SM Journal net

ISSN no. 2249-8451

DIAGNOSIS OF POLYCYSTIC OVARIAN SYNDROME BY EXCLUSION-ADVANCEMENT IN PREDICTION METHODOLOGY

By Vidhi Sharma, Anna Medical College, Mauritius

ABSTRACT:

A dawning endocrinological disorder adversely affecting millions of young women and disrupting their lives. The main causes of concern with which doctors are approached by the premenopausal women are amenorrhea, hirsutism, acne, polycystic ovaries and infertility also putting them at risk of disorders in future such as type2 diabetes mellitus, metabolic syndrome, cardiovascular ailments, depression, obstructive sleep apnea, endometrial cancer, and non-alcoholic fatty liver disease.

Though the genesis of PCOS is unknown for now, many researches so far have claimed it to be due to overproduction of male hormones owing to an imbalance in sex hormones which might be an effect of changing lifestyle and environmental factors such as a diet loaded with junks and deficit of antioxidants.

There is no peculiar diagnosis of PCOS as of now but health care professionals have diagnosed the convalescents with the help of clinical symptomatology stated by the patient; pelvic examinations; ultrasonography and blood tests to measure androgen levels, fasting cholesterol, triglyceride levels and glucose tolerance to estimate the body's response to sugar. Internationally a lot of research work is going on for determination of advanced methodologies which can give early diagnosis of the disease. Outcome of this study will help to assess the newer prediction models which are using Antimullerian hormone, obesity index, hypothalamic causes and hyperprolactinemia as a factor for the diagnosis of PCOS. The purpose of this context is to provide a balanced review of advancement taking place in the field of diagnostics of polycystic ovarian syndrome and the benefits of these new prediction models for the early diagnosis of new cases whose disease can be reversed by early interventions. A brief of diagnosis and long term-clinical management of women with PCOS, in accordance with current evidence-based clinical guidelines is also provided.

KEYWORDS:

Endocrinological disorder, PCOS, Antimullerian hormone, Changing lifestyle.

OBJECTIVE:

To make a compilation of various new era diagnostic methods used for PCOS in the field of medicine.

DESIGN:

Literature review of retrospective cohort studies done for assessment of new prediction models used in PCOS diagnosis.

STRENGTHS AND LIMITATIONS OF TH IS L ITERATURE REVIEW:

1. It is one of its kind in which the new trends of updated diagnostic methods are discussed and a compilation of the thoughts of author has been presented in an easy manner after going through research works conducted earlier.

2. Psychological view point for the diagnosis of PCOS are also added.

3. The underdiagnosis of cases during the conduct of studies due to lack of specific diagnostic methods for diagnosis of PCOS have turned up to be an issue.

4. Due to the inconsistency between diagnostic criteria and recruiting methods it is unlikely that all studies in this review are comparable enough to infer conclusive differences upon.

BACKGROUND:

A. Epidemiology and Definition:

As described by Stein and Leventhal in the 1930s polycystic ovarian syndrome (PCOS)is the most prevalent endocrine pathology in females of reproductive world ranging between 5% and 15% depending on the diagnostic criteria applied [1]. It is defined as endocrinological disorder in which androgen excess, chronic anovulation, polycystic appearance of the ovaries on ultrasound are found, it's not just a reproductive disorder but a lifelong metabolic disorder with increased rates of type 2 diabetes, hypertension, non-alcoholic fatty liver and cardiovascular events [2]. The diagnosis of PCOS on the basis of The Rotterdam criteria includes characteristic features like oligo/anovulation, clinical and/or biochemical hyperandrogenism, and a typical ovarian sonomorphology, but even this classification neglects a substantial number of clinical, metabolic, and endocrine parameters that are associated with PCOS. For instance, this classification does not take metabolic factors such as insulin resistance into account.

B. Signs and Symptoms:

The syndrome manifests at puberty and can last throughout lifetime. Women frequently experience anovulatory menstrual cycles, infertility hirsutism, obesity and increased risk of diabetes mellitus, hypertension, lipid abnormalities, and metabolic syndrome.
PCOS is a heterogenous disorder, and a diagnosis of exclusion. Individual contributions of hyperandrogenism and insulin resistance differ from patient to patient, which accounts for the heterogenous nature of PCOS and its presentation. The chief complaints with which women approach doctors are therefore menstrual irregularities, ultrasound findings of abnormal ovarian size and morphology, and clinical or laboratory evidence of hyperandrogenism which causes problems of hirsutism, acne or oily skin, male type baldness or thinning of hair, weight gain and infertility [3].

C. Pathophysiology:

On the basis of current understandings PCOS is heterogenous disorder and is due to the dysfunction of reproductive and metabolic systems. Hyperandrogenism and insulin resistance exacerbate one another during the development of PCOS, which is also affected by dysfunction of the hypothalamus-pituitary-ovarian axis. The factors responsible for the disorder can be genetic or environmental during the prenatal period, the follicular microenvironment, and lifestyle after birth [4].

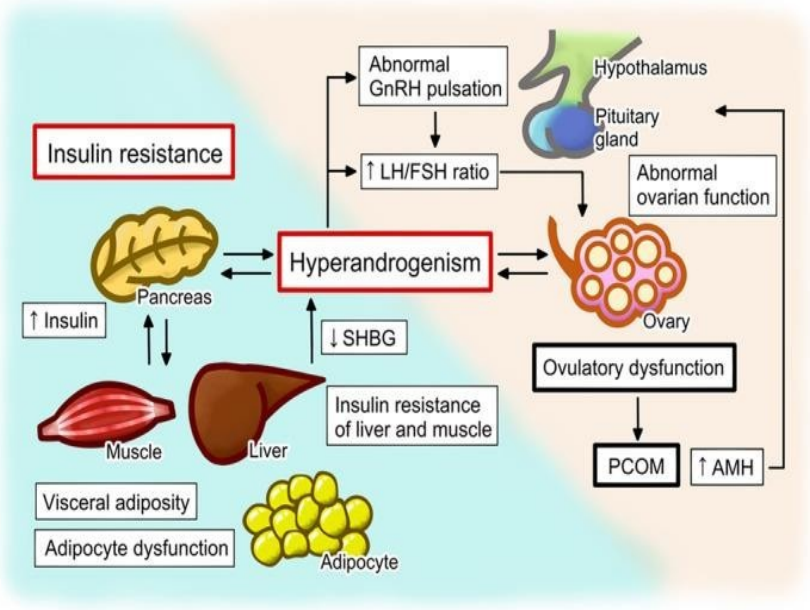

Fig.: Pathophysiology of polycystic ovary syndrome (PCOS)[4]

Hyperandrogenism has a synergistic effect with insulin resistance to induce the development of PCOS. Hyperandrogenism, ovulatory dysfunction, aberrant gonadotropin-releasing hormone (GnRH) pulsation and the resulting abnor mal gonadotropin secretion, and insulin resistance comprise the vicious cycle that underpins the pathophysiology of PCOS. The abnormalities in the ovarian function of women with PCOS include the hypersecretion of androgens and ovulatory dysfunction, which causes PCOM. The hypersecretion of androgens is caused by intrinsic dysfunction of theca cells and/or the hypothalamus-pituitary-ovarian axis, while hyperandrogenism causes abnormal GnRH pulsation and gonadotropin secretion through the aberrant negative or positive feedback of progesterone and oestrogen. The abnormal gonadotropin secretion in patients with PCOS is characterized by a high luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio, which induces ovarian dysfunction, including the hypersecretion of androgens. In addition, the high concentration of anti-Müllerian hormone (AMH), which is secreted by the pre−/small antral follicles that accumulate in the ovaries of women with PCOS, further exacerbates the ovarian dysfunction by having deleterious effects on the follicular

microenvironment and/or GnRH pulsation. Hyperandrogenism is further aggravated by hyperinsulinemia, which develops secondary to insulin resistance. Hyperinsulinemia causes an increase in androgen secretion by theca cells and an inhibition of the production of sex hormone-binding globulin (SHBG) in the liver, thereby increasing the circulating concentration of bioactive free testosterone. Insulin resistance develops in tissues such as liver and muscle, and is associated with visceral adiposity and adipocyte dysfunction, which are exacerbated by hyperandrogenism [4].

D. Complications:

Type 2 diabetes, obesity, obstructive sleep apnoea hypertension, dyslipidaemia, mood disorders, endometrial cancer and many more [5].

E. Differential diagnosis:

There are many other disorders having similar symptoms like:

- Hypogonadotropic hypogonadism: Nutrition, Excessive exercise, Chronic disease
- Hyperprolactinemia: Macroadenomas, Microadenomas, Idiopathic hyperprolactinemia
- Hypothyroidism
- Hypoadrenalism: Cushing syndrome, Cushing disease, Nonclassical congenital adrenal hyperplasia
- Androgen-secreting tumours: Ovarian, Adrenal
- Androgenic alopecia [6].

F. Management

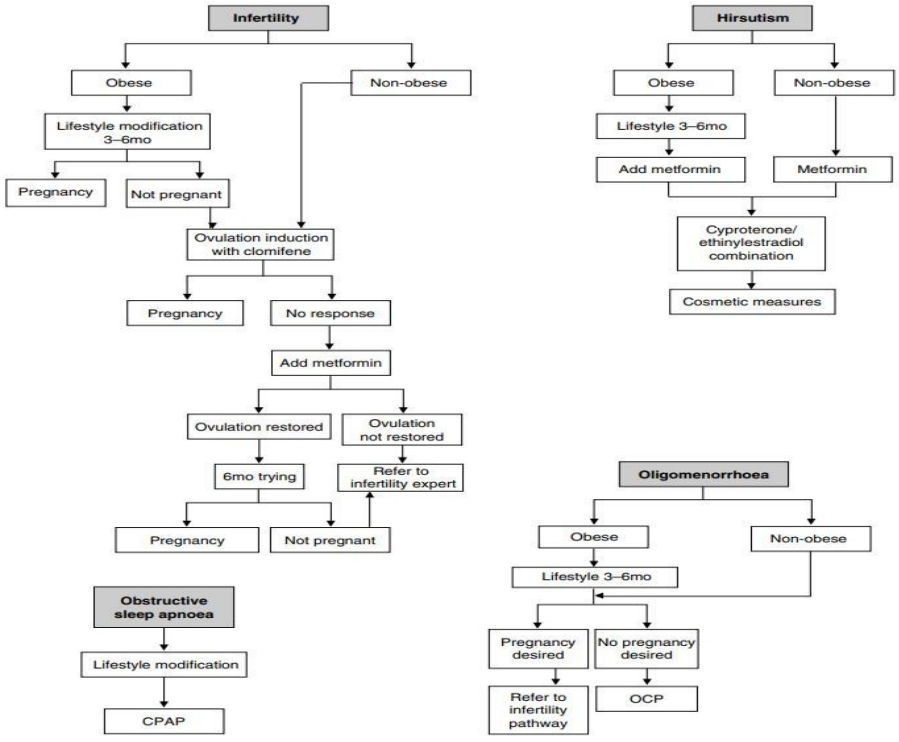

Fig. 1. Problem-based management flow chart for women with polycystic ovary syndrome (PCOS). Management is based on diagnosis and identification of the main presenting problem. **CPAP** = continuous positive airway pressure; **OCP** = oral contraceptive pill.

DISCUSSION:

So far there's no particular diagnostic method found that specifically diagnose polycystic ovarian syndrome. A correct diagnosis is challenging, particularly in patients who have minor clinical symptoms. Clinically a health care provider will try to investigate by asking about symptoms, genetic and environmental factors which pose towards PCOS. Then a physical examination for the signs of excessive hair growth, insulin resistance and acne are carried out.

Moving ahead for the confirmation of the clinical diagnosis the health care provider will recommend further investigations like:

- **Pelvic examination**: for checking the reproductive organs for masses, growths and other changes.
- **Clinical examination**: Clinical or biochemical signs of androgen excess (high levels of male hormones), Oligoovulation (irregular or infrequent periods)

Some clinical signs of androgen excess include:

Hirsutism (excess male pattern hair growth)
Acne
Clitoromegaly – enlarged clitoris (rare)

- **Blood tests**: measurement of androgen levels, fasting cholesterol and triglyceride levels; along with this a glucose tolerance test to measure body's response to sugar is also done. Congenital adrenal hyperplasia, a defect of the enzyme 21-hydroxylase. The hormone 17 hydroxyprogesterone (17-OHP) accumulates in the bloodstream in this condition, Cushing's syndrome, Androgen secreting tumour (very rare). Women with non-androgenic conditions such
as hyperprolactinemia, that can result in irregular periods and polycystic ovaries.
Following is observed in the test results positive for the cases of PCOS-

  Elevated serum testosterone (total testosterone)
  Elevated level of free testosterone
  Elevated dehydroepiandrosterone sulphate, also called DHEA sulphate, or DHEAS

- **Ultrasound**: commenting on the appearance of ovaries, the lining of uterus. A description of the adnexa helps to rule out other complications like endometriosis.

  At least one ovary is greater than 10 cm^3 in volume
  At least one ovary has 12 or more antral follicles seen by ultrasound

We currently see more antral follicles than we did in the past. In practice, patients with polycystic ovarian syndrome generally have 40 to 100 antral follicles (total).

- Diagnosis of PCOS with FSH and LH hormone levels:

  Normally this ratio is about 1:1 – meaning the FSH and LH levels in the blood are similar.
  FSH and LH are often both in the range of about 4-8 in young fertile women.

In women with polycystic ovaries the LH to FSH ratio is often higher – for example 2:1, or even 3:1.

With PCOS we often see the FSH in the range of about 4-8 as well – but often the LH levels are 10-20.
It is common for women that clearly fit the PCOS syndrome in other ways to have normal serum FSH and LH levels and a normal FSH to LH ratio.
For this reason, testing of FSH and LH hormone levels is not always helpful when trying to diagnose PCOS.

Fig.: Polycystic ovary with many antral follicles

- **Magnetic resonance imaging: to have better delineation of the ovarian morphology** [8]:

An approach to a patient with a possible PCOS should be 2-fold, directed towards making a diagnosis as well as screening for associated endocrine abnormalities. There is a certain overlap in clinical appearance with other ovulatory dysfunction conditions with variable phenotypes, so a clear differentiation from other central endocrine disorders is difficult. For example, obesity as a central clinical finding in PCOS is found in 30% to 60% of women with PCOS only.

ADVANCEMENT IN DIAGNOSIS OF PCOS—TIMELINE

Changes in the diagnostic criteria greatly affect the prevalence of PCOS. Prevalence rates have been reported as low as 1.6% using a combination of all three criteria [9] and as high as 18% [10]in similar Caucasian populations using the Rotterdam criteria [11,12] . A statistical report by Futterweit, estimated that 50–75% of women with PCOS are unaware that they even have this syndrome [13]. Over the past 2 decades, the use of the NIH Criteria, the Rotterdam Criteria, and the AE-PCOS Society Criteria have been useful in understanding the syndrome. The individual components of these criteria are difficult to measure, and it is not clear how each contributes to the outcomes of concern. The information provided further shows the criteria proposed by these authoritative bodies

- **NIH (1990):**

It is the first developed and most commonly used criteria today. According to this criterion for diagnosis of individuals with PCOS should have clinical and/or biochemical signs of hyperandrogenism (with exclusion of other aetiologies, e.g., congenital adrenal hyperplasia) and chronic anovulation are declared as the cases of this disease. Both the criterion should be present to diagnose an individual with PCOS [14]. Based on the NIH diagnostic criteria, there is a prevalence of PCOS between 6% and 9% documented across the United States, the United Kingdom, Spain, Greece, Australia, Asia, and Mexico
[15] .

- **Rotterdam (2003) [16]:**

According to the Rotterdam consensus,[17] polycystic ovarian syndrome (PCOS) is defined by the presence of two of three of the following criteria: oligo-anovulation, hyperandrogenism and polycystic ovaries (≥ 12 follicles measuring 2-9 mm in diameter and/or an ovarian volume > 10 mL in at least one ovary). 2 of 3 criteria needed amongst the ones mentioned above. This was formulated to expand on NIH diagnostic definition.

- **AE-PCOS Society 2006[18]:**

Based on the available data, it is the view of the AE-PCOS Society Task Force that PCOS should be defined by the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and the exclusion of related disorders. However, a minority considered the possibility that there may be forms of PCOS without overt evidence of hyperandrogenism, but recognized that more data are required before validating this supposition [18]. This was formulated to provide an evidence-based definition of PCOS.

- **NIH 2012/International PCOS Guidelines 2018 [19,20]:**

Based on the NIH 2012 workshop report, it is estimated that PCOS affects about 5 million reproductive-aged females in the United States. Multiple conditions have been associated with PCOS, including infertility, metabolic syndrome, obesity, impaired glucose tolerance, DM-2, cardiovascular risk, depression, OSA, endometrial cancer, NAFLD/NASH. According to this criterion for diagnosis of individuals with PCOS should

have at least 2 of 3 criterion which are hyperandrogenism, Oligo-and/or anovulation, Polycystic ovaries.

The above information included the previous guidelines which we have been using for the diagnosis PCOS cases. These guidelines either were deficient of rigorous evidence- based processes, did not engage consumer and international multidisciplinary perspectives, or were outdated.

Therefore, the diagnosis of PCOS still remains a controversial topic with its assessment and management being inconsistent. Hence the needs of women with PCOS are not being adequately met and evidence practice gaps still persist. The use of multiple classification systems is confusing and delays progress in understanding the syndrome. It also hinders the ability of clinicians to partner with women to address and manage the health issues that concern them. Each of these diagnostic criteria has inherent strengths and weaknesses.

So current standards do not take additional parameters into account, and the search for new assessment tools to facilitate and support the diagnosis of suspected PCOS is mandatory, especially in cases where the standard parameters are inconclusive.
Furthermore, genetic factors facilitating the diagnosis of PCOS are not available. However, a careful discrimination to other oligoanovulation disorders is needed for mainly two reasons: to allow proper counselling concerning the putative long-time cardiovascular and metabolic risks of PCOS and to give appropriate recommendations for infertility treatment.[21]

ADVANCEMENT IN DIAGNOSIS OF POLYCYSTIC OVARY SYNDROME— NEW ~~PREDICTION MODELS WITH STANDARD PARAME~~TERS[21]

- **Antimullerian hormone** (AMH) has been suggested as a diagnostic parameter because it is frequently elevated in PCOS due to the high follicular density. The International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2018 does not recommend AMH as a single-test parameter for the diagnosis of PCOS; rather, the guidelines recommend establishing cut-off levels or thresholds based on large-scale validation in populations first [22].
- **Obesity** is a simple clinical parameter of importance in patients with PCOS. Obesity is related to the grade of phenotypic expression of PCOS and has a negative impact on metabolic disorders such as the metabolic syndrome and diabetes mellitus type 2[23].

Research work done on this issue of Fertility and Sterility Vagios et al. [24] have addresses this topic and looked at a combination of both the parameters with PCOS as defined by the Rotterdam criteria. They compared these findings with body mass index (BMI) and AMH values in 93 patients with ovulation disorders unrelated to PCOS and a group of 689 patients with nonendocrine infertility. keeping the large variety of PCOS in mind, this prediction model might be used as an additional tool in particular for patients with a minor clinical form of PCOS. However, the heterogeneity of PCOS affords more than that. In the future, well-known parameters such as sex hormone binding globulin levels will be revisited and combined, and new parameters will be evaluated to expand our understanding of this disease toward a personalized differential diagnosis [21].

- **Future perspective:**

There is a need of future researches to determine a better diagnostic criterion which is more of a specific one and ways to improve diagnosis so that there can be reduction in the number of individuals who remain undiagnosed. Conversely, improved diagnostic criteria will help reduce over diagnosis. These field of future research will be one of the first steps to determining a more accurate prevalence, which can then be assessed according to sub-populations to achieve a better understanding of this multifaceted syndrome. A better understanding will enhance clinical outcomes and patient benefit.
This topic is in need of large-scale, random, population studies across the world that look at the prevalence of PCOS according to the established diagnostic criteria in specific sub-populations that can be repeated with many different sub-groups.

- **Psychological view point helping towards diagnosis of PCOS:**

Although a lot of attention has been given to physical symptoms of PCOS, very little is recognized about the psychological correlates of this frequent endocrine disorder.
There have been research works that have laid the association of PCOS with several mental health disorders such as depression and anxiety, body dissatisfaction and eating disorders, diminished sexual satisfaction, and lowered health-related quality of life.
Although the causal direction of these relationships has not been established, it is clear that effective and comprehensive treatment of women with PCOS must encompass careful attention to psychological symptomatology. It is recommended that assessment of specific mental health problems, management of related physical concerns, and treatment of obesity among women with PCOS should be carried out [25].

- **Genetic and Environmental factors playing a role in causing PCOS:** Extensive research suggests that the aetiology of PCOS involves an interaction between environmental factors and gene variants, although it has been suggested that genetic factors contribute less than 10% to disease susceptibility [26,27,28]. A large number of genetic and genome-wide association studies (GWAS) have identified common gene loci associated with PCOS phenotypes in different ethnic populations [29,30,31].These appear to be normal gene variants or polymorphisms, given the frequency and type of genes that have been identified. PCOS is therefore viewed as a polygenic trait that results from an interaction between susceptible genomic variants and the environment.

CONCLUSION:

PCOS is a common but heterogeneous disorder. This review article has summarized the upcoming research models which include use of Antimullerian hormone, obesity index, psychological, genetic and environmental factors for the precise diagnosis of PCOS. These advancements are proven to be beneficial for early diagnosis of the cases.
Substantial evidence and discussion support an evolutionary basis for the diagnosis of polycystic ovary syndrome, although many of the further correlates are yet to be determined. In conclusion, findings show there is a strong correlation between the new diagnostics, i.e., the concept of increased Antimullerian hormone for the diagnosis of cases, the correlation between increased BMI leading to PCOS and various other hormonal disbalances causing the disorder has been established.

REFERENCES:

[1] Rasquin Leon LI, Anastasopoulou C, Mayrin JV. Polycystic Ovarian Disease. 2022 Nov 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 29083730.

[2] Kumarendran B, O'Reilly MW, Manolopoulos KN, Toulis KA, Gokhale KM, Sitch AJ, Wijeyaratne CN, Coomarasamy A, Arlt W, Nirantharakumar K. Polycystic ovary syndrome, androgen excess, and the risk of nonalcoholic fatty liver disease in women: A longitudinal study based on a United Kingdom primary care database. PLoS Med. 2018 Mar 28;15(3):e1002542

[3] Lentscher JA, Decherney AH. Clinical Presentation and Diagnosis of Polycystic Ovarian Syndrome. Clin Obstet Gynecol. 2021 Mar 1;64(1):3-11.

[4] Harada M. Pathophysiology of polycystic ovary syndrome revisited: Current understanding and perspectives regarding future research. Reprod Med Biol. 2022 Oct 8;21(1):e12487.

[5] Palomba S, Santagni S, Falbo A, La Sala GB. Complications and challenges associated with polycystic ovary syndrome: current perspectives. Int J Womens Health. 2015 Jul 31;7:745-63.

[6] Lane DE. Polycystic ovary syndrome and its differential diagnosis. Obstet Gynecol Surv. 2006 Feb;61(2):125-35.

[7] Stankiewicz M, Norman R. Diagnosis and management of polycystic ovary syndrome: a practical guide. Drugs. 2006;66(7):903-12.

[8] Trivax B, Azziz R. Diagnosis of polycystic ovary syndrome. Clin Obstet Gynecol. 2007 Mar;50(1):168-77.

[9] Okoroh, E.M.; Hooper, W.C.; Atrash, H.K.; Yusuf, H.R.; Boulet, S.L. Prevalence of polycystic ovary syndrome among the privately insured, United States, 2003 – 2008. *Obstet. Gynecol.* **2012**, *207*, 299.e1–299.e7.

[10] March, W.A.; Moore, V.M.; Willson, K.J.; Phillips, D.I.; Norman, R.J.; Davies, M.J. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum. Reprod.* **2010**, *25*, 544–551.

[11] Azziz, R.; Woods, K.S.; Reyna, R.; Key, T.J.; Knochenhauer, E.S.; Yildiz, B.O. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 2745–2749.

[12] Lim, S.S.; Norman, R.J.; Davies, M.J.; Moran, L.J. The effect of obesity on polycystic ovary syndrome: A systematic review and meta-analysis. *Obes. Rev.* **2013**, *14*, 95–109.

[13] Garad, R.; Teede, H.; Moran, L. An evidence-based guideline for Polycystic Ovary Syndrome. *Aust. Nurs. J.* **2011**, *19*, 30–33.

[14] Zawadzki, J.K.; Dunaif, A. Diagnostic criteria for polycystic ovary syndrome: Towards a rational approach. In *Polycystic Ovary Syndrome*; Dunaif, A., Givens, J.R., Haseltine, F.P., Merriam, G.E., Eds.; Blackwell Scientific Inc.: Boston, MA, USA, 1992; pp. 377–384.

[15] Azziz, R.; Dumesic, D.A.; Goodarzi, M.O. Polycystic ovary syndrome: An ancient disorder? *Fertil. Steril.* **2011**, *95*, 1544–1548.

[16] Carmina, E. Diagnosis of polycystic ovary syndrome: From NIH criteria to ESHRE-ASRM guidelines. *Minerva Ginecol.* **2004**, *56*, 1–6.

[17] Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group . Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004; 19(1): 41–7.

[18] Azziz, R.; Carmina, E.; Dewailly, D.; Diamanti-Kandarakis, E.; Escobar- Morreale, H.F.; Futterweit, W.; Janssen, O.E.; Legro, R.S.; Norman, R.J.; Taylor, A.E.; et al. Task Force on the Phenotype of the Polycystic Ovary Syndrome of The Androgen Excess and PCOS Society: The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. *Fertil. Steril.* **2009**, *91*, 456–488.

[19] Johnson, T.; Kaplan, L.; Ouyang, P.; Rizza, R. *National Institutes of Health Evidence-Based Methodology Workshop on Polycystic Ovary syndrome*; National Institutes of Health: Bethesda, MD, USA, 2012

[20] Draft Summary and Recommendations of International Evidenced-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. 2018

[21] Strowitzki T. Advanced diagnosis of polycystic ovary syndrome-new prediction models with standard parameters. Fertil Steril. 2021 Jan;115(1):92-93.

[22] Costello MF, Misso ML, Balen A, Boyle J, Devoto L, Garad RM, et al. Evidence summaries and recommendations from the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome: assessment and treatment of infertility. Hum Reprod Open 2019; 2019: hoy021.

[23] . Pasquali R. Obesity and androgens: facts and perspectives. Fertil Steril 2006; 85:1319–40.

[24] Vagios S, James KE, Sacha CR, Hsu JY, Dimitriadis I, Bormann CL, Souter I. A patient-specific model combining AMH and BMI as a predictor of PCOS and other oligo - anovulation disorders. Fertil Steril 2020.

[25] Himelein MJ, Thatcher SS. Polycystic ovary syndrome and mental health: A review. Obstet Gynecol Surv. 2006 Nov;61(11):723-32.

[26] Cooper H., Spellacy W.N., Prem K.A., Cohen W.D. Hereditary factors in the Stein leventhal 1968. *Am. J. Obstet. Gynecol.* 1968;**100**:371–387. doi: 10.1016/S0002-9378(15)33704-2.

[27] Diamanti-Kandarakis E., Piperi C. Genetics of polycystic ovary syndrome: Searching for the way out of the labyrinth. *Hum. Reprod. Update.* 2005;**11**:631– 643. doi: 10.1093/humupd/dmi025.

[28] Parker J. Understanding the Pathogenesis of Polycystic Ovary Syndrome: A transgenerational evolutionary adaptation to lifestyle and the environment. *ACNEM J.* 2020;**39**:18–26.

[29] Day F., Karaderi T., Jones M.R., Meun C., He C., Drong A., Kraft P., Lin N., Huang H., Broer L., et al. Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria. *PLoS Genet.* 2018;**14**:e1007813. doi: 10.1371/journal.pgen.1007813

[30] Crespo R.P., Bachega T.A.S.S., Mendonça B.B., Gomes L.G. An update of genetic basis of PCOS pathogenesis. *Arch. Endocrinol. Metab.* 2018;**62**:352–361. doi: 10.20945/2359-3997000000049.

[31] Jones M.R., Goodarzi M.O. Genetic determinants of polycystic ovary syndrome: Progress and future directions. *Fertil. Steril.* 2016;**106**:25–32. doi: 10.1016/j.fertnstert.2016.04.040.