteria for polycystic ovarian morphology recommended the presence of at least twelve follicles in each ovary measuring two to nine millimeters in diameter and/or the presence of an ovarian volume that is higher than ten mL. Establishing threshold values for follicle number per ovary (FNPO) and ovarian volume has been an extremely complex task. A recent study demonstrated that more than half of normal young ovulatory females meet the follicle number per ovary criteria. In addition, significant interobserver variability is present in the technical methods used for counting and reporting follicle number per ovary. The transvaginal route allows accurate measurement of the follicles. When not possible, a transabdominal route could be used to measure ovarian volume. Females with Polycystic ovarian syndrome have been shown to have increased ovarian volume. The Ovarian size reaches its maximum during adolescence and then shrinks during and following menopause. Other measurements like ovarian stromal volume and ovarian blood flow have not been fully studied.

Management of polycystic ovarian syndrome

Goals for management of Polycystic ovarian syndrome include reducing the clinical manifestations of hyperandrogenic, preventing the development of endometrial hyperplasia, and addressing the underlying metabolic predisposing factors to delay the development of type 2 diabetes mellitus. Females who desire pregnancy might require the use of ovulation induction therapy.

Conclusions

Females who have Polycystic ovarian syndrome manifest with several signs and symptoms of chronic anovulation, hyperandrogenism, and metabolic dysfunctions. The NIH recently recommended the use of Rotterdam criteria to broadly detect all the subtype of Polycystic ovarian syndrome. Females who have Polycystic ovarian syndrome are usually overweight and have insulin resistance and thus have a higher risk of developing glucose intolerance and type 2 diabetes mellitus. Future studies must focus on the genetic, epigenetic and environmental predisposing factors of Polycystic ovarian syndrome to develop new treatment modalities to address the prevention of this medical conditions and its chronic associated adverse events.

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