Chapter 1

Introduction to and History of Polycystic Ovary Syndrome

Gabor T. Kovacs

Although the modern history of polycystic ovary syndrome (PCOS) started with the pivotal paper by Stein and Leventhal in 1935,[1] there are suggestions that the "syndrome" was referred to as early as in the time of Hippocrates (ca. 460–377 BC). Medical notes at the time referred to women "whose menstruation is less than three days or is meager, are robust, with a healthy complexion and a masculine appearance; yet they are not concerned about bearing children nor do they become pregnant" and suggest that they may have been describing women with PCOS.[2]

It has also been recorded that Soranus of Ephesus (ca. AD 98–138) described some women "who did not menstruate at all, whose bodies are of a masculine type . . . we observe that the majority of those not menstruating are rather robust, like mannish and sterile women." More recent accounts of women who probably had PCOS are given by Maimonides (1135–1204): "there are women whose skin is dry and hard, and whose nature resembles the nature of a man. However, if any woman's nature tends to be transformed to the nature of a man, this does not arise from medications, but is caused by heavy menstrual activity"; and by the sixteenth-century obstetrician and surgeon Ambroise Paré (1510–1590), who observed: "Many women, when their flowers or tearmes be stopped, degenerate after a manner into a certaine manly nature, whence they are called Viragines, that is to say stout, or manly women; therefore their voice is loud and bigger, like unto a mans, and they become bearded."

All these observations fit the symptomatology of PCOS – menstrual irregularity, subfertility, masculine features and obesity. However, it was the 1934 presentation and subsequent publication by Irving Stein and Michael Leventhal that identified this condition as a reproductive disorder and proposed an effective treatment – bilateral ovarian wedge resection (BOWR) – for the associated subfertility.[1]

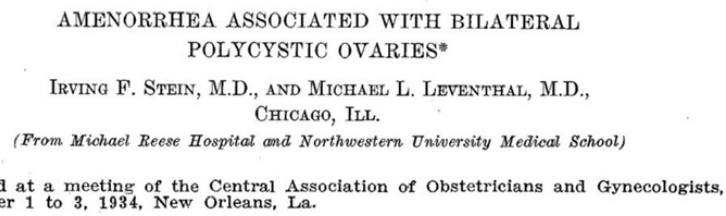
Irving Stein was born in Chicago on September 19, 1887, the seventh of ten children, to Adolf Stein and Emma Freiler. Stein initially completed a science degree at the University of Michigan and subsequently obtained a medical degree from Rush Medical College in Chicago in 1912. After a two-year internship at Michael Reese Hospital in Chicago, he joined the hospital's obstetrics and gynecology department as an assistant in surgery, focusing on women's reproductive health and obstetrics and reaching "attending physician" status by 1915. He married Lucile Oberfelder in 1921, and they had two children, a son, Irving F. Stein Junior, and a daughter, Eleanor H. Rusnak. Stein was also a professor at Northwestern University and established a private practice at Highland Park Hospital, Illinois.[3]

Stein was known as a warm and caring doctor as well as a dignified and respected teacher, often found with a large group of fellow doctors and nurses following him while he did his rounds. One of his colleagues, Melvin Cohen, stated that "Stein was meticulous in everything he did, including patient care, surgery, and even his appearance, as Stein often wore a boutonniere to the hospital."

Michael Leventhal joined Stein at the Michael Reese Hospital in 1926, where they collaborated on research into "sterility in women." Michael Leo Leventhal was also born in Chicago and graduated from Rush Medical College, but 12 years after Stein (1924). Apart from military service as a medical officer in the US Army, he spent his entire career working at the Michael Reese Hospital.

Before Leventhal, Stein was working with Robert Arens studying ovarian abnormalities and developed a method for imaging the reproductive organs by injecting carbon dioxide into the pelvis and iodized oil into the fallopian tubes, combined with X-ray examination. This enabled measuring the dimensions of the ovaries and the patency of the tubes. It was through using this technology

https://doi.org/10.1017/9781108989831.001 Published online by Cambridge University Press



AMENORRHEA ASSOCIATED WITH BILATERAL POLYCYSTIC OVARIES*

IRVING F. STEIN, M.D., AND MICHAEL L. LEVENTHAL, M.D.,
CHICAGO, ILL.

(From Michael Reese Hospital and Northwestern University Medical School)

*Read at a meeting of the Central Association of Obstetricians and Gynecologists, November 1 to 3, 1934, New Orleans, La.

Figure 1.1 The Stein and Leventhal paper of 1935

that Stein was able to observe a group of women with abnormally large ovaries – two to four times the normal size – who became the subject of Stein and Leventhal's seminal 1935 paper.

In an article commemorating the 80th anniversary of Stein and Leventhal's original publication, Ricardo Azziz and Eli Adashi wrote that the research, "although not flawless, was both seminal and transformative."[4] They pointed out that not only was the Stein and Leventhal paper the first report of a case series but it also described a possible therapy, BOWR. Azziz and Adashi concluded that "we have much to celebrate, as we commemorate the 80th anniversary of the publication of the report by Stein and Leventhal in 1935, for a new disorder was described, one that we know today affects, in its various forms, 1 in every 7–17 women worldwide." We will therefore look at the 1935 paper in detail. The title and details of this paper are shown in Figure 1.1.

In their paper, they commence by commenting that bilateral polycystic ovaries are usually described in association with uterine bleeding and endometrial hyperplasia, but no mention is made of bilateral polycystic ovaries and amenorrhea. They then describe a series of patients with ovaries enlarged up to four times the normal size, associated with absent menses. They described the cortex as hypertrophied and the tunica as tough fibrotic and thickened. The cysts were follicular, contained clear fluid and were confined to the surface of the cortex, numbering from 20 to 100 in each ovary. On section, the ovary was "oyster grey" with corpora lutea rarely found, and if present they were small and deeply placed. They described the uteri as either normal sized or smaller and firmer than normal. They also reported masculinizing changes in some patients, with rhomboid escutcheon and hirsutism on the arms, legs and face. The external genitalia were reported as normal in most, but some showed hypertrophied labia minora and clitoris.

They then described seven women with PCOS, all amenorrheic, who underwent bilateral wedge resection of the ovaries, all of whom reported a regular 28-day cycle postoperatively, with one woman (their first patient) conceiving two children. Stein and Leventhal recommended that diagnosis should include pneumo-roentgenography as pelvic examination of ovarian size was not reliable. Their reference for normal size of the ovary was "about one fourth the size of the uterine corpus." They also discussed the etiology of this condition and disputed the previous hypothesis that it was the result of an inflammatory process, as there was never any evidence of adhesions that one would expect if it was due to infection. They postulated an endocrine causal relationship.

In summary, they concluded that the treatment of PCOS by estrogenic hormone was unsatisfactory, whereas surgical wedge resection was successful in restoring physiologic function – menstruation – with pregnancies in two out of seven patients. A recurrence of polycystic change in the ovary was not found in the follow-up of any of these women. With respect to the pathophysiology of PCOS, they believed that mechanical overcrowding of the cortex by cysts interferes with the progress of normal Graafian follicle to the surface of the ovary.

By 1964, Stein had expanded his experience and reported on a successful series of 108 women treated by "wedge resection."[5] Consequently, BOWR became the standard treatment for anovulation associated with PCOS. An example of the efficacy and widespread acceptance of BOWR as a treatment for PCOS-associated anovulation came from Sweden, where Lunde and colleagues reported on 149 women with polycystic ovarian syndrome (PCOS), who were treated at a university teaching hospital 15–25 years after

https://doi.org/10.1017/9781108989831.001 Published online by Cambridge University Press

ovarian wedge resection (BOWR) and studied three times by means of a questionnaire.[6] Life-table analysis showed a cumulative rate of spontaneous pregnancies of 76%, increasing to 88% when induced pregnancies were included, with a cumulated live birth rate of 78% and with a regular menstrual pattern restored up to 25 years after BOWR.

When less invasive alternatives for the treatment of anovulation using oral clomiphene citrate and injectable follicle-stimulating hormone (FSH) preparations became available in the 1960s, the popularity of BOWR waned.[7, 8] Furthermore, evidence emerged that BWRO could be followed by periovarian/peritubal scarring, which had its own negative effect on fertility. Toaff and colleagues reported in 1976 that all seven patients who underwent laparoscopy subsequent to BOWR had extensive periovarian and peritubal adhesions.[9] They concluded that "our observations support the plea to relegate the surgical approach to a minor position in patients with Stein-Leventhal syndrome." The current status of surgical management of PCOS is discussed in detail in Chapter 12.

The Historical Development of Diagnostic Criteria for PCOS

Ovarian Enlargement/Appearance

In the time of Stein and Leventhal, PCOS was diagnosed on a history of irregular menses associated with some androgenization in the presence of enlarged ovaries. Ovarian enlargement was diagnosed by palpation, which is very subjective especially in obese women (as many PCOS patients are). Stein improved the diagnostic accuracy by introducing pneumo-roentgenography as in his 1935 report. As BOWR became popular, histological features of hypertrophied ovarian cortex with thickened fibrotic tunica became the criteria for diagnosis.[10]

Hormonal Assays

The next diagnostic criteria evolved with the availability of radioimmunoassay during the 1970s, and PCOS was diagnosed on the basis of elevated levels of luteinizing hormone (LH) and raised testosterone (T).[11] The limitations of using hormonal criteria include the imprecise nature of assays, the variability in hormone levels and the pulsatile manner of gonadotropin secretions. To improve preciseness not only absolute levels but ratios of LH:FSH between 2:1 and 3:1 were suggested as a diagnostic criterion. Nevertheless, many women had clinical symptoms of PCOS who did not fulfill the endocrine criteria.

Ultrasound Appearance

With the development of noninvasive visualization of the ovaries using ultrasonic scanning, it was possible to easily and reliably count ovarian follicles as well as measure ovarian and follicular size. In addition, the sclerotic stroma could also be identified. The first description of polycystic ovaries visualized on ultrasound came from Swanson and colleagues.[12] Both laparoscopic and histologic comparisons showed excellent correlations with ultrasonic examination. Adams and colleagues defined an ovary as polycystic if "there were multiple cysts (10 or more) 2–8 mm in diameter arranged either peripherally around a dense core of stroma or scattered throughout an increased amount of stroma."[13] This became the basis of the diagnosis of polycystic ovaries (PCO) in what is known as the "Rotterdam criteria."[14]

It also became apparent that many more women had PCO, now called polycystic ovarian morphology (PCOM), than those who had the syndrome (PCOS). Women could be separated into those with PCO appearance on ultrasound and those who had associated symptoms of oligo/amenorrhea and/or hyperandrogenism (PCOS). In population studies, it appeared that about half of the women with PCO developed PCOS sometime during their lifetime.[15]

Anti-Müllerian Hormone (AMH) Levels

It has been recognized for nearly two decades that anti-Müllerian hormone (AMH) is produced by the granulosa cells of pre-antral and small antral ovarian follicles.[16] Consequently, there is a correlation between the antral follicle count (AFC) and AMH levels, and it is hoped that the measurement of AMH will be a diagnostic tool for the presence of PCOM. Unfortunately, owing to the heterogeneity of the AFC and AMH levels, it should not yet be used for the diagnosis of PCOM. It is hoped that with improved and better standardized assays, as well as large-scale validation studies, the threshold level of AMH to diagnose PCOM may be established.[17]

https://doi.org/10.1017/9781108989831.001 Published online by Cambridge University Press

From Ovarian Pathology of Stein-Leventhal Syndrome to a Multisystem Endocrine Disease

Stein-Leventhal syndrome was a recognized disorder for more than five decades until the focus shifted to it being a "metabolic multisystem syndrome." In 1990, an expert conference was sponsored by the National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH). The expert group concluded that diagnostic criteria should include (in order of importance):

1. hyperandrogenism and/or hyperandrogenemia,
2. menstrual dysfunction with the exclusion of other known disorders.[18]

The subsequent discovery that many women with PCOS are insulin-resistant with compensatory hyperinsulinemia designated this condition as a reproductive-metabolic disorder, with broader implications than those defined by the NIH in 1990.

To arrive at an international agreement on the diagnostic criteria, and to define the clinical implications of PCOS, a consensus conference chaired by Basil Tarlatzis (Greece) and Bart Fauser (Netherlands) was held on May 1–3, 2003, in Rotterdam, the Netherlands.[14] A scientific committee consisting of Jeff Chang (USA), Ricardo Azziz (USA), Rick Legro (USA), Didier Dewailly (France), Steve Franks (UK), Basil Tarlatzis (Greece) and Bart Fauser (Netherlands) was established. Also invited were a number of international experts as discussants: Adam Balen (UK), Phillipe Bouchard (France), Eva Dahlgren (Sweden), Luigi Devoto (Chile), Evita Diamanti (Greece), Andrea Dunaif (USA), Marco Filicori (Italy), Roy Homburg (Israel), Lourdes Ibanez (Spain), Joop Laven (Netherlands), Dennis Magoffin (USA), John Nestler (USA), Rob Norman (Australia), Renato Pasquali (Italy), Michel Pugeat (France), Jerome Strauss (USA), Seang Lin Tan (Canada), Anne Taylor (USA), Robert Wild (USA) and Sarah Wild (UK). This symposium was financially sponsored by an unconditional grant from NV Organon and by the European Society of Human Reproduction (ESHRE) and the American Society for Reproductive Medicine (ASRM). They concluded that PCOS is a syndrome of ovarian dysfunction along with the cardinal features of hyperandrogenism and PCO morphology. A finding of at least 12 follicles in one ovary, or an ovarian volume of 10 cc, was considered the ultrasonic diagnostic criterion for PCO. They agreed that clinical manifestations may include menstrual irregularities, signs of androgen excess and obesity. They noted that insulin resistance and elevated serum LH levels were also common features in PCOS, and PCOS was associated with an increased risk of type 2 diabetes and cardiovascular events.[14]

Although the Rotterdam Conference concentrated on a definition for diagnosis, there was a need for consensus on which treatments should be offered. To define appropriate therapeutic guidelines another consensus conference was organized on March 2–3, 2007, in Thessaloniki, Greece. The experts invited included Basil Tarlatzis (Greece), Bart Fauser (Netherlands), Rick Legro (USA), Rob Norman (Australia), Kathleen Hoeger (USA), Renato Pasquali (Italy), Steve Franks (UK), Ioannis Messinis (Greece), Robert Casper (Canada), Roy Homburg (Israel), Rick Lobo (USA), Robert Rebar (USA), Richard Fleming (UK), B. R. Carr (USA), Phillipe Bouchard (France), J. Chang (USA), J. N. Hugues (France), R. Azziz (USA), Efstratios Kolibianakis (Greece), George Griesinger (Germany), Klaus Diedrich (Germany), Adam Balen (UK), Cindy Farquhar (New Zealand), Paul Devroey (Belgium), Pak Chung Ho (Hong Kong), John Collins (Canada), Dimitrios Goulis (Greece), René Eijkemans (Netherlands), Piergiorgio Crosignani (Italy), Alan DeCherney (USA) and Andre van Steirteghem (Belgium). This symposium was also supported by an unconditional grant from NV Organon and by ESHRE and ASRM.

A number of interventions were reviewed and recommendations were made including lifestyle modifications (diet and exercise), administration of pharmaceutical agents such as clomiphene citrate (CC), insulin-sensitizing agents, gonadotropins and gonadotropin-releasing hormone (GnRH) analogues, the use of laparoscopic ovarian drilling and the application of assisted reproductive techniques (ART).[19]

A third consensus conference was held in 2011 in Amsterdam to summarize the then current

https://doi.org/10.1017/9781108989831.001 Published online by Cambridge University Press

knowledge and to identify knowledge gaps regarding various women's health aspects of PCOS.[20] Topics addressed included PCOS in adolescence, the symptoms of hirsutism and acne, contraceptive options, menstrual cycle abnormalities, quality of life, ethnicity, pregnancy complications, long-term metabolic and cardiovascular health and, finally, cancer risk. Participants included Bart Fauser (Netherlands), Basil Tarlatzis (Greece), Robert Rebar (USA), Rick Legro (USA), Adam Balen (UK), Rick Lobo (USA), E. Carmina (Sicily), Jeff Chang (USA), Bulent Yildiz (Turkey), Joop Laven (Netherlands), J. Boivin (UK), F. Petraglia (Italy), C. N. Wijeyeratne (Sri Lanka), Rob Norman (Australia), Andrea Dunaif (USA), Steve Franks (UK), Robert Wild (USA), Daniel Dumesic (USA) and Kurt Barnhart (USA). For each aspect, the consensus committee published concluding statements (where there was agreement), a summary of areas of disagreement (if any) and knowledge gaps with recommended directions for future research.

Simultaneously, in Australia, the Australian government's Department of Health and Ageing funded a Guideline Development Group, chaired by Helena Teede. The Department of Health recognized that PCOS has potential for major metabolic consequences, including obesity and type 2 diabetes mellitus (DM2) as well as cardiovascular disease (CVD), all of which were national health priority areas. The recommendations of the group were published as a supplement to the *Medical Journal of Australia* in 2011.[21]

A European approach to define the criteria required for the diagnosis of PCO emphasized the phenotypic heterogeneity of the syndrome.[22] The group focused on the impact of metabolic issues, specifically insulin resistance and obesity, and the susceptibility to develop earlier than expected glucose intolerance states, including type 2 diabetes. They concentrated on an endocrine and European perspective in the debate on the definition of PCOS listed as etiological factors, such as early life events, potentially involved in the development of the disorder. They placed an emphasis on the laboratory evaluation of androgens and other potential biomarkers of ovarian and metabolic dysfunctions. They considered the role of obesity, sleep disorders and neuropsychological aspects of PCOS as well as the relevant pathogenetic aspects of cardiovascular risk factors. They also discussed how to target treatment choices according to the phenotype and individual patient's needs.

In November 2015, the American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology (ACE), and the Androgen Excess and PCOS Society (AE-PCOS) released new guidelines in the evaluation and treatment of PCOS. They recommended that diagnosis be based on the presence of at least two of the following three criteria: chronic anovulation, hyperandrogenism (clinical or biological) and PCO. They stated that free T levels are more sensitive than the measurement of total T and that the value of measuring levels of androgens other than T in patients with PCOS is relatively low. With respect to imaging, new ultrasound machines allow a threshold for diagnosis of PCOM in patients having at least 25 small follicles (2–9 mm) in the whole ovary, and ovarian size greater than 10 mL should be considered increased ovarian size. They felt that AMH was useful for diagnosis of PCOS.

They recommended that management of women with PCOS should include reproductive function, as well as the care of hirsutism, alopecia and acne. They also recognized the increased prevalence of endometrial hyperplasia and endometrial cancer. They highlighted that, in PCOS, hirsutism develops gradually and intensifies with weight gain and that girls with severe acne may have a 40% likelihood of developing PCOS. It was also pointed out that oral contraceptives can effectively lower androgens. They further warned against diagnosis in the first few years after menarche, as many features of PCOS, including acne, menstrual irregularities and hyperinsulinemia, are common in normal puberty.[23]

The Australian group was important, as it was the catalyst for the formation of the International PCOS Network driven by Helena Teede and Rob Norman, who then undertook the development of international evidence-based guidelines on the assessment and management of polycystic ovary syndrome. Funding for the group came principally from the Australian National Health and Medical Research Council (NHMRC) through the funded Centre for Research Excellence in Polycystic Ovary Syndrome (CREPCOS) as well as from ESHRE and ASRM.

The International Advisory Panel (representatives from six continents) was chaired by Bart Fauser (Netherlands), the deputy chair Rob

https://doi.org/10.1017/9781108989831.001 Published online by Cambridge University Press

Norman (Australia) and included JuhaTapanainen (Finland), Zephne van der Spuy (South Africa), Duru Shah (Inida), Rick Legro (USA), Frank Broekmans (Germany), Anuja Dokras (USA), Marie Misso (Austalia), Chir Ruey Tzeng (Taiwan), Jie Qiao (China) and Poli Mara Spritzer (Brazil).

The International PCOS Network was able to collaborate and engage with 37 organizations (including consumers) across 71 countries and organized 23 face-to-face international meetings over 15 months. The various groups involved more than 3000 health professionals and consumers internationally.[17] These international evidence-based guidelines included the assessment and management of PCOS and were designed to provide clear information to assist clinical decision-making and support optimal patient care. Addressing psychological, metabolic and reproductive features of PCOS, there were 60 prioritized clinical questions involving 40 systematic and 20 narrative reviews, generating 166 recommendations and practice points. This is discussed in detail in Chapter 5.

How Has PCOS Survived Natural Selection?

The inheritance of PCO/PCOS is still poorly understood and is discussed in detail in Chapter 2. However, there is consensus that there is some genetic hereditary factor. One may then ask, how did these series of symptoms, which have a reproductive handicap (subfertility, cardiac disease, diabetes), survive natural selection?

If we go back to the hunter-gatherer existence, while the phenotype of PCOS had a reproductive disadvantage, being a female with the greatest capacity for the energy storage necessary to endure prolonged episodes of starvation, the so-called thrifty genotype, was an advantage, as women with PCOS were able to survive during periods of food deprivation. Furthermore, insulin resistance that diminishes energy expenditure in times of famine was an additional evolutionary advantage. Also, despite a community belief that women with PCOS are sterile, they are certainly not but they do have lower fertility. Consequently, in the absence of contraception, they will have lower fecundity and therefore have longer spacing between pregnancies, which would have resulted in better maternal health. Birth-associated mortality was also high, so that having fewer pregnancies and births was also an advantage. For women who were nomadic hunters, having fewer children made it easier for them to be transported and, additionally, there were fewer mouths to feed. With delayed fecundity and aging parturition, PCOS women may have attained significant nurturing skills, given their wisdom and strength in surviving a physically demanding environment. They also created an environment suitable for child-rearing as it was not focused on or threatened by pregnancy.

At the individual level, the greater lean muscle mass and bone mineral density of women with PCOS would have been advantageous to their own survival and that of their progeny. It could therefore be argued that PCOS favored the survival of those family units containing women with PCOS.

With a change to human settlement in communities that underwent a shift to agricultural farming and animal husbandry, with sufficient food becoming available, there was a need to have several children in order to provide a rural workforce, therefore PCOS should have become a teleological disadvantage. However, for PCOS women, even in sedentary agricultural societies, they could still conceive, albeit at a rate lower than normal, and they may have had lower maternal mortality and would have been sturdier than average. Even for agricultural societies during the eighteenth and nineteenth centuries, significant periodic famines remained a fact of life for which women with PCOS were better suited to survive.

Considering the male genetically related relatives of PCOS women, they may have symptoms and signs of androgen excess and insulin resistance but neither their ability to attract partners nor their fertility has been shown to be impaired, and, as discussed, they also carry the metabolic advantage of being able to survive famine. All these factors seem to have potentially counterbalanced any disadvantages arising from the overall lower number of children conceived by PCOS women and explain why the condition has not been teleologically genetically eliminated.

We still have a lot to learn about PCO(M)/PCOS, especially about its etiology and pathogenesis. Long-term studies, or "big data" analysis, may answer some of these questions. Certainly, this introductory chapter on the history of PCOS will need to be updated for the fourth edition of *Polycystic Ovary Syndrome*.

https://doi.org/10.1017/9781108989831.001 Published online by Cambridge University Press

References

1 Stein, I. F. and Leventhal, M. L. Amenorrhoea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol* 1935; 29(2): 181–191.

2 Azziz, R. Dumesic, D. A. and Goodarzi, M. O. Polycystic ovary syndrome: An ancient disorder? *Fertil Steril* 2011; 95(5): 1544–1548.

3 Darby, A. Irving Freiler Stein Sr. (1887–1976). *Embryo Project Encyclopedia*, July 20, 2017. http://embryo.asu.edu/handle/10776/12956

4 Azziz, R. and Adashi, E. Y. Stein and Leventhal: 80 years on. *Am J Obstet Gynecol* 2016; (214) 2: 247.

5 Stein, I. F. Duration of fertility following ovarian wedge resection: Stein-Leventhal syndrome. *West J Surg Obstet Gynecol* 1964; 72: 237–242.

6 Lunde, O., Djoseland, O. and Grottum, P. Polycystic ovarian syndrome: A follow-up study on fertility and menstrual pattern in 149 patients 15–25 years after ovarian wedge resection. *Hum Reprod* 2001; 16(7): 1479–1485.

7 Greenblatt, R. B., Barfield, W. E. and Jungck, E. C. Induction of ovulation with MRL/41: Preliminary report. *JAMA* 1961; 178: 101–104.

8 Gemzell, C. A., Diczfalusy, E. and Tillinger, G. Clinical effect of human pituitary follicle-stimulating hormone (FSH). *J Clin Endocrinol Metab* 1958; 18(12): 1333–1348.

9 Toaff, R., Toaff, M. E., Peyser and M. R. Infertility following wedge resection of the ovaries. *Am J Obstet Gynecol* 1976; 124(1): 92–96.

10 Goldzieher, J. W. and Green, J. A. The polycystic ovary: I. Clinical and histological features. *J Clin Endocrinol Metab* 1962; 22: 325–328.

11 Yen, S. S. C., Vela, P. and Rankin, J. Inappropriate secretion of follicle-stimulating hormone and luteinizing hormone in polycystic ovarian disease. *J Clin Endocrinol Metab* 1970; 30: 442.

12 Swanson, M., Sauerbrei, E. E. and Cooperberg, P. L. Medical implications of ultrasonically detected polycystic ovaries. *J Clin Ultrasound* 1981; 9(5): 219–222.

13 Adams, J., Polson, D. W. and Franks, S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *Br Med J* 1986; 293 (6543): 355–359.

14 The 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): 41–47.

15 Lowe, P., Kovacs, G. and Howlett, D. Incidence of polycystic ovaries and polycystic ovary syndrome amongst women in Melbourne, Australia. *Aust N Z J Obstet Gynaecol* 45(1): 17–19.

16 Cook, C. L. et al. Relationship between serum müllerian-inhibiting substance and other reproductive hormones in untreated women with polycystic ovary syndrome and normal women. *Fertil Steril* 2002; 77(1): 141–146.

17 Teede, H., Misso, M. , Costello, M. et al. *International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome*. Melbourne: Monash University and NHMRC, Centre for Research Excellence in PCOS and the Australian PCOS Alliance, 2018.

18 Zawadski, J. K. and Dunaif, A. Diagnostic criteria for polycystic ovary syndrome: Towards a rational approach. In A. Dunaif, J. R. Givens, F. P. Haseltine and G. R. Merriam, eds. *Polycystic Ovary Syndrome*. Boston, MA: Blackwell Scientific Publications, 1992: 377–384.

19 The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril 2008; 89(3): 505–522.

20 The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Consensus on women's health aspects of polycystic ovary syndrome (PCOS). *Hum Reprod* 2011; 27(1): 14–24.

21 Teede, H., Misso, M. L., Deeks, A. A. et al. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. *Med J Aust* 2011; 195(6): S65.

22 Conway, G., Dewailly, D., Diamanti-Kandarakis, E. et al. The polycystic ovary syndrome: A position statement from the European Society of Endocrinology. *Eur J Endocrinol* 2014; 171: P1–29.

23 Goodman, N. F., Cobin, R. H., Futterweit, W. et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society disease state clinical review: Guide to the best practices in the evaluation and treatment of polycystic ovary syndrome–part 1. *Endocr Pract* 1915; 21(11): 1291–1300.

https://doi.org/10.1017/9781108989831.001 Published online by Cambridge University Press