0021-972X/99/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 84, No. 6
Printed in U.S.A.

COMMENTARY

Polycystic Ovary Syndrome (PCOS): Arguably the Most Common Endocrinopathy Is Associated with Significant Morbidity in Women

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Women's health is about the prevention, screening, diagnosis, and treatment of disorders that are unique to women. Polycystic ovary syndrome (PCOS) is extremely prevalent and probably constitutes the most frequently encountered endocrinopathy in women of reproductive age. Primary care providers do not commonly appreciate that the syndrome is associated with significant morbidity in terms of both reproductive and nonreproductive events. Having the disorder may significantly impact the quality of life of women during the reproductive years, and it contributes to morbidity and mortality by the time of menopause. A cohort of women with PCOS who were followed for many years after wedge resection (1) revealed several important findings by the time they reached the age of menopause. Their symptoms of PCOS had persisted over this time, they had a later menopause, and they had experienced a higher hysterectomy rate. Most importantly, there was a high prevalence of diabetes (16%) and hypertension (40%).

What is PCOS?

A uniform definition of PCOS does not exist, in large part because of its diverse and heterogeneous nature. It is clear to us, however, that the disorder is an endocrinopathy, and that it should be referred to as PCOS, a syndrome, rather than a disease (2). At a meeting held at the National Institutes of Health 10 years ago, there was no consensus but a general agreement that hyperandrogenism and chronic anovulation are the principal facets of the syndrome and that once other disorders (CAH, tumors) were ruled out, the diagnosis of PCOS may be presumed. In the literature, this general definition is quoted as the "NIH Consensus Statement." Indeed, this was not a consensus conference, and there was no consensus.

For the purpose of these comments we refer to PCOS using this most widely accepted definition, and we wish to bring attention to the fact that the diagnosis carries with it significant health risks for women. PCOS is extremely prevalent and is estimated to be present in 5–7% of reproductive-age women if we consider the diagnosis to be based on hyperandrogenism and anovulation (3, 4). However, the spectrum of the syndrome is wider still. We have recently became convinced that there is a mild form of PCOS that includes women who have hyperandrogenism and polycystic ovaries but who's ovulatory function is maintained (5). However, it is clear that the syndrome is milder and the hyperandrogenism is not as pronounced. These women have many of the same risks as women with more classic PCOS, which will be described below.

While PCOS occurs in at least 5% of the population, the isolated finding of polycystic-appearing ovaries (PAO), which meets the classic ultrasonographic criteria, occurs in 16–25% of the normal population (6). PAO or PCO (referring only to the ovarian morphology) is known to occur in hypothalamic amenorrhea and in CAH, where its prevalence is virtually 100% (7).

Normal ovulatory women with PAO cannot be considered to have PCOS although many clinicians have based the diagnosis on ultrasound findings. Nevertheless, it is curious that there is this high prevalence of PAO in the normal population, and yet there is a much smaller percentage of women who have PCOS. We have formulated a hypothesis that relates the polycystic ovary (PAO/PCO) to PCOS. It is known that PAOs may appear in childhood before any hormonal changes occur at puberty, and they probably arise from genetic and/or environmental influences. We have proposed that various "insults" need to come into play after puberty for women with PAO to develop PCOS (8). Usually more than one factor may be involved, and the list of these "insults" is long (for instance: insulin resistance, obesity, stress, and dopaminergic dysregulation). Simultaneously, various individual adaptive or compensatory mechanisms are probably opposing these insults, either to attenuate the expression of PCOS, or to prevent its development altogether. Thus, these adaptive factors may allow a woman never to develop PCOS despite having PAO, or to develop some form of the syndrome later than usual in reproductive life.

With our hypothesis, while PCOS is defined by charac-

Received March 22, 1999. Accepted March 22, 1999.
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teristic findings, a larger group of women with PAO are susceptible to developing the syndrome as well. Thus, these women may also be subject to the increased morbidity described below. Indeed, we have demonstrated that some normal women with PAO may have subtle metabolic abnormalities.

Reproductive concerns

The majority of women with PCOS have anovulation. With this comes infertility as well as problems of dysfunctional bleeding. Chronic unopposed estrogen leads to endometrial hyperplasia and, potentially, to cancer, as will be discussed below. Heavy persistent bleeding often leads to anemia.

Infertility due to anovulation may be treated effectively but may not be a simple manner. Clomiphene citrate is the mainstay of therapy. However, up to 10% of women may have clomiphene resistance and will fail to respond to doses as high as 150 mg daily for 5 days. The principal reason for this resistance is lack of an adequate ovarian response. Alternatives to clomiphene include gonadotropins, pulsatile GnRH, or ovarian diathermy. While all are efficacious, they all result in greater expense and often a higher complications rate. Gonadotropin therapy may lead to hyperstimulation, a condition to which all patients with polycystic ovaries (PAO or PCOS) are more susceptible. Multiple pregnancies are also more prevalent. In our experience pulsatile GnRH therapy is not as efficacious as the other treatments. Ovarian diathermy requires a surgical approach and can lead to pelvic and ovarian adhesions but is associated with a 50% pregnancy rate. Recently, promising results have been demonstrated with the use of metformin and insulin sensitizing agents such as troglitazone. Long-term results are not yet available.

Perhaps the most frustrating reproductive concern for women with PCOS is pregnancy loss (9). The spontaneous abortion rate in PCOS is approximately one third of all pregnancies. This is at least double the rate for recognized early abortions in normal women (12–15%). Reasons for this are unclear although hypotheses include elevated LH levels, deficient progesterone secretion, abnormal embryos from atretic oocytes, and an abnormal endometrium. Attempts to improve the live birth rate by lowering LH using GnRH agonist therapy was successful in retrospective studies (10), but this has not been confirmed in a prospective study (11).

Once pregnancy is established, the morbidity increases particularly if the woman is obese. Perinatal mortality is increased at least 1.5 times, and pregnancy complications are increased including preeclampsia, diabetes, premature labor, and an increased stillborn rate. Because of these complications and the increased likelihood of delivering a large infant, the C-section rate is also increased. Because most patients with PCOS have insulin resistance, it is not surprising that the rate of gestational diabetes increases, as confirmed by our own studies in Los Angeles and New York. However, this has not been a universal observation perhaps explained by the heterogeneity of the disorder and endogenous compensatory factors. It has recently been observed that patients with PCOS who develop gestational diabetes have alterations in insulin sensitivity noted as early as the first trimester (12).

Psychological caveats

Several studies have shown that women with PCOS, particularly those with hirsutism, have an increased prevalence of reactive depression and minor psychological abnormalities (13). There is also evidence of increased psychological stress and an increased catecholamine response to provoked stress. The overall quality of life is decreased in hirsute women (14). Thus among the morbidities associated with PCOS one has to consider the psychological impact of the disorder.

The presence of hirsutism and menstrual irregularities, especially in younger patients, is extremely distressing and has a significant negative impact on their psychosocial development.

Obesity

Overall obesity is present in approximately 44% of women with PCOS. This figure varies somewhat depending on ethnicity and geography. When present, obesity worsens the clinical presentation of PCOS increasing insulin resistance and resulting in a further elevation of ovarian and adrenal androgens and of unbound testosterone. As a consequence, the treatment of obesity is one of the main goals of any therapy for PCOS, although this may be more difficult because of insulin resistance and impaired lipolysis (15).

Because of hyperandrogenism and insulin resistance, the obesity of PCOS is of the android (central) type, which results in an increased waist-to-hip ratio and which is highly associated with diabetes mellitus and increased cardiovascular risk. These consequences of PCOS are worsened by obesity but appear to be present in all PCOS patients, including those who are not obese.

Impaired glucose tolerance and diabetes

In the longitudinal study following wedge resections (1), fully 16% of women with PCOS developed type 2 diabetes mellitus by the age of menopause. Insulin resistance occurs in the majority of women with PCOS, particularly if more sensitive probes are used, and is more severe in obese women, as noted above. All women with PCOS are therefore at risk to develop impaired glucose tolerance and overt type 2 diabetes. In a recent study, impaired glucose tolerance was found in 31% of women of reproductive age, with PCOS and diabetes in 7.5%. In nonobese PCOS these figures were 10.3% and 1.5%, a rate almost 3-fold that of the normal population (16). These results were similar in women of different races.

The morbidity of diabetes is well known. Therefore even young women with PCOS should be screened for diabetes and followed closely. In women desirous of fertility this takes on an even greater importance and should be a major facet of preconceptual counseling.

Cardiovascular consequence: dyslipidemia, hypertension, coronary disease

A spectrum of abnormal lipid and lipoprotein profiles may be found in patients with PCOS, as has been recognized for

some time (17). Characteristically, patients have elevated cholesterol, triglycerides, and LDL cholesterol and have lowered high density lipoprotein and Apo A1 levels. These findings, however, are highly variable and depend on the obesity status, diet and ethnicity of the population studied. While hyperandrogenism is likely to play some role in these abnormalities, hyperinsulinemia (insulin resistance) appears to be the most important contribution to these abnormalities, particularly the elevation in triglycerides. These abnormalities are known to be highly predictive of cardiovascular disease.

Hypertension is extremely prevalent, particularly in older women with PCOS and those who are obese. Again insulin resistance is highly correlated with this abnormality.

It has been calculated that based on the risk profile, women with PCOS have a 7-fold increased risk of myocardial infarction (18). Coronary disease is more prevalent in women with PCOS (19–21). Most of the metabolic and other abnormalities discussed above are likely to contribute to this risk. Because of the high prevalence of PCOS in the general population, and because cardiovascular disease is the major cause of death in older women, the prevention of cardiovascular disease in women with PCOS should be a major public health priority.

Cancer risk

Women with PCOS are at increased risk of endometrial cancer. Chronic unopposed estrogen exposure is probably the proximate risk factor. This may be confounded by obesity, hypertension, and diabetes, which are known correlates of endometrial cancer risk. It is imperative to screen all women with PCOS, even those who are considered too young to develop endometrial hyperplasia and carcinoma.

Ovarian cancer is also increased 2- to 3-fold in women with PCOS (22). Of interest, this risk is greater in those who are not obese and is greatest in women who have not been on oral contraceptives. Because of the known protective effect of oral contraceptives on ovarian and endometrial cancer risk, use of oral contraceptives should be strongly considered as a preventative therapy.

It is unclear if women with PCOS have an increased risk of breast cancer, partially because other factors like obesity and nulliparity are confounding variables. Because an association between PCOS and breast cancer is plausible, it is imperative to be vigilant about breast disease in the follow up care of all women with PCOS.

Women with PAO

As discussed previously, 16–25% of normal ovulatory women have polycystic appearing ovaries (PAO) without evidence of the full-blown syndrome. However, a subgroup of women with PAO (up to 30%) may have subtle abnormalities resembling PCOS (23). These characteristics include androgenic ovarian responses to stimulation with gonadotropins, as well as metabolic changes such as lowered high density lipoprotein-C levels and evidence of insulin resistance. While these data generated by our group need further assessment, these findings suggest that important yet silent abnormalities may exist in otherwise normal women who have a trait of PCOS (namely PAO).

Conclusions

PCOS is a common disorder of women that is associated with significant reproductive and nonreproductive morbidity as outlined here. Perception of this and preventative therapies are important for the health care of women. For PCOS, diet, exercise, and oral contraceptives are reasonable preventative therapies. Screening for hypertension, abnormal lipid profiles, insulin resistance, and reproductive disorders including cancer should be the mainstay of care for women with PCOS.

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