History of discovery of polycystic ovary syndrome

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Abstract

Stein and Leventhal are regarded to have been the first investigators of polycystic ovary syndrome (PCOS); however, in 1721 Vallisneri, an Italian scientist, described a married, infertile woman with shiny ovaries with a white surface, and the size of pigeon eggs. It was not until the early 1990s at a National Institute of Health (NIH) sponsored conference on PCOS that formal diagnostic criteria were proposed and afterwards largely utilized. Many scientists tried to explain the pathophysiology of PCOS and many studies were made. It is now accepted that it is multifactorial, partly genetic; however, a number of candidate genes have been postulated. Insulin resistance has been noted consistently among many women with PCOS, especially in those with hyperandrogenism, but it is not included in any of the diagnostic criteria. Now there is strong evidence that cardiovascular disease risk factors and disturbances in carbohydrate metabolism are all increased in patients with PCOS compared to the healthy population. The criteria established by a group of experts during a conference in Rotterdam held in 2003 are obligatory (The Rotterdam ESHRE/ASRM – Sponsored PCOS Consensus Workshop Group). The subsequent "Rotterdam criteria" incorporated the size and morphology, as determined by an ultrasound, of the ovary into the diagnostic criteria.

Key words: polycystic ovary syndrome, infertile, hyperandrogenism

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Although Stein and Leventhal are regarded as the first investigators of polycystic ovary syndrome (PCOS), it was Vallisneri, an Italian medical scientist, physician and naturalist, who in 1721 described a married, infertile woman with shiny ovaries with a white surface and the size of ovaries as pigeon eggs.[1] Another report can be found in 1844, when Chereau and Rokitansky described fibrous and sclerotic lesions in t ovaries of a degenerative character with hydrops follicle.[2,3] Bulius and Kretschmar described hyperthecosis for the first time.[4] In 1879 Lawson Tait presented the need for bilateral oophorectomy for the treatment of symptomatic cystic degeneration of the ovaries.[5] Partial resection of the ovaries was soon proposed.[6] In 1902 von Kahlden published a review on the pathology and clinical implications of these ovaries.[7] Because of many critical voices regarding ovarian resection, John A. McGlinn in 1915 suggested puncturing "those cysts which are upon the surface" rather than resorting to ovarian resection.[8] In 1935 Stein and Leventhal presented a group of 7 women with common features: menstruation disturbances, hirsutism and enlarged ovaries with the presence of many small follicles.[9] They were also the first to describe the lack of menstruation in women with increased volume of ovaries and to suggest using ovarian wedge resection. After this surgical intervention regular menstrual cycles returned in all 7 patients and 2 of them became pregnant. After a bilateral ovarian wedge resection, menstruation returned in almost 90% of women and 65% of them became pregnant.[10] However, as medical treatment became available with the use of clomiphene citrate, follicle stimulating hormone (FSH) and urinary source, surgical treatment became less often used.[11–13]

PCOS was described as a distinct masculinization and theca luteinization syndrome.[14,15] Many scientists tried to explain etiology of cystic ovaries. Fogue and Massabuau proposed 3 potential mechanisms: inflammation, congestion and dystrophy.[16] Stein and Leventhal in their original report thought that bilateral cystic ovaries result from abnormalities in hormonal stimulation, which was confirmed later.[9,17] Plate suggested that source of androgens in women may not be only adrenals but ovaries also.[18–20] Regardless of the source of androgens in PCOS, scientists in 1953 proposed to use cortisone therapy or to treat sclerocystic ovaries with exogenous testosterone.[21–23] In 1958, 3 investigators were the first to describe an increased level of luteinizing hormone (LH) and 17-ketosteroids in the urine of women with bilateral cystic ovaries.[24,25] Increased LH and testosterone levels were regarded to be of key importance in diagnosing PCOS.[17,26] Later, abnormal release of gonadotropins, LH/FSH ratio and androgens were confirmed.[27] Finally the condition of abnormal concentrations of gonadotropins for the diagnosis of PCOS was rejected.[28] However, following the description of a method of testosterone level measurement in plasma in 1961, increased circulating level of androgens in women with PCOS was demonstrated shortly thereafter.[29,30] Because of the limitations of laboratory tests in measuring the total androgenic hormone levels, many women met the clinical criteria of PCOS, without confirmation of hormones secretion disorders in laboratory tests.[31] Secretion of hormones released by the pituitary gland and gonads is pulsative, so maximal and minimal concentrations may differ significantly during the day, which is why a single determination may be misleading, especially in women with rather low androgens levels compared to men. Researchers were looking for such a diagnostic tool which would replace roentgenography or reconnaissance laparotomy used before to diagnose polycystic ovaries. Surgical treatment of resistant anovulation has had a resurgence with the laparoscopic method popularized by Gjoanness H.[32] Ultrasound examination of the reproductive system was a great progress in the clinical practice. Benefits of this research method, including its non-invasive character, repeatability, its simplicity in use and precision in assessing the ovary stroma and ovary follicles were immediately appreciated. Swanson was the first who described a structure of ovaries in women with PCOS using ultrasonography.[33] The improved technology and utilization of ultrasound in medicine led to the ultrasound definition of polycystic ovaries, defined primarily on the morphology and the number of small antral follicles. A study performed by Fox in 1991, aimed at comparing the use of transvaginal and transabdominal ultrasound, proved the presence of falsely negative results in the case of examination through the abdominal lining in case of as many as 30% examined women.[34] Progress made in the ultrasound diagnose enabled to verify of the ultrasound criteria.[35] It seemed that the ovarian stroma area to total area ratio had been the best condition of a PCOS diagnosis. Almost one quarter of the population had the appearance of polycystic ovaries when examined ultrasonically, but more than half of these had no clinical signs or symptoms. These women are referred to have polycystic ovaries.

The list of the various names of the same disorder which can be found in the literature are the following: polycystic ovaries disorder, a syndrome of polycystic ovaries, functional ovary androgenism, hyperandrogenic, chronic anovulation, polycystic ovarian syndrome, ovarian dysmetabolic syndrome, sclerotic polycystic ovary syndrome, polycystic ovary syndrome.[36]

It was not until the early 1990s at a National Institutes of Health (NIH) sponsored conference on PCOS that formal diagnostic criteria were proposed and afterwards were largely utilized. These criteria, known as "the NIH criteria", were published as the conference proceedings and received large scale of acceptance in the research and clinical communities. According to these criteria, PCOS is defined as unexplained hyperandrogenic anovulation. PCOS can be diagnosed in women if the following criteria are found: symptoms of excess of androgens (clinical or biochemical), rare ovulations, exclusion of other disorders with similar clinical symptoms.[37]

Thus, PCOS remains a diagnosis of exclusion. In the light of many later research studies, modification of the definition seemed to be necessary. The 2004 criteria established by a group of experts during a conference in Rotterdam in the Netherlands held in 2003 are obligatory (The Rotterdam ESHRE/ASRM – Sponsored PCOS Consensus Workshop Group). The subsequent "Rotterdam criteria" incorporated the ultrasound determined size and morphology of the ovary into the diagnostic criteria.[38] According to them the presence of 2 out of 3 following criteria are necessary to make a PCOS diagnosis:

1. rare ovulations or lack of ovulations,
2. excessive activity of androgens confirmed by a clinical or laboratory examination,
3. features of polycystic ovaries in the ultrasound after the exclusion of other pathologies characterized by hyperandrogenism, such as adrenocorticotropic hormone-dependent or independent hypercortisolemia, thyroid gland disorders, a classical and non-classical form of congenial adrenal glands hypertrophy, tumors of adrenal glands or ovary tumors producing androgens, as well as the influence of received medication.

Clinical features of hyperandrogenemia are: hirsutism assessed according to Ferriman-Gallwey score (giving the points according to the scheme), seborrheic skin disease, androgenic balding and symptoms of virilization in the form of clitoris overtrophy or lowered tone of voice. An analysis of concentrations of testosterone, 17-OH progesterone, cortisol, sex hormone-binding globulin, albumins and hormones released from the pituitary gland including thyroid-stimulating hormone, prolactin, are useful in the assessment of hyperandrogenism. Ultrasound criterion is diagnostic if made by using a transvaginal ultrasound, performed during follicular phase, more than 12 follicles of the diameter of < 10 mm are visible or an increased ovary volume is a value > 10 mL. What is important, these lesions do not have to be bilateral.

The Rotterdam definition is much wider and includes more patients, in particular those without clinical or biochemical hyperandrogenism, while into the NIH definition biochemical hyperandrogemia was necessary for making the POCS diagnosis. The Rotterdam criteria have been criticized for including more mild phenotypes, especially for the combination of polycystic ovaries with oligomenorrhea. Critics of this Rotterdam definition are of the opinion that the results obtained on the basis of examinations in patients with an excess of androgens cannot be extrapolated to normoandrogenic patients. These additional phenotypes may lead to the generalization of clinical trials to treat PCOS and may also elevate the prevalence of PCOS in the general population.

In 2006 the Androgen Excess Society (AES) issued a statement – criteria attempted to establish hyperandrogenism as a sine qua non diagnostic condition in combination with other signs of the syndrome.[35] The focus on hyperandrogenism was to eliminate milder phenotypes (without excessive amount of androgens, with menstruation disorders and a typical ultrasound image PCOS) and based on evidence that hyperandrogenism tends to track with both reproductive (i.e. acne, hirsutism, and androgenic alopecia) and metabolic (i.e. insulin resistance, dyslipidemia, and elevated cardiovascular risk) symptoms of the syndrome. However, it was also emphasized, that further work on defining PCOS is necessary for the appropriate progress in medicine, research studies and the treatment of patients, as PCOS not only causes menstruation disorders, infertility, obstetric complications and hyperandrogenism, but also increases the risk of more frequent occurrence of cardiovascular diseases and cancers of the reproductive system.

Many years have passed since the first publication concerning PCOS, but the etiology of PCOS is still puzzling. It is now accepted that it is multifactorial and partly genetic; however, a number of candidate genes have been postulated. Insulin resistance has been noted consistently among many women with PCOS, especially in those with hyperandrogenism, but it is not included in any of the diagnostic criteria. Now there is strong evidence that cardiovascular disease risk factors and disturbances in carbohydrate metabolism are all increased in patients with PCOS compared with the healthy population. The other very important point that has been made is that the basis of treatment is the modification of lifestyle. As the primary biochemical abnormality is insulin resistance, metformin can be used in the treatment. There have been a number of recommendations for the use of insulin sensitizing agents not only to restore ovulation but to facilitate weight loss, counteract androgenic symptoms, prevent long-term complications, decrease the risk of early pregnancy loss, decrease the risk of ovarian hyperstimulation syndrome, and even improve the outcome of in vitro fertilization therapy. There is still research conducted on improving therapy in PCOS women.

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