Polycystic Ovary Syndrome

edited by

R. Jeffrey Chang

Jerrold J. Heindel

Andrea Dunaif

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R. Jeffrey Chang
University of California, San Diego
La Jolla, California

Jerrold J. Heindel
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

Andrea Dunaif
Northwestern University Medical School
Chicago, Illinois

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Preface

More than a decade has passed since the first NIH conference on polycystic ovary syndrome was held in Washington, D.C., to discuss and codify this perplexing reproductive endocrinopathy. As anticipated, a variety of opinions were elicited from the participants, which reflected the broad clinical perspective underlying this disorder. Importantly, the meeting established some common understanding of the similarities and differences of opinion among those in attendance and underscored the need for further investigation. Since that time, substantial progress has been made in both basic and clinical investigation, which has widened the spectrum of the syndrome while, at the same time, raising more questions. In addition, it appears that direct and indirect consequences of this disorder extend to all phases of a woman's life.

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrinopathy of women in their childbearing years and is responsible for an estimated 70% of cases of anovulatory infertility. In addition to the clinical features of hyperandrogenism and chronic anovulation, many women are insulin resistant and at increased risk for type 2 diabetes. They may also be at increased risk for cardiovascular disease. The relationship between these metabolic effects and the etiology of PCOS has not been defined. Familial clustering of cases suggests a genetic component, but a clear mode of inheritance has not been delineated. It is also probable that an environmental component to the initiation and/or progression of PCOS exists. With the encouragement and support of the National Institutes of Environmental Health and Safety, a meeting of a multidisciplinary group of scientists—cellular and molecular biologists, endocrinologists, toxicologists, epidemiologists, and clinicians—was convened at Research Triangle Park, North Carolina, to disseminate the most up-to-date research on the etiology, mechanisms, and treatment of PCOS. The primary goal of this gathering was to identify data gaps and needs, future research directions, and new approaches and technologies that might possibly lead to a better understanding of this syndrome, as well

as to improved intervention and prevention strategies. This book summarizes the proceedings of that meeting.

The book is divided into eight parts, which correspond to sessions of the meeting. Part I presents a historical perspective on PCOS. Part II, ''Epidemiology of Polycystic Ovary Syndrome,'' covers cardiovascular epidemiology, puberty and adolescent PCOS, and long-term health consequences. Part III, ''Reproductive Abnormalities,'' addresses ovarian structure/function correlates, ovarian imaging, altered steroidogenesis, adrenal abnormalities, and neuroendocrine dysfunction in PCOS. In Part IV, ''Animal Models of Polycystic Ovary Syndrome,'' studies from various animal models and their relevance to PCOS are presented. Part V, ''Metabolic Abnormalities and Their Relationship to Polycystic Ovary Syndrome,'' focuses on the relevance of obesity and the metabolic syndrome, abnormal insulin secretion and action, lipids and cardiovascular risk, and endothelial dysfunction in PCOS. Part VI, ''Genetics and Environmental Influences,'' discusses the potential genetic/environmental influences on PCOS (such as genetic approaches and gene susceptibility, obesity, and environmental toxins). Part VII, ''Intervention/Prevention Strategies,'' outlines therapeutic strategies, including manipulation of diet and lifestyle, metabolic phenotyping, treatment of hyperandrogenism, and treatment of insulin resistance. Finally, Part VIII summarizes the group discussion of diagnostic criteria.

Clearly, PCOS has become an important consideration for the health and well-being of women during all phases of life, and, as we advance our knowledge, the enormous complexity of this problem becomes increasingly apparent. Nevertheless, improved treatment alternatives continue to emerge with the hope of resolving and, for some, eliminating clinical symptomatology.

We are deeply appreciative of the generous educational grants from Organon, Ferring, Parke-Davis, and Bristol-Myers Squibb, without which the success of this conference would not have been possible.

R. Jeffrey Chang
Jerrold J. Heindel
Andrea Dunaif

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Contributors

David H. Abbott, Ph.D. Department of Obstetrics and Gynecology and Wisconsin Regional Primate Research Center, University of Wisconsin, Madison, Wisconsin

Yves Ardaens, M.D. Department of Radiology, Lille University Hospital, Lille, France

Silva A. Arslanian, M.D. Department of Pediatrics, University of Pittsburgh and Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania

Ricardo Azziz, M.D., M.P.H., M.B.A. Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, Alabama

Alain D. Baron Indiana University School of Medicine, Indianapolis, Indiana

John D. Brunzell, M.D. Department of Medicine, University of Washington, Seattle, Washington

Deborah J. Burks, Ph.D. Department of Anatomy, Universidad de Salamanca, Salamanca, Spain

R. Jeffrey Chang, M.D. Department of Reproductive Medicine, University of California, San Diego, La Jolla, California

Ricki J. Colman, Ph.D. Wisconsin Regional Primate Research Center, University of Wisconsin, Madison, Wisconsin

Michael J. Davies Reproductive Medicine Unit, Department of Obstetrics and Gynecology, The University of Adelaide, Woodville, South Australia, Australia

Didier Dewailly, M.D. Department of Reproductive Endocrinology, Lille University Hospital, Lille, France

Deborah A. Driscoll, M.D. Division of Reproductive Genetics, Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Daniel A. Dumesic, M.D. Department of Obstetrics and Gynecology, The Mayo Clinic, Rochester, Minnesota

Andrea Dunaif, M.D. Department of Medicine, Northwestern University Medical School, Chicago, Illinois

Christine A. Eagleson, M.D. Department of Internal Medicine, University of Virginia Health System, Charlottesville, Virginia

David A. Ehrmann, M.D. Department of Medicine, University of Chicago, Chicago, Illinois

Marinus J. C. Eijkemans, M.Sc. Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands

Joel R. Eisner Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Northwestern University Medical School, Chicago, Illinois

Gregory F. Erickson, Ph.D. Department of Reproductive Medicine, University of California, San Diego, La Jolla, California

Bart C. J. M. Fauser, M.D., Ph.D. Division of Reproductive Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

Stephen Franks, M.D. Department of Reproductive Science and Medicine, Imperial College Faculty of Medicine, Hammersmith Hospital, London, England

David Geller, M.D., Ph.D. Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, California

Neda Gharani Imperial College Faculty of Medicine, Hammersmith Hospital, London, England

Joseph W. Goldzieher, M.D. Metropolitan Professional Building, San Antonio, Texas

David S. Guzick, M.D., Ph.D. Department of Obstetrics and Gynecology, University of Rochester Medical Center, Rochester, New York

J. Dik F. Habbema, Ph.D. Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands

Claude L. Hughes, M.D., Ph.D. Department of Medical and Scientific Services, Quintiles, Inc., Research Triangle Park, North Carolina

Babek Imani, M.D. Department of Obstetrics and Gynecology, Erasmus University Medical Center, Rotterdam, The Netherlands

Joseph W. Kemnitz, Ph.D. Department of Physiology and Wisconsin Regional Primate Center, University of Wisconsin, Madison, Wisconsin

Richard S. Legro, M.D. Department of Obstetrics and Gynecology, The Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania

Christophe Lions, M.D. Department of Radiology, Lille University Hospital, Lille, France

Rogerio A. Lobo, M.D. Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, New York

John C. Marshall, M.D., Ph.D. Department of Internal Medicine, University of Virginia Health System, Charlottesville, Virginia

Ruchi Mather, M.D. Department of Internal Medicine, Cedars-Sinai Medical Center, Los Angeles, California

Mark McCarthy Imperial College Faculty of Medicine, Hammersmith Hospital, London, England

Christopher R. McCartney, M.D. Department of Internal Medicine, University of Virginia Health System, Charlottesville, Virginia

John H. Nilson, Ph.D. Department of Pharmacology, Case Western Reserve University School of Medicine, Cleveland, Ohio

Robert J. Norman, M.D. Reproductive Medicine Unit, Department of Obstetrics and Gynecology, The University of Adelaide, Woodville, South Australia, Australia

Gabe E. Owens Case Western Reserve University School of Medicine, Cleveland, Ohio

Giancarlo Paradisi Indiana University School of Medicine, Indianapolis, Indiana

Marguerite K. Shepard, M.D. Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, Indiana

Shunichi Shimasaki, Ph.D. Department of Reproductive Medicine, University of California, San Diego, La Jolla, California

Caren G. Solomon, M.D., M.P.H. Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Richard S. Spielman, Ph.D. Department of Genetics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Helmut O. Steinberg, M.D. Division of Endocrinology and Metabolism, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana

Jerome F. Strauss III, M.D., Ph.D. Center for Research on Reproduction and Women's Health, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Evelyn O. Talbott, Dr.Ph. Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania

Ann E. Taylor, M.D. Harvard Medical School, Boston, Massachusetts, and Pfizer Global Research and Development, Groton, Connecticut

Egbert R. te Velde, M.D., Ph.D. Department of Obstetrics and Gynecology, University Hospital, Utrecht, The Netherlands

Margrit Urbanek, Ph.D. Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Northwestern University Medical School, Chicago, Illinois

Morris F. White, Ph.D. Howard Hughes Medical Institute, Joslin Diabetes Center, Boston, Massachusetts

Robert A. Wild, M.D., M.P.H. Departments of Obstetrics and Gynecology, Cardiology, and Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

Selma Witchel, M.D. Department of Pediatrics, University of Pittsburgh and Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania

Xinqi Wu Division of Women's Health, Brigham and Women's Hospital, Boston, Massachusetts

Robert Yann, M.D. Department of Radiology, Lille University Hospital, Lille, France

1
Historical Perspectives

Joseph W. Goldzieher
San Antonio, Texas

We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.

—T. S. Eliot

I. INTRODUCTION

Polycystic ovary syndrome (PCOS) has special features. First, it is not an arena for simple linear thinking: A causes B, B causes C, and so on. PCOS is a complex web of interactions whose connections are still far from resolved and therefore present a perpetually fascinating intellectual challenge. Second, it is a field of inconsistent symptomatology and histopathology and of a variety of proposed endocrinopathic models and a testing ground where alternative theories compete. It has even been difficult to obtain consensus to define what we are talking about and how to name something we call, for the moment, polycystic ovary syndrome [1]. In this context one may recall the 1964 Supreme Court case of *Jacobellis v. State of Ohio*, where Justice Potter Stewart said, in reference to pornography, ''I can't define it, but I know it when I see it.''

Historical overviews of a subject are traditionally assigned to old geezers who—one hopes—are familiar with literature prior to that accessible on Pubmed on the Internet. I plead guilty to these specifications. My polycystic ovary (PCO) reprint file, starting with the earliest articles, is contained in more than 9 linear feet of letter-file boxes, which I will happily bequeath to anyone with the soul (and space) of a librarian.

II. PERCEPTIONS

The first description of enlarged, smooth polycystic ovaries is apparently that of Chereau [2] in 1844. This report was followed by other European observations in the second half of the 19th century, including the description of hyperthecosis in 1897 [3]. Many gynecologists recommended unilateral or bilateral ovariectomy or wedge resection (Gusserow, Martin, Wiedow, Zweifel, and others). Similar recommendations were made in the United States in 1872 by Battey and others, some of whom preferred the more conservative wedging procedures to oophorectomy [4]. The situation crystallized in 1935 with Stein and Leventhal's article [5], which associated a particular symptomatology with the ovarian changes and reported a highly successful outcome of their wedging procedure.

Naturally, gynecologists were delighted to have a readily identifiable syndrome that produced a candidate for remedial surgery which was effective and long-lasting [6]. Later, endocrinologists also became involved as their steroid methodology and biological insights, especially as related to hyperandrogenism, developed.

Alas, the simplicity was not to last, much to the annoyance of Irving Stein [7]. The ''syndrome'' dissolved: Polycystic ovaries were found associated with other ovarian pathologies, such as hilus cell tumors and hyperthecosis, and also with nonovarian hyperandrogenism of various types, such as adrenal hyperplasia and Cushing's syndrome. Even the histology [8] of PCO was found to be inconsistent [9–12]. On the other hand, typical polycystic ovaries were found to exist without any symptoms at all [9] and in fact were later shown to be present (by ultrasound) in a significant percentage of ''normal'' women (some of whom actu-

Table 1 1962 Review of Literature: Incidence of Signs and Symptoms in PCO

		Incidence (%)	
Observation	No. cases	Average	Range
Obesity	344	33	16–49
Hirsutism	457	56	17–83
Virilization	204	17	0–31
Amenorrhea	350	47	19–77
Irregular menses	289	21	0–19
Regular menses	253	16	7–28
Infertility	296	75	35–94
Corpus luteum	322	19	0–71
Biphasic BBT	77	13	14–40

Source: Ref. 8.

ally had subtle endocrine disorders [1]). The wide spectrum and variable frequency of symptoms associated with surgically proven polycystic ovaries destroyed hopes of establishing a consistent clinical picture (Table 1) as shown by a comprehensive review of the literature until 1962 [8]. When ultrasound examination became available, the situation expanded even more [13]. This technology at least made it possible to standardize what was to be called a polycystic ovary [14–16] and to exclude, for example, the multicystic ovaries sometimes found in children [17].

III. PREVALENCE

The data of Table 1 are seriously flawed by selection bias: They really summarize the clinical symptomatology which sufficed to justify surgical intervention in those years. Other statistical problems were emphasized by Donesky and Adashi [18]. Subsequently, laboratory data such as elevated luteinizing hormone (LH) levels or LH/follicle stimulating hormone (FSH) ratios as well as increased androgen production expanded the criteria, although Givens in 1976 [19] found a continuum of LH values in PCOS, and the same was found by many others for elevated androgens. By clinical and laboratory assessment in 369 consecutive women ages 18–45 seen for a routine physical, Knochenhauer et al. [20] identified 4.7% of Caucasians and 3.4% of African Americans as meeting their clinical criteria of PCOS.

The introduction of ultrasonography changed the perspective entirely. A number of large studies of normal women have yielded PCO prevalences ranging from 16 to 33% [21–24]. Prevalences associated with various symptoms have been described by Franks [25] and others: menstrual dysfunction, from 53 [22] to 94% [25]; hirsutism, from around 64% in many populations [25] to as little as 10% or less in Asians [26]; among those seeking simply electrolysis, over 12% [27]; acne, 37% [28]; hypothyroidism, 36% [22]; and type 2 diabetes, 82% [29]. Patients complaining primarily of infertility have such a variety of pathogenetic factors that a simple estimate of PCO prevalence is not really meaningful, but McGoogan's literature review of PCO yielded an overall incidence of 1.1% [30] of all sterility cases. Far from being the uncommon entity originally envisioned, conditions associated with polycystic ovaries turn out to be a wide-ranging, major area of concern in reproductive endocrinology and in general metabolism studies as well.

IV. THE EVOLUTION OF LABORATORY PARAMETERS

In the face of an inconstant clinical picture (and, eventually, with the wide variety of conditions sonographically associated with polycystic ovaries), it was reason-

able to seek greater diagnostic sensitivity and specificity as well as insight into the abnormal endocrinology by means of laboratory investigations. The very early steroid studies of simple hirsutism and other hyperandrogenic conditions indicated that elevated urinary 17-ketosteroids and, occasionally, glucocorticoids were associated with polycystic ovaries [31] and that many, but not all, changes in these parameters were normalized by wedge resection [8]. They also indicated a likelihood that adrenal malfunction was often involved as well, and laboratory studies of the effect of adrenal versus ovarian stimulation or suppression [32,33] attempted to distinguish the source of hyperandrogenism, which turned out to be of combined origin in about half the cases with the rest evenly divided between just ovarian or just adrenal sources. Rosenfield et al. [34] believe combined origin occurs in only one-third of cases.

Once again, however, the problem proved not to be simple. While some diagnostic reliance was placed on elevated LH levels or increased LH/FSH ratios, later studies such as those of Robinson et al. [35] and Eden [36] found these parameters to be present in less than 50% of cases (as high as 70% for Obhrai et al. [37]), whereas Dunaif et al. [38] found ratios as low as 0.3. Adams et al. [39], Robinson et al. [35], Fox et al. [40], and others found plasma testosterone (T) and/or androstenedione elevation in up to 78% of PCO patients; Carmina et al. [41] found elevated DHEAS in 70% and 11β-hydroxyandrostenedione (11-OHA) in 53%. On the other hand, Clayton et al. [23] found the median values of testosterone and androstenedione to be normal in their PCO patients, and Rodin [42] found free testosterone to be no better an indicator than total T.

11β-Hydroxyandrostenedione is known to be an important secretory product of the adrenal, produced either by 11-hydroxylation of androstenedione or by 17,20 desmolase action on the C_{21} substrate [43]; however, some is produced by peripheral enzymatic cleavage of cortisol [44].

In the early 1970s we received an antibody steroid specific for 11-OHA [45] from P. N. Rao of Len Axelrod's group at our Institution which promised to be a selective indicator of adrenal androgen synthesis. If it could be shown to move in parallel with androstenedione in ovariectomized women, we would have an excellent, specific way to distinguish adrenal from ovarian androgen (particularly androstenedione) production. (It would not necessarily parallel testosterone production.) We undertook an extensive series of clinical studies, at the end of which we started to exchange plasma samples with Jürgen Hammerstein of Berlin, who had an 11-OHA antibody of his own. Highly discordant results were obtained and ultimately they were traced to an imperfection in our antibody, which cross-reacted unpredictably with some apparently nonsteroid substance in various plasmas. This effectively destroyed any interpretation of our results—a catastrophic and depressing end to several years' work. A decade later, Hammerstein and his colleagues demonstrated ovarian secretion of 11-OHA by direct

vein catheterization [46] and after another decade others also took up the exploration of plasma 11-OHA levels and cell biosynthesis [41]. Owen et al. [47] confirmed the elevated plasma 11-OHA levels in PCO patients and showed, in incubations of granulosa cells, that 11-hydroxylase activity was absent and inferred that the biosynthesized ovarian 11-OHA was produced by cleavage of cortisol (present in high concentrations in surgically stressed patients) rather than by 11-hydroxylation of androstenedione. However, ovarian 17,20-desmolase activity on substrate cortisol was not demonstrated either. In any event, the hope that 11-OHA might be a specific indicator of adrenal androgenic activity was not realized until 1992 [48].

Very recently, Turhan et al. [50] undertook a logistic regression analysis of the diagnostic sensitivity and reliability of various laboratory parameters and found that free T was useful and an LH or LH/FSH ratio of 2.5 or even 3 was accurate in only 63%, but that the combination of this ratio with plasma insulin levels had the best predictive value. There is at the present time no consensus as to what set of laboratory parameters is the most useful and cost-effective in the diagnosis of the polycystic ovary syndrome [22].

A. Steroidogenesis

Early on, urinary steroid excretion and, subsequently, steroid levels in blood indicated a dual source of abnormalities in many cases of PCOS. In particular, both ovary and adrenal were eventually shown by direct venous catheterization to secrete an excess of androgens [46,50]. Studies of steroidal content of ovarian cyst fluid and in vitro incubations of polycystic ovary tissue minces in the 1960s [51,52] demonstrated (1) aromatase deficiency (which was shown much later to be a secondary phenomenon [53–55]) and (2) excessive production of androstenedione as well as other androgens [34]. Defects in 17-hydroxylation and 3β-ol dehydrogenase activity [56] were subsequently shown to occur in both ovaries and adrenals; adrenal 21-hydroxylase deficiency has also been shown in PCO patients [22] as well as 11β-hydroxylase deficiency in idiopathic hirsutism and PCO [22,57] and also increased 5α-reductase in PCO follicles [58]. More recent studies of tissue and cell steroidogenesis and its deficiencies are presented elsewhere in this book.

B. Chronobiology

Clinical observations have long suggested a hereditary factor (also observed in patients' male kin and in hereditary baldness), suggesting a modified dominant form of inheritance in polycystic ovary syndrome [59,60].

However, another, nongenetic early-onset factor has been revealed by a

series of studies of the endocrinology of puberty and adolescence. The group of Italian investigators studying these phenomena [61] and their relation to PCO have shown that the exaggerated 24-h periodicity of LH secretion that is typical of puberty disappears normally with time, but persists in anovulatory adolescents [62]. Further, children with premature pubarche show exaggerated stages of ovarian androgen synthesis [62], and functional ovarian hyperandrogenism is also seen in adolescents [62,63]. Both FSH-secretion abnormalities and adrenal hyperresponsiveness have been demonstrated in this age group [63]. These similarities appear to provide a bridge to the older age group which is most often surveyed for polycystic ovaries [64].

C. Carbohydrate Metabolism

The ''Achard-Thiers'' syndrome (''diabète des femmes a barbe'') of adrenal hyperandrogenism and diabetes was actually described before the 1921 report of these authors [65]; sclerotic ovaries were noted. However, it was not until 1976, with description of the HAIR-AN syndrome [66] by Kahn et al. and the reports of Burghen et al. [67] in 1980, that the association of PCOS, obesity, and carbohydrate metabolism abnormalities was given serious attention. The increasing insulin levels and IGF-1 activity present during normal puberty have been considered to be inducing factors in the development of PCOS in susceptible (i.e., obese) individuals [68,69]. A decrease in insulin sensitivity of 25 to 37% in lean subjects with PCOS and 20–30% in obese patients has since been reported [70] and confirmed. Postbinding impairment of insulin-receptor-mediated signal transduction resulting in a marked decrease in insulin sensitivity may be a unique feature of PCOS [71]. This entire subject, particularly the complex relationship of insulin resistance, hyperandrogenism, and obesity, has become a major area of interest and research related to PCO in the past 2 decades and is reviewed in other chapters in this book.

V. PATHOGENESIS

I have labored long and manfully to historicize and give proper attribution and priority to the multitude of hypotheses which have been generated to explain the pathogenesis and mechanisms associated with morphological polycystic ovaries and polycystic ovary syndromes. I was taught long ago that ''every original idea has a pedigree.'' My efforts therefore might incur the risk of arousing territorial instincts in friends and colleagues, a prospect I would rather avoid; I will leave enumeration and summarization to historians with more courage than I have [59].

VI. THERAPEUTIC MODALITIES

The success of wedge resection and its immediate endocrine consequences (Table 2) [73] suggested that the effect was apparently due to reduction in functional ovarian mass, and this is in keeping with the benefit of simple unilateral oophorectomy [25,74]. Greenblatt demonstrated decades ago that this unilateral operation worked and that the thickened capsule of the remaining polycystic ovary did not interfere mechanically with ovulation, so it would not be expected to counteract ovulation induction and, hence, fertility. However, popularity of the wedging procedure was greatly lessened by reports of postoperative adhesion formation

Table 2 Results of Laparoscopic Surgery of Polycystic Ovaries

1st Author	Year	No. patients	Procedure	Menstr.	% Ovul./Preg.
Palmer	1967	17	Unipolar EC	60	20
Neuwirth	1972	1	Unipolar EC	100	100
Campo	1983	45	Unipolar EC	45	41
		12	Multiple biopsy	45	42
Gjonnaess	1984	62	Unipolar EC	92	69
Katz	1984	149	Sharp	96	75
Aakvaag	1985	58	Unipolar	72	N/A
Greenblatt	1987	6	Unipolar	83	67
Van der Weiden	1987	11	Unipolar	82	45
Sumioki	1988	7	Punch biopsy	86	57
Daniell	1989	85	CO_2 KTP laser	70	56
Huber	1989	8	ND:YAG laser	62	0
Kojima	1989	12	ND:YAG laser	83	58
Armar	1990	21	Unipolar EC	81	52
Gadir	1990	29	Unipolar EC	71	34
Sakata	1990	9	Unipolar EC	89	33
Tasaka	1990	11	Unipolar EC	91	36
Keckstein	1990	19	CO_2 laser	79	44
		11	ND:YAG laser	—	27
Gurgan	1991	7	Unipolar EC	71	57
		10	ND:YAG laser	70	40
Rosmanith	1991	11	ND:YAG	73	36
Weise	1991	39	Unipolar EC	—	59
Gurgan	1992	40	ND:YAG laser	—	51
Naether	1994	206	Unipolar EC	—	70
Heylen	1994	44	Argon laser	79	73
				Overall:	54

which interfered with later fertility [75–77]. The conservatism of some gynecologists is seen in that a discussion of wedge resection did not even appear in TeLinde's textbook until the 1953 edition [78]. This turned out to be somewhat of an overreaction, as shown by a 1992 review of women who had had wedge resections in the period 1956–1965 [79]. Preoperatively, 81% of patients were oligomenorrheic; postoperatively this decreased to 61% and, in the latest decade of follow-up, to 28%. Long-term follow-up, however, also highlighted an increasing incidence of hypertension and diabetes.

Another factor in the decreased use of wedge resection was the advent of antiestrogenic compounds such as MER-25, TACE, and clomiphene, the latter a highly effective ovulation-inducing drug. In clomiphene-resistant cases the addition of very small doses of a corticosteroid such as prednisone or dexamethasone was found to improve results. Wedge resection was now reserved for clomiphene-resistant cases; another recourse was to administer gonadotropic preparations (which improved progressively) [80] and optimize regimens for their use in ovulation induction, including the use of growth hormone [81], taking into account the marked hypersensitivity of the polycystic ovary to such stimulatory procedures. Clomiphene had increased the incidence of twinning somewhat, but gonadotropin therapy presented a much higher risk of multiple pregnancy and hyperstimulation, occasionally with serious consequences. Efforts to avoid this problem included prior ovarian suppression with oral contraceptives or GnRH agonists or antagonists [82–85].

What goes around comes around: The use of the laparoscope and electrocautery [86] revived interest in ovarian surgery, especially after 1984, when Gjonnaess [87,88] reported ovulation in up to 96% and pregnancy in nearly 80% of patients treated by this procedure. These results were confirmed by others [see 89,90]. The correction of menstrual irregularities persisted for long periods of time [88], but signs of the prior endocrine malfunction could still be detected [89]. Pregnancy occurrence tended to level off about 3 years postop [89,90]. The overall average pregnancy rate was calculated as about 56% (range 20 to 87.5%) by Donesky and Adashi [18].

Other investigators used multiple biopsy, capsule resection, or various types of lasers with excellent results [91,92]. Eventually, the problem of adhesion formation was raised again [93,94], but appeared to be less significant than with the previously used wedging procedure. Moreover, Naether and Fischer [93] reported that abdominal lavage and artificial ascites reduced the adhesion problem even further.

Thus, the hyperandrogenism and the ovarian function problems can now be addressed with a wide variety of therapeutic options, evidently with a high degree of success. This is of course the paramount concern for the clinician. Appropriate monitoring can avert or detect rare events such as endometrial malignancy or androgenic tumors of various kinds. In addition, management must now take into consideration the cardiovascular and carbohydrate-metabolism compli-

cations that have come to the fore in recent years [95]. Clearly, the care of a patient with PCOS, however defined, is a sophisticated affair.

I saw my first case of Stein–Leventhal syndrome during my gynecological endocrinology training under Ed Hamblen at Duke University Hospital in Durham, North Carolina, in the summer of 1946. I was fascinated. Today, over 50 years later, the clinical and intellectual challenges of polycystic ovary problems seem just as fascinating. May they be thus for you for at least another 50 years.

REFERENCES

1. Lobo RA. A disorder without identity: ''HCA,'' ''PCO,'' ''PCOS,'' ''PCOS,'' ''SLS.'' What are we to call it? Fertil Steril 1995; 63:1158–1160.
2. Chereau A. Mem. Pour Servir a l'Etude des Malades des Ovaires. Paris: Fortin, Masson & Cie, 1844.
3. Bulius G, Kretschmar C. Angiodystrophia Ovarii. Stuttgart: F. Enke, 1897:8.
4. Futterweit W. Polycystic Ovarian Disease. New York: Springer-Verlag, 1984: xi.
5. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol 1935; 29:181–191.
6. Stein IF. Duration of infertility following ovarian wedge resection. West J Surg 1964; 72:237–241.
7. Stein IF. Wedge resection of the ovaries: the Stein Leventhal syndrome. In: Greenblatt RB, ed. Ovulation: Stimulation, Suppression, Detection. Philadelphia: Lippincott, 1966:150–157.
8. Goldzieher JW, Green JA. The polycystic ovary I. Clinical and histological features. J Clin Endocrinol Metab 1961; 22:325–338.
9. Roberts DW, Haines M. Is there a Stein–Leventhal syndrome? Br Med J 1960; 5187: 1709–1711.
10. Goldzieher JW, Elkind-Hirsch K. Polycystic ovarian disease. Trends Gynaecol Obstet 1985; 1:7–80.
11. Smith KD, Steinberger E, Perloff WH. Polycystic ovarian disease (PCOS): a report of 301 patients. Am J Obstet Gynecol 1965; 93:994–1001.
12. Hughesdon PE. Morphology and morphogenesis of the Stein–Leventhal ovary and of so-called ''hyperthecosis.'' Obstet Gynecol Surv 1982; 37:59–77.
13. Conway GS, Honour JW, Jacbos HS. Heterogeneity of the polycystic ovary syndrome: clinical, endocrine and ultrasound features in 556 patients. Clin Endocrinol 1989; 30:459–470.
14. Adams J, Franks S, Polson DW et al. Multifollicular ovaries: clinical and endocrine features and response to pulsatile gonadotrophin releasing hormone. Lancet 1985; 2:1375–1378.
15. Pache TD, Wladimiroff JW, Hop WCJ et al. How to discriminate between normal and polycystic ovaries: transvaginal US study. Radiology 1992; 183:421–423.
16. Dewailly D, Robert Y, Helin I et al. Ovarian stromal hypertrophy in hyperandrogenic women. Clin Endocrinol 1994; 41:557–562.
17. Bridges NA, Cooke A, Healy MJ et al. Standards for ovarian volume in childhood and puberty. Fertil Steril 1993; 60:456–460.

18. Donesky BW, Adashi EY. Surgically indiced ovulation in the polycystic ovary syndrome: wedge resection revisited in the age of laparoscopy. Fertil Steril 1995; 63: 439–463.
19. Givens JR, Andersen RN, Umstot ES et al. Clinical findings and hormonal responses in patients with polycystic ovary syndrome with normal versus elevated LH levels. Obstet Gynecol 1976; 47:388–394.
20. Knochenhauer ES, Key TJ, Kahsar-Miller M et al. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 1998; 83:3078–3082.
21. Polson DW, Adams J, Wadsworth J, Franks S. Polycystic ovaries—a common finding in normal women. Lancet 1988; 1:870–872.
22. Abdel Gadir A, Khatim MS, Mowafi RS et al. Implications of ultrasonically diagnosed polycystic ovaries. I. Correlations with basal hormonal profiles. Hum Reprod 1992; 7:453–457.
23. Clayton RM, Ogden V, Hodgkinson J et al. How common are polycystic ovaries in normal women and what is their significance for the fertility of the population? Clin Endocrinol 1992; 37:127–134.
24. Michelmore KF, Balen AH, Dunger DB et al. Polycystic ovaries and associated clinical and biochemical features in young women. Clin Endocrinol 1999; 51:779–786.
25. Franks S. Polycystic ovary syndrome: a changing perspective. Clin Endocrinol 1989; 31:87–120.
26. Carmina E, Koyama T, Chang I et al. Am J Obstet Gynecol 1992; 167:1807–1812.
27. Farah L, Lazenby AJ, Boots RL et al. Prevalence of polycystic ovary syndrome in women seeking treatment from community electrologists. Alabama Professional Electrology Association Study Group. J Reprod Med 1999; 44:870–874.
28. Timpatanapong P, Rojanasakul A. Hormonal profiles and prevalence of polycystic ovary syndrome in women with acne. J Dermatol 1997; 24:223–229.
29. Conn JJ, Jacobs HS, Conway GS. The prevalence of polycystic ovaries in women with type 2 diabetes mellitus. Clin Endocrinol 2000; 52:81–86.
30. McGoogan LS. Sterility and ovarian pathology. Obstet Gynecol 1954; 3:254–262.
31. Axelrod LR, Goldzieher JW. The polycystic ovary. II. Urinary steroid excretion. J Clin Endocrinol Metab 1962; 22:425–430.
32. Givens JR, Andersen RN, Ragland JR et al. Adrenal function in hirsutism. I. Diurnal change and response of plasma androstenedione, testosterone, 17-hydroxyprogesterone, cortisol, FSH and LH to dexamethasone and 1/2 unit ACTH. J Clin Endocrinol Metab 1975; 40:988.
33. Givens JR, Andersen RN, Wiser WL, Fish SA. Dynamics of suppression and recovery of plasma FSH, LH, androstenedione and testosterone in polycystic ovarian disease using an oral contraceptive. J Clin Endocrinol Metab 1974; 38:727.
34. Rosenfield RL, Ehrmann DA, Barnes RB et al. Ovarian steroidogenic abnormalities in polycystic ovary syndrome: evidence for abnormal coordinate regulation of androgen and estrogen secretion. In: Dunaif A et al., eds. Polycystic Ovary Syndrome. Cambridge, MA: Blackwell Scientific, 1992:83–110.
35. Robinson S, Rodin DA, Deacon A et al. Which hormone tests for the diagnosis of polycystic ovary syndrome? Br J Obstet Gynaecol 1992; 99:232–238.

36. Eden JA. Which is the best test to detect the polycystic ovary? Aust NZ J Obstet Gynaecol 1988; 28:221–224.
37. Obhrai M, Lynch SS, Holden G et al. Hormonal studies on women with polycystic ovaries diagnosed by ultrasound. Clin Endocrinol 1990; 32:467–474.
38. Dunaif A, Mandeli J, Fluhr H et al. The impact of obesity and chronic hyperinsulinemia on gonadotropin release and gondal steroid secretion in the polycystic ovary syndrome. J Clin Endocrinol Metab 1988; 66:131–139.
39. Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. Br Med J 1986; 293:335–339.
40. Fox R, Corrigan E, Thomas PA, Hull MRG. The diagnosis of polycystic ovaries in women with oligo-amenorrhoea: predictive power of endocrine tests. Clin Endocrinol 1991; 34:127–131.
41. Carmina E, Gonzalez F, Chang L, Lobo RA. Reassessment of adrenal androgen secretion in women with polycystic ovary syndrome. Obstet Gynecol 1995; 85:971–976.
42. Rodin DA, Thakkar H, Taylor NF et al. Urinary steroid excretion in women with polycystic ovary syndrome (abstr). J Endocrinol 1988; 117(suppl 223).
43. Axelrod LR, Kraemer DC, Burdett J, Goldzieher JW. Biosynthesis of 11-beta-hydroxy androstenedione by human and baboon adrenals. Acta Endocrinol 1973; 72:545–550.
44. Goldzieher JW, Beering SC. Metabolism of 11-beta-hydroxyandrostenedione, adrenosterone and hydrocortisone to urinary 11-oxy 17-ketosteroids. J Clin Endocrinol Metab 1969; 29:171–178.
45. Rao PN, Moore PH, Goldzieher JW. Specific antisera suitable for solid-phase radioimmunoassay of 11-beta-hydroxyandrost-4-ene 3,17-dione. Steroids 1974; 24:793–801.
46. Moltz L, Schwartz U, Sorensen R et al. Ovarian and adrenal vein steroids in patients with nonneoplastic hyperandrogenism. Selective catheterization findings. Fertil Steril 1984; 42:69–75.
47. Owen EJ, Jacobs HS, Holownia P et al. 11β-hydroxy androstenedione in plasma, follicular fluid, and granulosa cells of women with normal and polycystic ovaries. Fertil Steril 1992; 58:713–718.
48. Carmina E, Miles RA, Stanczyk F et al. The ratio of androstenedione: 11βOH androstenedione is an important marker of adrenal androgen excess in women. Fertil Steril 1992; 58:148–152.
49. Kirschner MA, Jacobs JB. Combined ovarian and adrenal catheterisation to determine the site of androgen overproduction in hirsute women. J Clin Endocrinol Metab 1971; 33:199–209.
50. Turhan NO, Toppare MF, Seckin NC et al. The predictive power of endocrine tests for the diagnosis of polycystic ovaries in women with oligoamenorrhea. Gyn Obstet Invest 1999; 48:183–186.
51. Axelrod LR, Goldzieher JW. Enzymic inadequacies of human polycystic ovaries. Arch Biochem Biophys 1961; 95:547–548.
52. Axelrod LR, Goldzieher JW. The polycystic ovary. III. Steroid biosynthesis in normal and polycystic ovarian tissue. J Clin Endocrinol Metab 1962; 22:431–446.
53. Erickson GF, Hsueh AJW, Quigley ME et al. Functional studies of aromatase activ-

ity in human granulosa cells from normal and polycystic ovaries. J Clin Endocrinol Metab 1979; 49:514–519.
54. Barnes RB. Polycystic ovarian syndrome and ovarian steroidogenesis. Semin Reprod Endocrinol 1991; 9:360–366.
55. Erickson GF, Garzo VG, Magoffin DA. Insulin-like growth factor I regulates aromatase activity in human granulosa and granulosa luteal cells. J Clin Endocrinol Metab 1989; 69:716–724.
56. Axelrod LR, Goldzieher JW, Ross SD. Concurrent 3β-hydroxysteroid dehydrogenase deficiency in adrenal and sclerocystic ovary. Acta Endocrinol 1965; 48:392–411.
57. Guthrie GP, Wilson EA, Quillen D, Jawad MJ. Adrenal androgen excess and defective 11-beta-hydroxylation in women with idiopathic hirsutism. Arch Int Med 1982; 142:729–733.
58. Jakimiuk AJ, Weitsman SR, Magoffin DA. 5α-reductase activity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1999; 84:2414–2418.
59. Futterweit W. Pathophysiology of polycystic ovary syndrome. In: Redmond GP, ed. Androgenic Disorders. New York: Raven Press, 1995:27–166.
60. Hague WM, Adams J, Reeders ST et al. Familial polycystic ovaries: A genetic disease? Clin Endocrinol 1988; 29:593–605.
61. Ibanez L, Street ME, Potau N et al. Girls diagnosed with premature pubarche show an exaggerated ovarian androgen synthesis from the early stages of puberty: evidence from gonadotropin-releasing hormone agonist testing. Fertil Steril 1997; 67: 849–855.
62. Porcu E, Fabbri R, Venturoli S et al. Chronobiologic evolution of luteinizing hormone secretion in adolescence: developmental patterns and speculations on the onset of the polycystic ovary syndrome. Fertil Steril 1997; 67:842–848.
63. Ibanez L, Potau N, Zampolli M et al. Source localization of androgen excess in adolescent girls. J Clin Endocrinol Metab 1994; 79:1778–1784.
64. Venturoli S, Porcu E, Fabbri R et al. Menstrual irregularities in adolescents: hormonal pattern and ovarian morphology. Horm Res 1986; 24:269–279.
65. Duncan GG, Fetter F. Suprarenal tumor-hirsutism-diabetes. Med Clin N Am 1934; 18:261–264.
66. Kahn CR, Flier JS, Bar RS et al. The syndromes of insulin resistance and acanthosis nigricans. Insulin receptor disorders in man. N Engl J Med 1976; 294:739–745.
67. Burghen GA, Givens JR, Kitabchi AE. Correlation of hyperandrogenism with hyperinsulinism in polycystic ovary syndrome. J Clin Endocrinol Metab 1980; 50:113–116.
68. Nobels F, Dewailly R. Puberty and polycystic ovary syndrome: the insulin/insulin-like growth factor I hypothesis. Fertil Steril 1992; 58:655–666.
69. Apter D, Butzow T, Laughlin GA, Yen SSC. Metabolic features of polycystic ovary syndrome are found in adolescent girls with hyperandrogenism. J Clin Endocrinol Metab 1995; 80:2966–2973.
70. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 1989; 38: 1165–1174.

71. Ciaraldi TP, El-Roaey A, Madar Z et al. Cellular mechanisms of insulin resistance in polycystic ovary syndrome. J Clin Endocrinol Metab 1992; 75:577–583.
72. Crowley WF Jr, Hall JE et al. An overview of the diagnostic considerations in polycystic ovary syndrome. In: Crowley WF Jr, Hall JE, et al. eds. Intraovarian Regulators and Polycystic Ovarian Syndrome: Recent Progress on Clinical and Therapeutic Aspects. New York: New York Academy of Science, 1993; 687:235–241.
73. Katz M, Carr PJ, Cohen BM, Millar RP. Hormonal effects of wedge resection of polycystic ovaries. Obstet Gynecol 1978; 51:437–444.
74. Greenblatt RB. The Hirsute Female. Springfield, IL: Charles C Thomas, 1963:159–160.
75. Kistner RW. Peritubal and periovarian adhesions subsequent to wedge resection of the ovaries. Fertil Steril 1969; 20:35–42.
76. Weinstein D, Polishuk WZ. The role of wedge resection of the ovary as a cause for mechanical sterility. Surg Gynecol Obstet 1975; 141:417–418.
77. Buttram VC Jr, Vaquero C. Post-ovarian wedge resection adhesive disease. Fertil Steril 1975; 26:874–876.
78. TeLinde RW. Operative Gynecology. 2d ed. Philadelphia: Lippincott, 1953.
79. Dahlgren E, Janson PO, Johansson S et al. Women with polycystic ovarian syndrome wedge resected in 1956–1965: a long-term followup focusing on natural history and circulating hormones. Fertil Steril 1992; 57:505–513.
80. Wang CF, Gemzell C. The use of human gonadotropins for the induction of ovulation in women with polycystic ovary syndrome. Fertil Steril 1980; 33:479–486.
81. Homburg A, Eshel A et al. Growth hormone facilitates ovulation induction by gonadotropins. Clin Endocrinol (Oxf) 1988; 29:113–117.
82. Gadir AA, Alnaser HMI, Mowafi RS, Shaw RW. The response of patients with polycystic ovary syndrome to human menopausal gonadotropin therapy after ovarian electrocautery or a luteinizing hormone-releasing hormone agonist. Fertil Steril 1992; 57:309–313.
83. Farhi J, Soule S, Jacobs HS. Effect of laparoscopic ovarian electrocautery on ovarian response and outcome of treatment with gonadotropins in clomiphene citrate-resistant patients with polycystic ovary syndrome. Fertil Steril 1995; 64:930–935.
84. Taskin O, Yalcinoglu AI, Kafkasli A. Comparison of the effects of ovarian cauterization and gonadotropin releasing hormone agonist and oral contraceptive therapy combination on endocrine changes in women with polycystic ovary disease. Fertil Steril 1996; 65:1115–1118.
85. Rimington MR, Walker SM, Shaw RW. The use of laparoscopic ovarian electrocautery in preventing cancellation of in vitro fertilization treatment cycles due to risk of ovarian hyperstimulation syndrome in women with polycystic ovaries. Hum Reprod 1997; 12:1443–1447.
86. Palmer R, deBrux J. Histologic, biochemical and therapeutic results obtained in women whose ovaries were diagnostic of Stein–Leventhal at celioscopy. Bull Fed Soc Gynecol Obstet Lang Fr 1967; 19:405–412.
87. Gjonnaess H. Polycystic ovarian syndrome treated by ovarian electrocautry through the laparoscope. Fertil Steril 1984; 41:20–25.
88. Gjonnaess H. Late endocrine effects of ovarian electrocautery in women with polycystic ovarian syndrome. Fertil Steril 1998; 69:697–701.

89. Naether OGJ, Baukloh V, Fischer R, Kowalczyk T. Long-term followup in 206 infertility patients with polycystic ovarian syndrome after laparoscopic electrocautery of the ovarian surface. Hum Reprod 1994; 9:2342–2349.
90. Naether OGJ, Geiger-Kotzler L, Fischer R et al. Laparoscopic electrocoagulation of the ovarian surface in infertile patients with polycystic ovary syndrome. Fertil Steril 1993; 60:88–94.
91. Gurgan T, Yarali H, Urman B. Laparoscopic treatment of polycystic ovary syndrome. Hum Reprod 1994: 9:573–577.
92. Heylen SM, Puttemans PJ, Brosens IA. Polycystic ovarian disease treated by laparoscopic argon laser capsule drilling: comparison of vaporization versus perforation technique. Hum Reprod 1994; 9:1038–1042.
93. Naether OGJ, Fischer R. Adhesion formation after laparoscopic electrocoagulation of the ovarian surface in polycystic ovary patients. Fertil Steril 1993; 60:95–98.
94. Greenblatt EM, Casper RF. Adhesion formation after laparoscopic ovarian cautery for polycystic ovarian syndrome: lack of correlation with pregnancy rate. Fertil Steril 1993; 60:766–770.
95. Wild RA, Painter PC, Coulsen RB et al. Lipoprotein lipid concentrations and cardiovascular risk in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1985; 61:946–951.

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Are Women with Polycystic Ovary Syndrome at Risk for Cardiovascular Disease?

David S. Guzick
University of Rochester Medical Center
Rochester, New York

Evelyn O. Talbott
University of Pittsburgh
Pittsburgh, Pennsylvania

I. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder of chronic anovulation and androgen excess that occurs with a prevalence in the female population rate of approximately 4–6% [1]. Women with PCOS typically present for health care because of immediate concerns about irregular bleeding, infertility, and/or symptoms of androgen excess. The clinical response—generally oral contraceptives for oligomenorrhea, ovulation induction for infertility, and hirsutism treatment—provides short-term relief and ignores the underlying pathophysiology. In recent years, however, a longer term view has received increasing attention because of accumulating evidence that the pathophysiological features of PCOS may be associated with cardiovascular risk.

Are women with PCOS at increased risk for cardiovascular disease? At the present time, the answer to this question is as follows: Women with PCOS have a risk profile that would be predictive of a greater incidence of cardiovascular disease, but available data on actual cardiovascular events do not definitively support this prediction.

We first review background studies suggestive of a link between PCOS

and cardiovascular risk. Second, we present results from a large, ongoing case-control study of cardiovascular risk conducted by the authors. Third, we review the limited data available on the relationship between PCOS and actual cardiovascular events.

II. BACKGROUND LITERATURE

In 1985, Wild and his colleagues [2] were the first to show that women with PCOS had lower high-density lipoprotein (HDL) levels, higher low-density lipoprotein (LDL)/HDL ratios, and higher triglyceride levels than regularly menstruating control (Fig. 1). Since the PCOS women were heavier, it was possible that

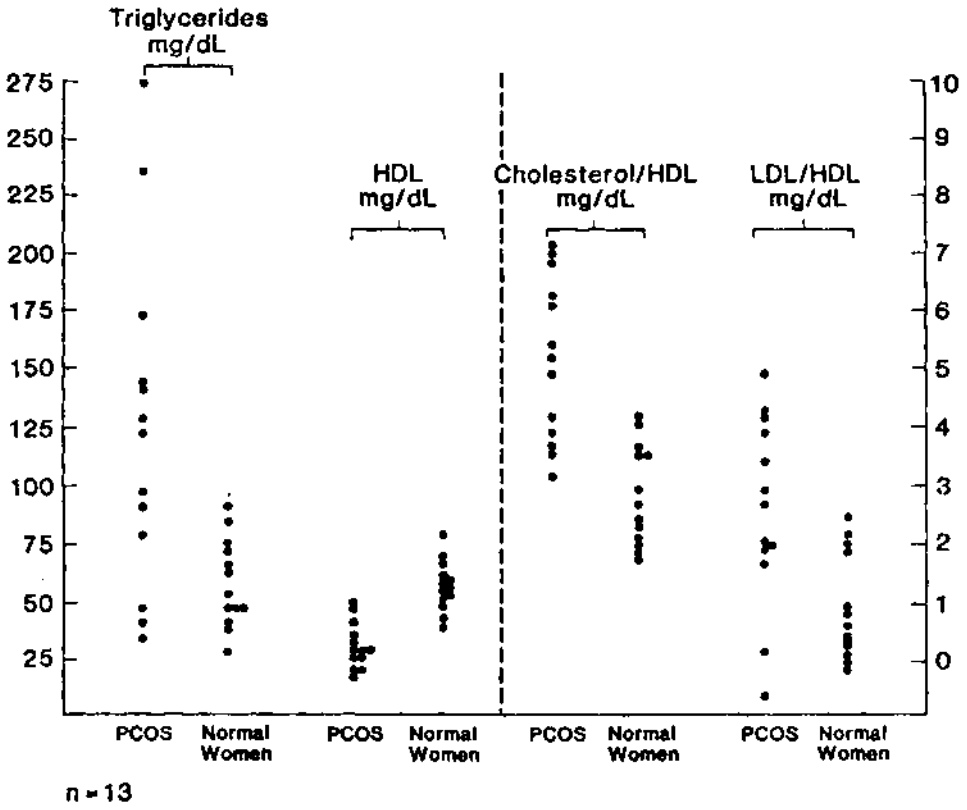

Figure 1 Cholesterol and lipid measurements in PCOS cases and controls. (From 4.)

these results could be explained by weight rather than PCOS status. Data from a subsequent, confirmatory study, in which a small number ($n = 13$) of cases and controls were matched by weight [3], confirmed these results. Slowinska-Srzednicka and collaborators [4] drew attention to the role of insulin in the lipid abnormalities observed in hyperandrogenic women with PCOS. These investigators compared 27 PCOS women with 22 eumenorrheic controls, stratified by weight (obese vs. nonobese). Women with PCOS had significantly lower levels of HDL2, higher levels of apolipoprotein B, and higher triglycerides. Multiple-regression analysis within PCOS cases, adjusting for age, body mass index (BMI), and sex steroids, revealed that fasting insulin was a significant explanatory variable for total triglycerides and apolipoprotein A1. These results suggested that insulinemia, independent of obesity, plays a role in the lipid disturbances of PCOS. These results were also consistent with a 1992 study by Wild et al. [5], in which 31 women with evidence of androgen excess were treated with a gonadotropin agonist for 3 months, which suppressed ovarian estradiol and testosterone. Lipid profiles remained aberrant despite the sex steroid suppression and remained correlated with insulin resistance. It was concluded that lipoprotein abnormalities appeared to be associated more with insulin than with alterations in androgens or estrogens.

In addition to lipids, cardiovascular risk factors such as type 2 diabetes and hypertension have also been studied. Dahlgren et al. [6] evaluated a cohort of 33 older women (mean age of 50) who were found to have ovarian histopathology typical of PCOS at wedge resection 22–31 years previously and also obtained follow-up information on 132 age-matched controls. Thirty percent of cases and 56% of controls had reached menopause. Compared with controls, PCOS patients had a higher prevalence of central obesity and a higher mean waist-to-hip ratio. Cases were found to have a sevenfold higher incidence of diabetes and a threefold higher prevalence of treated hypertension than controls.

These investigators subsequently reported a statistical risk-factor model [7] that applied their statistical estimates of the increase in risk factors (e.g., hypertension, diabetes, and waist-to-hip ratio) among PCOS women to existing models linking these risk factors to myocardial infarction. Using such a statistical model, they predicted a 4- to 10-fold increase in risk of myocardial infarction in women with PCOS. As a purely statistical prediction model based on a small number of cases, this study led to a prediction of excess risk that was far in excess of the estimates provided by more recent studies, to be discussed below, that were based on reported cardiovascular events.

An alternative approach to this question was taken by Birdsall et al. [8], who evaluated 143 women who had undergone coronary angiography for investigation of chest pain over a 2-year period. When the ovaries of these women were examined by transvaginal ultrasound, 42% were found to have polycystic appearing ovaries, which was twice the background prevalence of polycystic ap-

pearing ovaries reported in a general population of women. Moreover, women with polycystic appearing ovaries had more advanced coronary artery disease.

Given that the fundamental pathophysiological feature of PCOS in insulin resistance, if PCOS women are unable to overcome their peripheral insulin resistance by secreting excess insulin, they will have impaired glucose tolerance. This may place them at risk for the development of frank type 2 diabetes. Indeed, several recent studies have confirmed Dahlgren's initial finding of increased diabetes prevalence among women with PCOS. Using data from the Nurse's Health Study Cohort, Solomon and collaborators [9] studied the association of abnormal cycle length (as a marker of possible anovulation) and subsequent development of type 2 diabetes. In this cohort of 106,000 women, 7,837 (7.4%), ages 18–22 years, reported a usual cycle length of >40 days or a cycle too irregular to estimate. Over 6 years of follow-up, 344 cases of type 2 diabetes were confirmed. The age-adjusted relative risk of type 2 diabetes in women reporting an abnormal menstrual cycle length was 2.42 (95% confidence interval, 1.81–3.24). As well, Legro and coworkers [10] reported prevalence rates of 31.5% for impaired glucose tolerance and 7.5% for diabetes in a group of 254 women with PCOS. Looking at this from the other direction, women with gestational diabetes appear to demonstrate a high prevalence of PCOS features [11].

III. RESULTS FROM UNIVERSITY OF PITTSBURGH CASE-CONTROL STUDY

A large-scale epidemiological study of coronary heart disease (CHD) risk factors in women with the diagnosis of PCOS has been ongoing at the University of Pittsburgh since 1992. At that time, cohorts of PCOS cases and controls in the Pittsburgh, Pennsylvania, region were identified. PCOS cases were defined retrospectively from a chart review of women seen between 1970 and 1990. A clinical diagnosis of PCOS was defined by a combination of chronic anovulation and androgen excess (clinical and/or biochemical). Normally cycling control women, matched by age, race, and neighborhood, were identified from voter registration tapes and then contacted by telephone. From these procedures, 206 PCOS cases and 206 matched controls who were willing to undergo a current clinical and endocrinological evaluation were studied. Our initial results were reported in 1995 [12]. Selected demographic and clinical characteristics are shown in Table 1 and selected outcome measures relating to cholesterol, lipids, and triglycerides are shown in Table 2. An intentional decision was made not to use weight-matched controls. This was done so that we would be able to study the differences in body composition between cases and controls and also because of practical considerations in recruiting weight-matched controls in a large-scale study.

Table 1 Selected Sociodemographic and Reproductive Factors in PCOS Case and Matched Control Subjects

	Case subjects (n = 206)	Control subjects (n = 206)
Race		
White	185 (90%)	185 (90%)
Other	21 (10%)	21 (10%)
Currently smoking	46 (22%)	57 (28%)
Hysterectomy with bilateral oophorectomy (n)	10 (5%)	12 (5.8%)
Pregnancies (n)	1.57 ± 1.7	2.02 ± 1.7*
Age (years)	35.9 ± 7.4	37.2 ± 7.8
Education (years)	14.2 ± 2.2	14.4 ± 2.0
BMI (kg/m^2)	30.5 (8.3)	26.3 (6.46)**
Waist/hip ratio	0.823 (0.14)	0.76 (0.07)***

Note: PCOS indicates polycystic ovary syndrome; BMI, body mass index. * $P < 0.01$. ** $P < 0.001$. *** $P < 0.05$.

As can be seen in Table 1, the body mass index was significantly higher in PCOS women than in controls. The hip ratio, which has been associated with insulin resistance, was also higher among PCOS cases than controls. Table 2 shows that PCOS cases had an adverse lipid profile, as reflected in higher total cholesterol, higher HDL, and triglycerides as well as lower HDL and HDL2. Multiple-regression analysis was performed to obtain estimates of the independent effects of PCOS on lipids, controlling for BMI and other potentially confounding factors, including age, hormone use, and fasting insulin. After adjusting BMI and these other variables, PCOS cases had total and LDL cholesterol levels

Table 2 Case-Control Comparisons for Salient Risk Factors

	Case subjects (n = 206) (Mean ± SD)	Control subjects (n = 206) (Mean ± SD)	t	df	P
Total cholesterol (mg/dL)	195.4 ± 33.5	185.6 ± 37.8	2.61	1.53	0.01
Total HDL cholesterol (mg/dL)	51.1 ± 14.5	57.8 ± 14.5	−4.05	153	<0.0001
HDL (mg/dL)	7.8 ± 6.22	11.7 ± 7.34	−5.11	153	<0.0001
LDL cholesterol (mg/dL)	118.4 ± 31.5	110.7 ± 34.6	2.17	153	0.032
Fasting insulin (μU/L)	23.5 ± 17.9	13.6 ± 8.7	4.8	94	<0.0001
Triglycerides (mg/dL)	129 ± 88.8	85.9 ± 63.4	5.58	153	<0.001

that were 9.5 mg/dL and 9.9 mg/dL higher than controls, respectively, while their HDL cholesterol level was 5.4 mg/dL lower than that of controls [12].

These data, while provocative, nonetheless beg the question: Do biochemical changes (i.e., lipids) translate into clinical events? To get closer to an answer, we used carotid artery ultrasound scanning to assess intima-media thickness (IMT) as a preclinical measure of atherosclerosis. In a pilot study of 16 premenopausal women aged ≥40 years with a history of clinical PCOS and 16 age-matched cycling controls [13], we found that the mean carotid IMT was significantly greater for women with PCOS (Fig. 2).

We have now scanned 125 PCOS cases and 142 controls over a wider age group. As shown in Figure 3, there is no difference in IMT in women less than 40 years of age, but the difference in IMT between PCOS cases and controls increases with age after age 40 [14]. To control for the effects of age, BMI, and LDL, multivariate linear regressions were performed (outcome variable: IMT). As can be seen in Table 3, PCOS status still has a significant, independent impact on PCOS status for women ≥45 years of age, even after adjusting for age and BMI [14]. Interestingly, the addition of LDL, which itself has a significant impact on IMT, does not alter or attenuate the estimated coefficient or significance of PCOS.

These data raise the question of whether there is a relation between the age-related changes in carotid IMT and age-related changes in lipid profiles. We recently evaluated the age-specific risk profiles in women with PCOS and matched controls [15]. Risk profiles were compared across four age groups (19–24, 25–34, 35–44, and 45 years). After adjustment for BMI, hormone use, and insulin levels, PCOS women had substantially higher LDL and total cholesterol

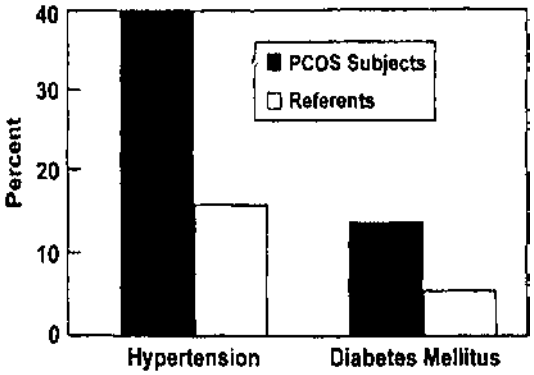

Figure 2 Hypertension and diabetes in women previously diagnosed with polycystic-appearing ovaries based on wedge resection. (From 6.)

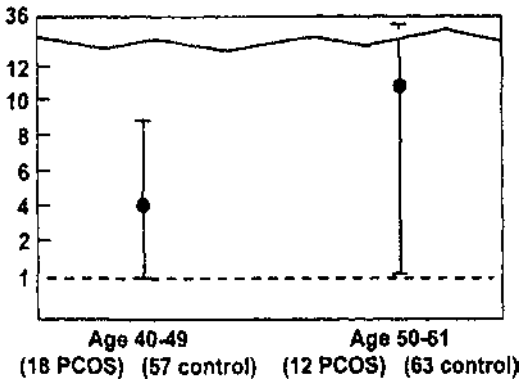

Figure 3 Predicted relative risk of myocardial infarction in PCOS women based on a statistical model. (From 7.)

Table 3 Multiple Linear Regression Models of the Effect of PCOS Adjusted for Age, BMI, and LDL ($N = 240$)

	<45		≥45	
	B	Sig.	B	Sig.
PCOS	0.031	0.675	0.260	**0.007**
Age	0.029	**0.006**	0.020	0.152
PCOS	0.072	0.370	0.200	**0.068**
Age	0.034	**0.001**	0.030	**0.030**
BMI	0.017	**0.002**	0.019	**0.002**
PCOS	0.049	0.526	0.190	**0.060**
Age	0.034	**0.001**	0.024	0.079
BMI	0.018	**0.001**	0.017	**0.008**
LDL	0.001	**0.039**	0.002	0.155

Note: For bold entries $P < 0.05$; for bold and underlined entries PCOS <0.10.

levels at each age group <45+ years. Above the age of 45, however, little difference was noted in risk factors between groups. From these data, one might speculate that long-standing exposure to adverse serum lipid concentrations in younger women with PCOS may lead to preclinical atherosclerotic change when they get older, even as their lipid profile improves.

We have also explored further the issue of preclinical atherosclerosis by conducting a pilot study of Electron Beam Computed Tomography (EBCT). EBCT permits the noninvasive evaluation of aortic and coronary arterial atherosclerosis by providing a quantitative measure of coronary calcification [16]. Coronary calcification correlates with the degree of atherosclerosis found on pathological exam and predicts incident cardiovascular events [17]. Coronary artery calcification is an active, organized, and regulated process that occurs only when other aspects of atherosclerosis are present. While calcified deposits are found with greater frequency in elderly individuals and in advanced lesions, calcium deposition may occur as early as the second decade of life, just after fatty streak formation [18]. The presence of calcium is likely a marker for future cardiac events, since it is an indicator of the total coronary artery atherosclerotic burden. In our preliminary sample, women with PCOS were found to have measurable levels of primary calcification twice as often as controls. Calcification was also related to waist-to-hip ratio, fasting insulin, and lipid levels; however, PCOS status appears to have an independent effect on coronary and aortic calcification above and beyond these factors (unpublished data).

IV. CARDIOVASCULAR EVENTS AND POLYCYSTIC OVARY SYNDROME

Thus far, we have presented data on risk factors for cardiovascular disease in women with PCOS and preclinical measures of atherosclerosis. However, the central question is whether PCOS during the reproductive years leads to subsequent cardiovascular *events*. In a recent study from the United Kingdom [19], 786 women diagnosed with PCOS between 1939 and 1979 were traced from hospital records and followed for an average of 30 years. Histopathology at the time of ovarian wedge resection was the major basis for diagnosis. Observed death rates in these women were compared to expected death rates using standardized UK mortality ratios. There were 59 deaths from all causes observed in the PCOS group. This was not statistically different from the expected number of deaths. Similarly, the number of all circulatory deaths in the PCOS group was not statistically different from the expected number. Only the number of deaths related to complications of diabetes was higher in the PCOS group, but the numbers here were extremely small. In a follow-up study [20], the same investigators sent questionnaires to 345 cohort members from the initial PCOS sample and to 1107 control women obtained from the age–sex register at the same general practice. From these questionnaire data, it was found that the odds ratios (95% CI) for coronary heart disease (CHD) was 1.5 (0.7–2.9) based on 15 CHD events in the PCOS group. After adjusting for BMI, the odds ratio estimate was reduced to

1.2 (0.5–2.6). The odds ratio for cerebrovascular disease was higher and reached statistical significance [2.8 (1.1–7.1)]. The PCOS women also were found to have significant underlying risk factors for circulatory disease, including an increase in the prevalence of diabetes, hypertension, and high cholesterol.

These studies are extremely important, as they provide evidence that appears to contradict the accumulated data linking PCOS with increased cardiovascular risk. As a possible explanation for the discrepant findings, we would point out that case ascertainment based on anatomic and inpatient discharge records may lead to a significantly underascertainment of PCOS syndrome as defined by chronic anovulation and androgen excess in an outpatient population. Moreover, 23% of the women diagnosed with PCOS could not be traced. To the extent that deaths in the untraceable group were higher than in the group that was traced, there may be a downward bias in the estimates of mortality rates in the PCOS group, although the authors did not believe that this was present. Further, a relative risk of 1.5 for cardiovascular disease is clinically significant, but was not statistically significant in this study because of the limited number of events. The issue of sample size becomes especially important when it is recognized that the average age of the PCOS women in the two British studies was in the low 50s. Thus, on average, they are not yet at an age when CV events occur more frequently. With further follow-up of this cohort, more events will occur and it will be valuable to see if the rate in women with PCOS continues to be 50% higher than that in control women. Finally, the wedge resection itself may have altered the mortality risk profile in these PCOS women, as this procedure is known to be associated with long-term ovulation and in an associated return to normal hormonal parameters [21,22].

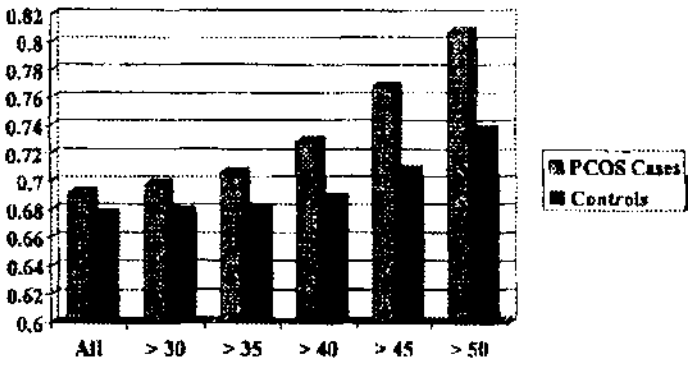

Figure 4 Age-specific differences in intima-media thickness between PCOS cases and controls. (From CHARM study unpublished data.)

To address further the question of an association between PCOS and cardiovascular events, the authors are organizing a multisite study in the United States in women who were first diagnosed with PCOS before 1985 and who are now at least 45 years of age to be matched with eumenorrheic controls. Both groups will then be traced to determine the relative risk of cardiovascular risks.

V. CONCLUDING COMMENTS

In clinical practice, women with PCOS are seen for three major reasons: infertility, menstrual regularity, and androgen excess. Treatment is typically targeted at the immediate presenting complaint. However, to the extent that the chronic anovulation, hyperandrogenemia, and insulin resistance associated with PCOS leads to a metabolic profile similar to Syndrome X, it is perhaps more appropriate to approach the management of PCOS as a chronic condition. In this regard, behavioral weight control and exercise play an extremely important role. The use of insulin-lowering drugs has been reported in short-term studies to have a beneficial effect on endocrine parameters, lipids, and ovulation. The long-term impact of these medications deserves to be explored if the link between PCOS and cardiovascular disease becomes more firm.

REFERENCES

1. Knochenhauer ES, Key TJ, Kahsar-Miller M et al. Prevalence of the polycystic ovary syndrome in unselected black and white women of southeastern United States: a prospective study. J Clin Endocrinol Metab 1998; 83:3078–3082.
2. Wild R, Painter P, Coulson P, Carruth K, Ranney G. Lipoprotein lipid concentrations and cardiovascular risk in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1985; 61:946–951.
3. Wild RA, Bartholomew MJ. The influence of body weight on lipoprotein lipids in patients with polycystic ovary syndrome. Am J Obstet Gynecol 1988; 159:423–427.
4. Slowinska-Szrednicka J, Zgliczynski S, Wierzbicki M, Szrednicki M, Stopinska-Gluszak U, Zgliczynski W, Soszynski P, Chotkowska E, Bednarska M, Sadowaki Z. The role of hyperinsulinemia in the development of lipid disturbances in non-obese and obese women with polycystic ovary syndrome. J Endocrinol Invest 1991; 14:569–575.
5. Wild R, Alaupovic P, Givens J, Parker I. Lipoprotein abnormalities in hirsute women. Am J Obstet Gynecol 1992; 167:1191–1197.
6. Dahlgren E, Janson P, Johansson S, Mattson L, Lindstet G, Crona N, Knutsson F, Lundberg P, Oden A. Women with polycystic ovary syndrome wedge resected in 1956–1965: a long-term follow-up focusing on natural history and circulating hormones. Fertil Steril 1992; 57(3):505–513.