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Introduction: Polycystic ovary syndrome is an intergenerational problem

Gabor T. Kovacs and Robert Norman

The polycystic ovary syndrome (originally called the Stein–Leventhal syndrome), was popularized by the two Americans whose names have been attached to the condition for 70 years (Stein and Leventhal 1935), and was considered as a problem of anovulation and infertility. They described their treatment of anovulation using wedge resection with remarkable success. However as medical treatment became available with the utilization of clomiphene citrate (Greenblatt 1961), and subsequently the use of follicle stimulating hormone of pituitary (HPG) (Kovacs *et al.* 1989) and urinary source (Wang and Gemzell 1980), surgical treatment became less often used. Interestingly, surgical treatment of resistant anovulation has had a resurgence with the laparoscopic approach initially described by French gynecologists, but popularized by Gjoanness (1984). The history and current status of surgical treatment are discussed in Chapter 11.

It was the use of ultrasound that transformed visualization of the ovaries (Swanson *et al.* 1981). (The use of imaging techniques is described in detail in Chapter 5.) It then became apparent that there were two different clinical spectrums. Almost one quarter of the population had the appearance of polycystic ovaries when examined ultrasonically, but more than half of these had no clinical symptoms whatsoever (Lowe *et al.* 1995, Balen and Michelmore 2002). These women are referred to as having polycystic ovaries (PCO). If the ultrasonic appearance is accompanied by other symptoms, such as hyperandrogenism, the term used is polycystic ovary syndrome (PCOS).

Although the exact definition of PCO/PCOS has had different parameters when described by various experts, following a Consensus Conference held in Rotterdam in 2003, an internationally accepted definition has been adopted by the European Society for Human Reproduction and Embryology and the American

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Society for Reproductive Medicine, known as the ESHRE/ASRM Rotterdam consensus (Rotterdam consensus). This is described in detail throughout this book; its full text is given in The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004).

The etiology of PCO/PCOS is still puzzling. It is now accepted that it is multifactorial, partly genetic, but although a number of candidate genes have been postulated, the mode of inheritance and the responsible gene remain aloof. The other important point that has been made is that the mainstay of treatment is "diet and exercise" (Clark *et al.* 1998) and that greater emphasis needs to be placed on lifestyle factors when consulting these women. The obesity epidemic in the West may unmask more women with PCOS.

There is still no firm clinical evidence that PCO is a health hazard, although there is strong circumstantial evidence that cardiovascular disease risk factors are all increased if we look at surrogate markers in PCOS. Diabetes mellitus is clearly more common.

As the primary biochemical abnormality is insulin resistance, and metformin can restore menstrual regularity (Velazquez *et al.* 1994), there have been a number of advocates 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 (IVF) therapy. The role of insulin sensitizing agents is reviewed in Chapter 13.

In this second edition of *Polycystic Ovary Syndrome*, we have decided to be more holistic, and we have included chapters on the role of vitamins and nutrients (Chapter 20), as well as the role of bariatric surgery (Chapter 19).

We believe that this book is an up-to-date comprehensive reference manual for all aspects of this fascinating condition.

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Introduction and history of polycystic ovary syndrome

Cindy Farquhar

Since the classical observation of Stein and Leventhal in 1935 (Stein and Leventhal 1935), interest in polycystic ovaries (PCO) and its associated syndrome (PCOS) has evolved from a "gynaecological curiosity to a multisystem endocrinopathy" (Homburg 1996). It is probably the most common endocrine disorder in women, accounting for the majority of cases of hirsutism, of menstrual disturbance, and anovulatory infertility. It is also one of the most poorly defined endocrinological conditions with a complex pathophysiology that has produced considerable scientific debate. Evidence of the ongoing interest in this disorder is not difficult to find; an electronic search on MEDLINE from 1966 to 2005 using the search term "polycystic ovary syndrome" produces 5112 citations; 934 are review articles, and 200 are randomized controlled trials (Fig. 2.1), and the majority of publications occur after 1985.

Recognition

Although Stein and Leventhal were first in the modern medicine era to describe this condition, an earlier description dating back to 1721 reads: "Young married peasant women, moderately obese and infertile, with two larger than normal ovaries, bumpy, shiny and whitish, just like pigeon eggs." (Vallisneri 1721; translated from Italian.) There was further recognition in the nineteenth century when sclerocystic changes in the ovary were described (Chereau 1844), but it was not until Stein and Leventhal first presented their paper at the Central Association of Obstetricians and Gynecologists in 1935 that the syndrome was more comprehensively described. They reported on seven women who had amenorrhea, hirsutism, and enlarged ovaries, with multiple small cysts and thickened tunica (Fig. 2.2). While there had been reports of menometrorrhagia in women with microcystic disease

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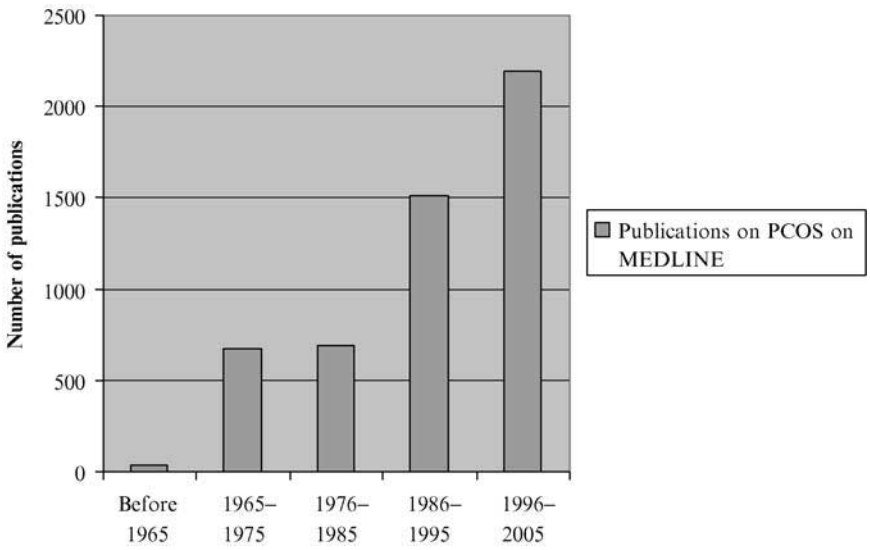

Fig. 2.1 The medical literature on polycystic ovarian syndrome.

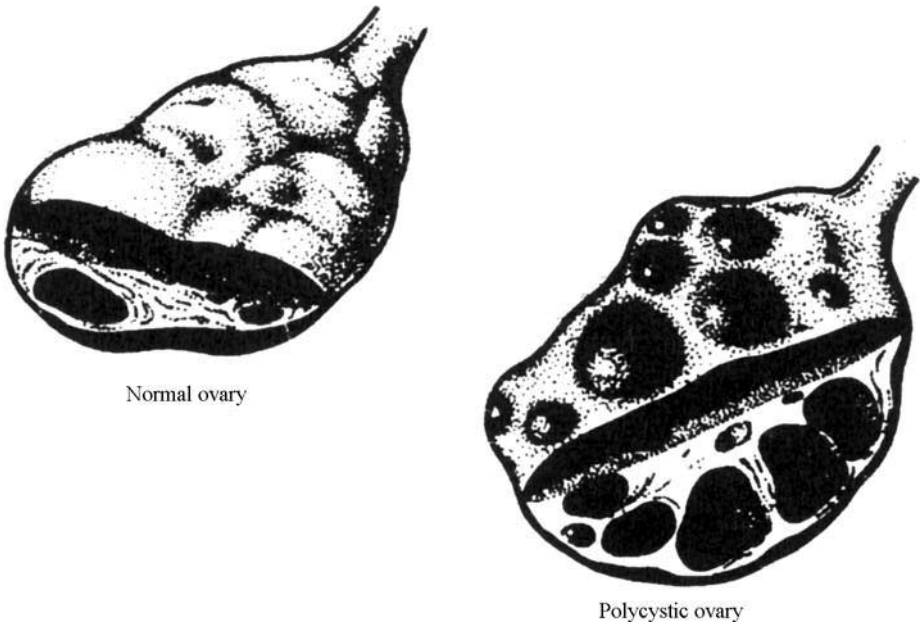

Fig. 2.2 The polycystic ovary compared to the normal ovary.

of the ovary, amenorrhea had not been recognized or reported in such cases until Stein and Leventhal's report. Stein and Leventhal had also performed ovarian wedge resection which resulted in a return of ovulatory cycles. Of the seven patients who underwent wedge biopsy, all returned to regular menstruation and two conceived. It is not clear whether other cases of the disorder were observed that did not fit this particular pattern. Stein subsequently reported on 75 women who underwent bilateral wedge resection reporting that nearly 90% began to have spontaneous menstrual cycles and 65% seeking fertility conceived (Stein *et al.* 1948).

The diagnosis of polycystic ovary syndrome

The advances that have taken place in the past century with regard to diagnosis of this condition have been considerable. Stein and Leventhal's method of diagnosis rested primarily on observing enlarged sclerocystic ovaries at either pneumoroentgenography or at laparotomy in women who were either anovulatory or hirsute or both (Stein and Leventhal 1935). Prior to this there was little choice but to perform repeated vaginal and rectal examinations which did not always reveal the presence of polycystic ovaries. At pneumoroentgenography air was admitted into the peritoneum by an abdominal incision and when the ovaries were three quarters as large as the uterine shadow on x-ray then polycystic ovaries were confirmed. Several examples of this technique are given in Stein and Leventhal's original publication. They often used Lipiodol instillations at the same time to outline the fallopian tubes. However this technique did not really gain popularity and eventually laparotomy and wedge biopsy became the mainstay of both diagnosis and treatment (Goldzieher and Green 1962).

With the development of radioimmunoassay techniques in the 1970s and the introduction of clomiphene citrate, laparotomy and biopsy were largely abandoned as a diagnostic method. In 1958 McArthur, Ingersoll, and Worcester first described elevated urinary levels of luteinizing hormone (LH) in women with bilateral PCO (McArthur *et al.* 1958). Throughout the 1970s and 1980s, elevated serum concentrations of LH and testosterone (T) were considered an essential prerequisite for diagnosis (Yen *et al.* 1970, Rebar *et al.* 1976). For example, Yen (1980) stated that "true PCOS" had typical abnormalities of gonadotropin and androgen secretion. There have been a number of interesting evolutions in the search for diagnostic criteria. Not only was an elevation in the LH level felt to be necessary but in time the LH:follicle stimulating hormone (FSH) ratio was also required to be elevated. Initially it was 2 : 1, then 3 : 1 and even 2.5 : 1 (Yen 1980, Lobo *et al.* 1981, Shoupe *et al.* 1983, Chang *et al.* 1983). Eventually the concept of a ratio was abandoned and the absolute values were relied on for diagnosis (Fox *et al.* 1991, Robinson *et al.* 1992). However, by only defining PCOS in the

presence of elevation of LH concentrations, then obviously all patients will have the condition (Waldstreicher *et al.* 1988, Fauser *et al.* 1991, 1992) and LH becomes a sine qua non for the diagnosis (Franks 1995, Homburg 1996). Elevations in androgens are similarly unhelpful in defining the syndrome as the levels are modestly and inconsistently elevated (Gadir *et al.* 1990). Other limitations of the biochemical diagnosis of PCOS included the variable and imprecise nature of the assays and the dynamic nature of hormonal steroidal release from the ovary (Fauser *et al.* 1991, 1992). LH is secreted in a pulsatile manner and the difference between the peak and nadir of each pulse can be substantial (Santon and Bardin 1973), and therefore measuring the hormone levels only once may be misleading (Franks 1989). Furthermore, there were still many women who were noted to have the clinical symptoms but whose LH and T levels did not fall within the diagnostic criteria (Adams *et al.* 1985). There was a need for a diagnostic test that could observe the ovary without damaging the surface of the ovary and potentially reducing fertility, but that did not just "take a snapshot" of the endocrine state of a patient as a single serum concentration of ovarian hormones does.

Fortunately, real-time ultrasound was developing into a useful diagnostic tool. Ultrasound examination of the ovary has many advantages over observation at laparoscopy or laparotomy; it is non-invasive, simple, and allows careful repeatable measurements, and it is possible to clearly see the follicular structures just below the surface of the ovary as well as demonstrate the dense and frequently increased stroma. Swanson *et al.* (1981) first reported on the ultrasound description of polycystic ovaries. The cysts ranged from 2 to 6 mm and were either peripherally distributed or throughout the parenchyma. Ultrasound descriptions have been shown to correlate with both laparoscopic findings and histological findings (Eden *et al.* 1989, Saxton *et al.* 1990). In the study by Eden *et al.* (1989), direct laparoscopic inspection of the ovaries was considered the reference test for the diagnosis of PCO, and the sensitivity (97%) and specificity (100%) with ultrasound was very good. In the study by Saxton *et al.* (1990) women who were undergoing open hysterectomy and bilateral oophorectomy had an ultrasound within 24 h of surgery where careful measurements and morphological descriptions were made. The measurements were repeated the following day in theater and again in the histopathology laboratory by independent observers with no prior knowledge of the ultrasound findings. There was 100% sensitivity and specificity in the 28 ovaries (of 14 women) that were studied.

The diagnostic criteria described by Adams *et al.* (1985) are frequently cited and although there are ongoing discussions about the number of follicles and the size of the ovary (Fox *et al.* 1991) there has been little change to these criteria (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004). The ultrasound diagnostic criteria rest on the observation of more than 12

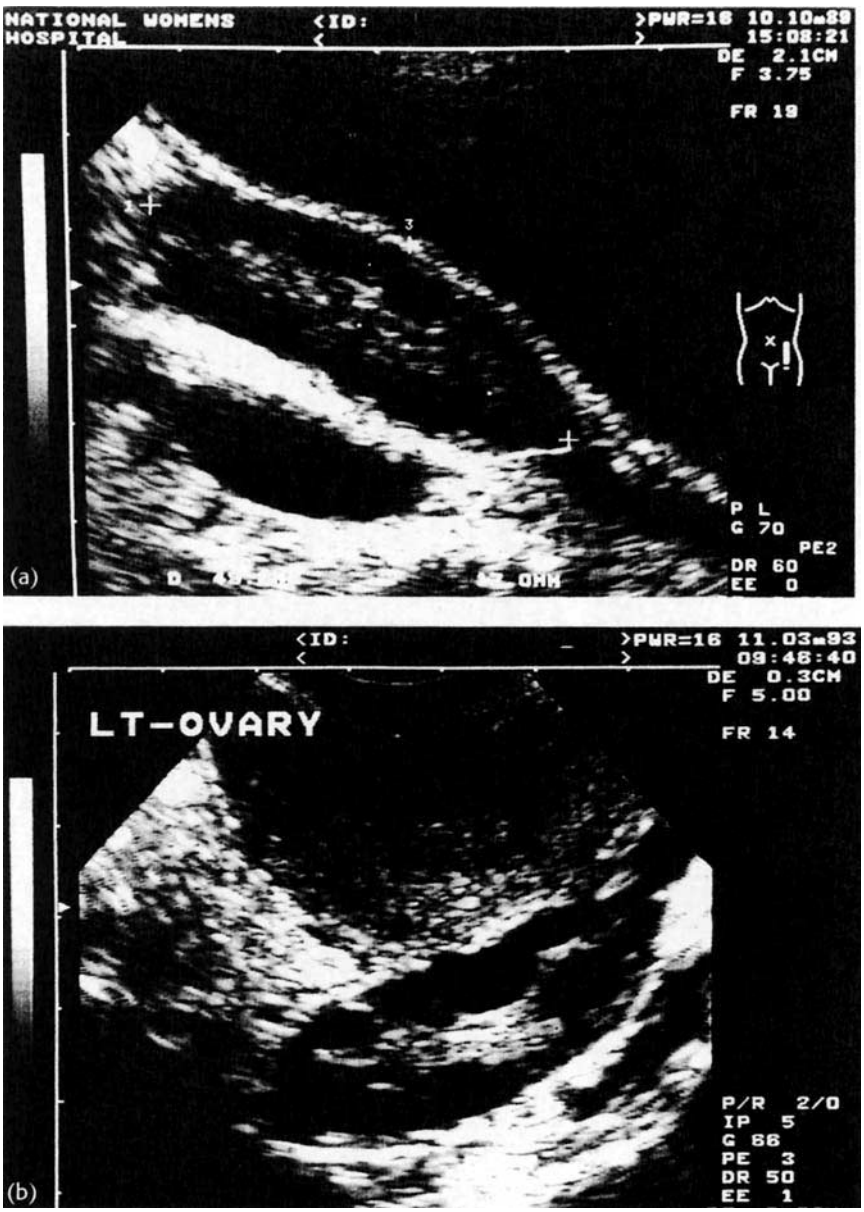

Fig. 2.3 Ultrasound view of polycystic ovary: (a) transabdominal, (b) transvaginal.

discrete follicles of <10 mm, usually peripherally arranged around an enlarged, hyperechogenic, central stroma at either transabdominal or transvaginal ultrasound (Fig. 2.3). The upper limit for ovarian volumes has decreased from >10 cm^2, to as low as >5.5 cm^2 (Orsini *et al.* 1985, El Tabbakh *et al.* 1986, Polson *et al.* 1988, Ardaens *et al.* 1991, Farquhar *et al.* 1994a, Dewailly 1997). A comparison of

transvaginal (TVS) ultrasound and transabdominal (TA) ultrasound by Fox *et al.* 1991 suggested that TA ultrasound failed to detect 30% of PCO compared to an almost 100% detection rate with TVS. However other studies reported similar detection rates for TA and TVS (Farquhar *et al.* 1994b) although TVS has many practical advantages. Recent advances in ultrasound include an objective and quantitative method of measuring the ovarian stroma using a computerized ultrasonic technique (Dewailly 1997) which has demonstrated that women with PCO have a greater stroma than women with normal ovaries. They conclude that an increased ovarian stroma is the most valuable diagnostic factor for PCOS. However, the absence of stroma does not exclude the diagnosis.

Ongoing problems with the diagnostic definitions of PCOS and the variation in diagnostic criteria across research groups and countries led to a new set of definitions. In 1990 the first international conference on polycystic ovary syndrome was held at the National Institutes of Health in the USA. The meeting did not lead to consensus although a questionnaire eventually led to diagnostic criteria being developed. In 2003, a further consensus meeting was held in Rotterdam and it was agreed that two of three of the following criteria were sufficient to diagnose the syndrome: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004).

Prevalence studies

When discussing the prevalence in the population it is important to be clear on the difference between the definitions that are commonly used. Polycystic ovaries should not be confused with the polycystic ovary syndrome. Polycystic ovaries may be diagnosed in the absence of any clinical syndrome (Polson *et al.* 1988). The polycystic ovary syndrome refers to the presence of polycystic ovaries in a woman with a particular cluster of symptoms which usually includes amenorrhea, oligoamenorrhea, hirsutism, anovulation, and other signs of androgen excess such as acne and crown pattern baldness (Franks 1995, Homburg 1996, Jacobs 1996). However, some women may be diagnosed with polycystic ovaries at the time of having an ultrasound examination for other reasons, who have none of these symptoms. Once ultrasound became commonly used in the 1980s it was recognized that polycystic ovaries were frequently reported in asymptomatic women and this was one of the reasons that prevalence studies were undertaken. The first prevalence study was reported in a group of patients from a population of volunteers who were predominantly hospital workers and medical students (Polson *et al.* 1988). This group reported the prevalence of polycystic ovaries of 23% but the large majority of these women had clinical manifestations of the

Table 2.1. Summary of prevalence studies of polycystic ovaries (PCO) and polycystic ovarian syndrome (PCOS)

Author(s)	Setting	*n*	PCO (%)	PCOS[a] (%)
Polson *et al.* 1988	Volunteers, London, UK	258	23	76
Clayton *et al.* 1992	GP practice, London, UK	190	22	30[b]
Farquhar *et al.* 1994a	Electoral roll, Auckland, New Zealand	183	21	59
Botsis 1995	Women volunteers undergoing PAP smears, Athens, Greece	1078	17%	>80
Cresswell *et al.* 1997	Hospital patients, UK	235	21%	>41
Michelmore *et al.* 1998	GP practice volunteers, Oxford, UK	224	34	65
Lowe *et al.* 2005	Partners of azoospermic men undergoing IVF, Melbourne, Australia	100	23	55

Notes:

[a] Defined as either hirsutism or irregular cycles or both amongst the women diagnosed with PCO on ultrasound.

[b] Irregular or very irregular cycles (does not include hirsutism).

syndrome, namely hirsutism or oligoamenorrhea. Several other prevalence studies have been undertaken (Clayton *et al.* 1992, Farquhar *et al.* 1994a, Michelmore *et al.* 1998, Lowe *et al.* 2005), and a prevalence rate of between 16% and 33% was reported. With the exception of Clayton *et al.*'s study, the other three prevalence studies found that women with PCO were also more likely to have symptoms suggestive of the PCOS, namely hirsutism or menstrual disturbances. The findings of these prevalence studies are summarized in Table 2.1.

Concept of a spectrum

The prevalence studies have led to a greater understanding of this condition. It is now widely recognized that there is a continuum or spectrum of clinical presentations (Balen *et al.* 1995). At one end of the spectrum are the women who ovulate and who have no dermatological manifestations such as acne or hirsutism. These women may have had an ultrasound scan for some other completely unrelated reason. At the other end of the spectrum there may be women with menstrual disturbances; oligoamenorrhea, increased hair growth, acne, crown pattern baldness, evidence of insulin resistance. The patients described by Stein and Leventhal in 1935 probably represented one extreme of the clinical spectrum. The presence of a woman in this continuum is likely to be predetermined by genetic factors but the position on the continuum is likely to be related to