Long-term consequences of Polycystic Ovarian syndrome

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Introduction

Stein and Leventhal

They were the first to recognize an association between the presence of polycystic ovaries and signs of hirsutism amenorrhea (oligomenorrhea,obesity)

Polycystic Ovarian Disease

After successful wedge resection of the ovaries in women diagnosed with Stein-Leventhal syndrome, menstrual cycles become regular and the patients were able to conceive. Primary ovarian disorder come to be known as polycystic ovarian disease

- ## Polycystic ovarian syndrome
- Biochemical, clinical and endocrinological abnormalities have shown an array of underlying abnormalities,; hence condition known as polycystic ovarian syndrome(PCOS)

- ## Syndrome O
- gets to the real heart of the problem and indicates: Ovarian confusion and Ovulation disruption caused primarily by Over nourishment and Overproduction of insulin

- In reality PCOS, infertility, and other health problems may be all consequences of syndrome O

Introduction (cont.)

- Most attention has been paid to the management of the presenting complaint (infertility, hirsutism..etc.)
- It has become clear that the polycystic ovary phenotype is linked to a number of metabolic disturbances, including type II diabetes and possibly atherosclerosis
- Since PCOS frequently diagnosed by gynecologists, it is therefore, important that gynecologists have a good understanding of the long-term implications of the diagnosis

Prevalence of PCOS

- Estimates of the prevalence of the disorder must be made with caution, since there is no overall consensus concerning the diagnostic criteria that must be satisfied in order to make the diagnosis
- It was suggested that approximately 20% of women of reproductive age demonstrate the ultrasound picture of polycystic ovaries, with half that number having clinical or biochemical signs of anovulation and androgen excess

Pathophysiology

- Abnormalities in the metabolism of androgens and estrogen and in the control of androgen production
- High serum androgen may be found (testosterone, anderostendione)
- Peripheral insulin resistance and hyperinsulinemia… elevated insulin levels may have gonadotropin-augmenting effects on the ovarian function and is responsible for the dyslipidemia and elevated levels of plasminogen activator inhibitors which constitute a risk factor for intravascular thrombosis

Pathophysiology (cont.)

- Proposed mechanism for anovulation and increased androgen:
- 1-* increased LH stimulates the ovarian theca cells with increase production of androgens
- 2-*Decreased FSH leads to decrease ability of Granulosa cells to aromatize androgens

Gross appearance of ovaries

- Polycystic ovaries are enlarged bilaterally and have a smooth thickened capsule that is avascular
- On cut section, subcapsular follicles in various stages of atresia are seen in the peripheral part of the ovary
- The most striking ovarian features of PCOS is hyperplasia of the theca stromal cells surrounding arrested follicles
- Microscopically luteinizing theca cells are seen

Presentation

- Patients with PCOS present with various symptoms including the following:
- *Amenorrhea
- *Oligomenorrhea
- *Infertility
- *Hirsutism
- *Obesity
- *Acne Vulgaris
- *Asymptomatic

Physical Signs

- *Hirsutism
- Patients may have excess body hair in male distribution pattern and acne. In some patients virilizing signs such as male pattern balding or alopecia, increased muscle mass, deepening of voice or clitoromegally may be encountered and should prompt the search for other causes of hyperandrogenism
- *Obesity: approximately 50% of patients are obese
- *Acanthosis Nigricans
- This is diffuse velvety-thickening hyperpigmentation of the skin. It may present at the nape of the neck, axillae, area beneath the breasts and exposed areas (elbows, knuckles)
- This is thought to be the result of insulin resistance in these patients

Laboratory studies

- *Increased androgen levels in blood (testosterone and androstendione)
- *Increased LH, exaggerated surge
- *Increased fasting insulin
- *Increased prolactin
- *Increased estradiol and estrone levels
- *Decreased SHBG levels

Imaging studies

- Using ultrasonographgy the number of cysts in subcapsular region varies between 8-10 cysts with diameter of 2-8 mm.
- However, there is significant intra-observer and inter-observer variability and ultrasonography alone may not be a reliable method of diagnosis or excluding PCOS

PCOS and risk of type II diabetes

- Evidence from small long-term cohort studies, case-control studies and case series, points to a risk of type II diabetes in middle age of 10-20% with higher rate of impaired glucose tolerance suggesting that further cases of diabetes will develop later
- Increased body mass particularly obesity and strong family history of diabetes both increase the risk of developing type II diabetes in the presence of polycystic ovaries phenotype

PCOS and risk of cardiovascular disease

- Women with PCOS frequently have abnormal lipid profiles with raised triglycerides and total and low-density lipoprotein cholesterol
- There is evidence that risk factors in PCOS women are elevated at an earlier age than among women without PCOS and therefore the risks of developing atherosclerotic conditions, hypertension and myocardial infarction are greater

PCOS and Pregnancy

- Women with PCOS have greater risk of developing gestational diabetes: the risk is believed to be greater in obese women with PCOS who required ovulation induction in order to conceive
- Women who have been diagnosed in pregnancy with gestational diabetes have been found to have a higher prevalence of PCOS on subsequent screening
- This association is more common in women with raised body mass index

PCOS and pregnancy

- The risk of pregnancy induced hypertension among patients with PCOS was shown to be increased in some studies, however, other studies showed no relation between PCOS and development of hypertension during pregnancy
- Studies on association between PCOS and increased rate of abortion and recurrent abortion could not demonstrate any significant relationship with PCOS

PCOS and Cancer

- Oligo- and amenorrheic women with PCOS are shown to be at increased risk for endometrial hyperplasia and endometrial carcinoma due to the prolonged continuous estrogenic effect on the endometrium
- Regular induction of withdrawal bleed with cyclical gestogens is advisable, however, there is no consensus on the optimal progestin duration and frequency of treatment to prevent endometrial carcinoma in women with PCOS

PCOS and Cancer

- Epithelial ovarian cancer was shown to increase 2.5 folds among patients with PCOS than controls. The association was shown to be stronger among women who never used oral contraceptive
- Further investigations with regard to the association between PCOS and ovarian cancer are awaited
- Studies examining the relationship between PCOS and breast carcinoma have not always identified a significant increased risk

Identification of patients at risk for long-term consequences of PCOS

The association of clinical features of truncal obesity, oligo- or amenorrhea and hirsutism with biochemical evidence of hyperandrogenemia, elevated luteinizing hormone and suppressed SHBG and characteristic ovarian morphology on ultrasound has formed the basis of the diagnosis of PCOS

However, the key underlying abnormalities that lead to long-term health risk appears to be insulin resistance-hyperinsulinemia in the presence of normoglycemia

- Identification of patients with metabolic complications of PCOS should focus on biochemical criteria to diagnose the syndrome particularly hyperandrogenemia together with an assessment of fasting glucose and insulin, lipids and triglycerides

Strategies for reduction of risk Exercise & Weight control

*Improvement in diet and exercise in obese young women with PCOS is accompanied by normalization in glucose metabolism, therefore, life style alteration will reduce the likelihood of developing type II diabetes later in life

*No clear evidence of an effect of diet or exercise on the long-term health of women with PCOS who have normal body habitués. However, it seems prudent to advise such patients to maintain their body weight within normal range

Reduction of risk
Drug therapy

- There is interest in using insulin-sensitizing agents like metformin to reduce insulin-resistance and thereby reduce the risk of developing diabetes and other metabolic sequel.
- Studies to date have only assessed the impact of insulin-sensitizing agents in the short-term and well-designed long-term randomized control trials with regard to long-term safety and efficacy in non-diabetic women are needed

Reduction of risk
Surgery

- Laparoscopic ovarian electrocautery has shown persistence of ovulation and normalization of serum androgens and SHBG over many years in over 60% of patients and the long-term benefits of ovarian drilling, including alterations in endocrine profile have been confirmed
- However, the effect on insulin resistance and serum lipids is not assessed and at present the risk of surgery do not justify recommendation of this treatment purely in attempt to ameliorate the chances of developing diabetes or coronary artery disease in later life

RCOG Guidelines (May 2003)

Evidence based guidelines for reduction of long-term PCOS consequences

Classifications of evidence levels

- Ia: Evidence obtained from meta-analysis of randomized controlled trials
- Ib: Evidence obtained from at least one randomized controlled trial
- IIa: Evidence obtained from at least one well-designed controlled study without randomization
- IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study
- III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
- IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grades of Recommendations

- A- Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
- B- Requires the availability of well controlled clinical studies but no randomized clinical trials on the topic of recommendations (Evidence levels IIa, IIb, III)
- C- Requires evidence obtained from expert committee reports or opinions and/ or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Guidelines (RCOG, May 2003)

- 1-Patients presenting with PCOS particularly if they are obese, should be offered measurement of fasting blood glucose and urine analysis for glycosuria. Abnormal results should be investigated by a glucose tolerance test.
- Such patients are at increased risk of developing type II diabetes (Evidence level IIb[C])
- 2- Women who have been diagnosed as having PCOS before pregnancy (eg those requiring ovulation induction for conception) should be screened for gestational diabetes in early pregnancy, with referral to a specialized obstetric diabetic service if abnormalities are detected (evidence level IIb[B])

Guidelines (RCOG, May 2003)

- 3-Measurement of fasting cholesterol, lipids and triglycerides should be offered to patients with PCOS, since early detection of abnormal levels might encourage improvement in diet and exercise (Evidence level III[C])
- 4- Olig- and amenorrhoeic women with PCOS may develop endometrial hyperplasia and later carcinoma. It is good practice to recommend treatment with progestogens to induce withdrawal bleed at least every 3-4 months (Evidence level IIa[B])

Guidelines (RCOG, May 2003)

- 5-A body of evidence has accumulated demonstrating safety and in some studies efficacy of insulin-sensitizing agents in the management of short-term complications of PCOS, particularly anovulation. Long-term use of these agents for avoidance of metabolic complications of PCOS can not as yet be recommended (Evidence level IV[B])
- 6- No clear consensus has yet emerged concerned regular screening of women with PCOS for later development of diabetes and dyslipidemia but obese women with a strong family history of cardiac disease or diabetes should be assessed regularly in a general practice or hospital outpatient setting. Local protocols should be developed and adapted as new evidence emerges (Evidence level IV[C])

Guidelines (RCOG, May 2003)

- Young women diagnosed with PCOS should be informed of the possible long-term risks to health that are associated with their condition. They should be advised regarding weight and exercise (Evidence level III[C])