REVIEW

Polycystic ovary syndrome (PCOS) – the long-term implications

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It is well recognised that polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women in their reproductive years, affecting 5 - 10% of this segment of the population.

The current diagnosis of PCOS is based on the Rotterdam consensus statement 2003,[1] and is based on three main criteria:

- oligo- or anovulation
- clinical or biochemical signs of hyperandrogenism (with exclusion of congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumours, thyroid abnormalities and hyperprolactinaemia)
- polycystic ovaries on ultrasound.

To diagnose PCOS, and bearing in mind that it is a syndrome and does not exist as a single symptom, two of the three criteria must be present.

When a woman presents with PCOS, clinicians usually concentrate on treating infertility if she desires a pregnancy. Since PCOS has recently been recognised as an endocrinopathy with metabolic disturbances, it is appropriate to modify the goal of treatment, which is to prevent the long-term effects. PCOS is associated with an array of metabolic disturbances (hyperinsulinaemia and insulin resistance, dyslipidaemia, hypertension and cardiovascular disease) as well as an increased risk of neoplasia in affected patients who are not managed appropriately.[2]

It has been established that several factors influence the presentation of PCOS. Diet and lifestyle may play a role.[3]

Pathogenesis

Environmental factors are also significant in the pathogenesis. Fetal undernutrition results in intrauterine growth adaptation and increases the prevalence of coronary heart disease, stroke, hypertension and type 2 diabetes mellitus in later life.[4] This finding is based on the Barker hypothesis. Barker and Clark demonstrated in 1997 that size at birth is related to the risk of developing disease in later life. In particular, connections between reduced birth weight, increased risk of coronary heart disease, hypertension, diabetes and stroke in adulthood are well established.[5] These relationships are modified by patterns of postnatal growth. The most widely accepted mechanisms thought to cause these relationships are those of fetal programming by nutritional stimuli or excess fetal glucocorticoid exposure. It has been suggested that the fetus makes physiological adaptations in response to changes in its environment to prepare itself for postnatal life. These changes may include epigenetic modification of gene expression. Currently, active research in this field will have direct relevance to future obstetric practices.

Today's challenge

It is clear that gynaecologists need to be aware of the long-term complications in their patients, and to pay attention to modifiable factors. They should have a holistic approach to patients with PCOS and not only deal with their reproductive issues such as menstrual dysfunction, complaints of hyperandrogenism, and infertility.

Evidence-based medicine should be the cornerstone of clinical practice. Appropriately designed longitudinal studies are usually not available, and most of the available information on the risks and prevalence of long-term outcomes of PCOS depends on case-series reports, non-randomised studies using historical controls, and non-randomised studies with a concurrent control group.

According to the work of Norman and colleagues, it is very important to obtain a family history, since insulin resistance is common in apparently unaffected relatives of women with PCOS.[6] Events in the patient's **own** intrauterine period should be recorded if available. Environmental factors and the patient's lifestyle should be taken into consideration.

Long-term risks

Hyperinsulinaemia and insulin resistance

Insulin resistance is defined as the body's inability to deal with a normal glucose load or the inability of insulin to

exert its physiological effect. This is a problem in obese and non-obese women with PCOS.[2] Dahlgren did a follow-up on women for 11 years and demonstrated that women with PCOS are more likely to develop type 2 diabetes mellitus.

Insulin increases the action of luteinising hormone (LH) on theca cells, resulting in overproduction of androgens. The overall result of hyperinsulinaemia and insulin resistance on the ovaries is that of anovulation and the appearance of acanthosis nigricans owing to hyperandrogenic effects on the skin and abnormal hepatic function, especially decreased sex hormone-binding globulin (SHBG), resulting in increased free bio-available testosterone.[7]

Insulin resistance seems to be more than just a marker for future diabetic risk – it is also significant in the pathophysiology of PCOS and cardiovascular risks.

Reaven[8] described syndrome X, also known as metabolic syndrome, which is characterised by lipid abnormalities, hypertension, central obesity and abnormalities in glucose dynamics. It is frequently evident that PCOS and metabolic syndrome coexist in the same patient. Glueck *et al*.[9] reported a 46% prevalence of metabolic syndrome in women with PCOS, compared with 23% in the general population over the age of 20 years.

Given the significant morbidity and mortality risk, the importance of screening all women with PCOS for these associated diseases and assuring further management[10] is again illustrated.

Obesity

Obesity is a complex problem with far-reaching effects and serious health implications. Associated with obesity is an increased risk of psychosocial impairment, type 2 diabetes mellitus, cardiovascular disease, osteoarthritis, sleep apnoea, and uterine cancer.[11] The significant impact that all these conditions can have on our economy is notable.

A range of research methods is available for precise measurement of the amount and localisation of fat and lean mass, e.g. skinfold thickness, underwater weighing, dual energy X-ray absorptiometry, magnetic resonance imaging (MRI) and infrared spectroscopy. However, a simple and reliable definition of obesity is needed for the clinical setting. Body mass index (BMI) is a useful clinical tool that correlates well with adiposity (Table I).[12]

The well-known classification adapted from the work of JC Seidell in 1995 is used in the clinical setting to help establish the risk of co-morbidity.[13]

The waist-hip ratio is an easy and practical tool to use. It provides a reasonable estimate of abdominal fat without distinguishing between visceral or subcutaneous fat.[14] A ratio ≥0.8 in women and 0.9 in men indicates an increased risk for cardiovascular disease.[15]

In 2001, Dobbelsteyn *et al*.[16] suggested another clinical measuring tool – waist circumference (Table II), which is measured midway between the lowest rib and the iliac crest. It predicts risk of metabolic complications associated with obesity. If a patient falls in the increased risk group, this finding should alert the clinician to the potential risk of cardiovascular disease. If a patient falls in the substantially increased risk group, therapeutic action should be initiated.[17]

According to a local report by the Medical Research Council (MRC), obesity is becoming an enormous problem.[18] This study by Puoane *et al*. revealed that the situation in South Africa is similar to the American epidemic.

In a sample of 7 726 South African women aged 15 - 95 years, black women had the highest prevalence of obesity, followed by women of mixed ancestry, with white women in the third position. Indian women had a prevalence of 48.9%. Urban women had a slightly higher BMI compared with their rural counterparts; BMI in both groups was found to increase with age.[18]

The African continent is known for malnutrition; however, the picture is changing (Table III). Obesity is not only a problem of developed nations but is also becoming an increasing problem in countries undergoing epidemiological transition, such as South Africa, Mexico

Table II. Waist circumference predicts risk of metabolic complications associated with obesity (adapted from Seidell[13])

	Increased risk	Substantially increased risk
Men	≥94 cm	≥102cm
Women	≥80cm	≥88cm

Table I. Classification of overweight in adults according to body mass index (BMI)

Classification	BMI	Risk of co-morbidities
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal range	18.5 - 24.9	Average
Overweight	≥25	Moderate
Pre-obese	25 - 29.9	Increased
Obese class 1	30.0 - 34.9	Moderate
Obese class 2	35 - 39.9	Severe
Obese class 3	≥40	Very severe

polycystic.indd 49 8/28/09 9:06:46 AM

Table III. **Mean BMI of African countries categorised by age and gender (adapted from International Obesity Task Force: Global Burden of Disease Analyses 2002[19])**

		Age in years						
Country	**Sex**	**5 - 14**	**15 - 29**	**30 - 44**	**45 - 59**	**60 - 69**	**70 - 79**	**80+**
Cameroon	M		243.7	24.4	24			
	F		24.6	24.8	25			
Ethiopia	M	14.2	17.5	18.3	18	18	17.9	19.8
	F	14.5	18.9	18.6	17.3	16.7	17.6	18.6
Gambia	M		19.6	20.5	20.9	21	20	
	F		21	21.9	21.8	21.3	20.9	
Ghana	M							
	F		21.8	22.4	21.4			
Kenya	M							
	F		21.7	22.3	22			
Malawi	M				19.8	19.8	19.7	
	F				20.5	20.5	19.6	
Mali	M		18.9	20.5	20.8	20.3	19.6	20.2
	F		19.9	21.1	20.6	20	19.5	20.8
Nigeria	M		19.8	20.9	21.5			
	F		21	21.8	20.3			
Senegal	M		18.2	19.9	21	20.7	19.8	19.2
	F		19.6	21.4	22.1	22.2	21.3	20.7
Seychelles	M		22.9	23.5	23.1	23.2		
	F		23.2	25.7	27.2	27.5		
South Africa	M	13.8	21.5	24.2	25.3	24.8	24.4	
	F	14	24.4	28.5	29.9	28.8	27.7	
Tanzania	M							
	F		21.8	22.3	21.6			
Zimbabwe	M	15.3	19.5	20.8	21	21	20.1	20
	F	15.4	21.3	23	23.5	21.8	20.5	20.3

and South America.[18] In South Africa, where malnutrition, poverty and epidemic infectious disease are widespread, the problem of obesity could be viewed as less pressing. According to these current statistics, however, a significant problem of overnutrition in adults and young women exists; urban black women are at greatest risk.

Different abdominal fat regions may additionally confer differing risks, with evidence suggesting that abdominal visceral fat correlates more strongly with insulin resistance and markers of metabolic syndrome, whereas subcutaneous fat has a far lower risk profile. This observation was confirmed by Yamashita *et al.*[20]

In a study by Hartz *et al.*,[21] it was found that the relative risk of irregular menstruation and oligomenorrhoea in women with upper body fat predominance was 1.56 and 2.29 respectively, compared with women with lower body fat predominance.

Further studies are needed to distinguish between the effects of visceral and subcutaneous fat.

The link between obesity and infertility is complex. In addition to altered gonadotrophin levels, obese women exhibit varied reproductive hormone profiles;[22] they have increased serum androgen levels, especially testosterone and androstenedione, as well as reduced SHBG levels. Extensive work by Pasquali *et al.*,[23] Seidell *et al.*[24] and Holte *et al.*[25,26] demonstrated that abdominal fat is related to decreased SHBG and increased androgenicity.

Convincing evidence[23,25,27,28] exists to confirm the strong association between obesity, abdominal obesity and insulin resistance. Increased androgen production and reduced binding of androgens to SHBG contributes to hyperandrogenism, resulting in anovulation through inhibition of follicle maturation.

Work by Poretsky and Kalin[29] and by Plymate *et al.*[30] indicates that hyperinsulinaemia increases ovarian androgen production and decreases SHBG, with significant effect on PCOS. A study by Dunaif *et al.*[7] supported that insulin resistance is consistently documented in lean and obese women when compared with weight-matched controls. Obesity and abdominal obesity may therefore contribute to the already altered hormonal profile of women with PCOS, with a further increase in the prevalence of anovulation, menstrual irregularities and infertility.

Other systems affected

It has become apparent that PCOS is associated with multiple risk factors for cardiovascular disease. The risk factors include hypertension, dyslipidaemia,

coagulation abnormalities, endothelial dysfunction and hyperhomocysteinaemia.[31]

Bengtsson *et al*.[32] published their findings on lipid abnormalities in women with PCOS. This study took place in Gothenburg over 20 years and demonstrated that an increased serum triglyceride concentration and central obesity is associated with an increase in mortality. Work by Robinson *et al*.[33] and Wild[34] confirmed these findings that an abnormal lipid profile can ultimately influence morbidity in the long term.

Dahlgren[2] reviewed women with PCOS over a period of decades and found that hypertension was a common diagnosis among women with PCOS. Another study from Amsterdam[35] confirmed the presence of hypertension in women with PCOS and linked it to the presence of obesity in ageing women with PCOS.

Evidence has shown that disruption or alteration of coagulation and fibrinolytic factors in PCOS may affect cardiovascular risk. A study on endothelial function by Talbott *et al*.[36] suggested that endothelin-1, as an indicator of vasculopathy, is elevated in PCOS. Current opinion supports the view that plasminogen activator and vascular reactivity implicate PCOS in the evolution of cardiovascular disease.[37]

A buzzword of the new millennium was homocysteinaemia, and the work of Loverro *et al*.[38] published in 2002 demonstrated hyperhomocysteinaemia in women with PCOS, which may lead to increased risk for cardiovascular disease. Homocysteine levels appear to vary with ethnicity and correlate with insulin levels.[31] Diastolic dysfunction, in association with hyperhomocysteinaemia, are risk factors contributing to cardiovascular risk.[39]

Birdsall *et al*.[40] demonstrated clinical evidence of an association between cardiovascular disease and PCOS. In this study, women <60 years underwent coronary angiography, and 42% were found to have PCOS. These women also had associated hirsutism, increased testosterone and abnormal lipid profiles. The extent of their coronary artery disease was also far worse than that of unaffected patients. These results suggested that PCOS carries a risk for coronary artery disease. It remains important to be aware of these risk factors but to bear in mind that they do not have a predictive value.

Cancer risk

Women with PCOS have a risk of developing a hormone-dependent carcinoma.[41] Undoubtedly, they have an increased risk for endometrial carcinoma owing to unopposed oestrogen levels.[42] Risk for breast cancer and benign disease of the breast have not been confirmed.[43]

Dahlgren[2] and Hardiman *et al*.[44] advised that women known to have PCOS and subsequent anovulatory cycles should receive endometrial protection, and serial follow-up was advised to detect endometrial hyperplasia. Screening for endometrial hyperplasia has long been known to prevent progression to endometrial carcinoma. However, no good data are available to support the increased risk for breast cancer in women with PCOS. Most studies have failed to demonstrate a particular risk for breast cancer in these women with a hyperoestrogenic state.[45] Cattral and Healy[46] published a study, but their data did not support an increased risk for ovarian carcinoma in PCOS patients.

Management

The mainstay of therapy is to treat obesity. This statement implies adequate **weight loss** as a precursor to pharmacological intervention. Reduction of visceral and abdominal fat will result in an improvement of menstrual function and lessened infertility, resulting in decreased metabolic risks.[47] Insulin resistance will also be reduced.[26] Women with PCOS need to be treated properly, in their reproductive years as well as in the postmenopausal period.

Weight reduction is no easy task. One needs to be realistic in planning this strategy. Each patient should be treated individually. It is of utmost importance that the patient is co-operative and motivated. Most women with obesity have a psychosocial barrier and need to be treated with respect and understanding. They need to understand the reason for this initial therapy and how their general health will benefit when losing the desired amount of weight.

One question is: how much weight loss is the goal? Hollmann *et al*.[48] as well as Clark and co-workers[47,49] showed that only a small amount of weight loss is needed for resumption of ovulatory function. As little as 2 - 5% reduction of body weight was associated with restoration of ovarian function, an 11% reduction of abdominal fat, a 4 cm waist circumference reduction and the added benefit of a 71% increase in insulin sensitivity.[47,49] It is therefore not necessary to lose large amounts of weight to regain reproductive function, and one can use this as a motivational tool. Metabolic risks will decrease, and the patient should be encouraged to adopt a healthy lifestyle.

The World Health Organization (WHO) proposed a few strategies for weight loss.[11] Initial management should involve dietary changes to restrict energy intake. Physical activities should be increased, which will lead to a decrease in visceral fat that is usually not altered by diet alone.

Behaviour modification includes the discussion of social habits, with special reference to smoking and alcohol consumption. Reduction of psychosocial stressors should also be attempted. These principles were applied in the Fertility Fitness Programme in Adelaide, Australia,[45] a programme involving weekly dietetic and psychological intervention in a group and multi-team approach for 6 months, with remarkable success. Weight loss of 6.2 kg was associated with restoration of ovulation in 12 previously anovulatory women and pregnancy in 11 women. A decrease in insulin resistance and testosterone was also observed.

polycystic.indd 51 8/28/09 9:06:48 AM

The timeframe for patients to lose weight should be realistic and should be discussed with them. Wadden[50] showed in 1993 that short-term energy restriction can result in rapid weight loss with improvement of the reproductive symptoms – but 90% of women will regain the lost weight.

Lifestyle modifications are non-invasive and frequently successful, and should be the initial treatment. The NIH document[51] includes logical, multifaceted and easy-to-implement guidelines to assist in planning effective weight loss in patients with obesity (Table IV).

Pharmacotherapy and surgical options should only be considered if no success has been achieved with the above strategies.[52] Literature on the use of metformin to improve insulin sensitivity is becoming more available. Metformin acts primarily by inhibiting hepatic glucose output and increasing insulin sensitivity in peripheral tissues.[53] In PCOS, metformin improves insulin resistance but also improves ovarian function, regulates cycles, lowers androgen levels and leads to an improvement in clinical hyperandrogenism. Some evidence seems promising regarding improved long-term outcomes, but unfortunately the studies are of short duration.[54] For future recommendations, more evidence is still needed.

Natural progression of PCOS

Dahlgren[2] and Elting *et al*.[35] focused especially on the natural history of PCOS. From this information, it was learned that, towards menopause, resumption of menstrual cyclicity is often experienced. Androgen levels tend to fall and, with ovarian ageing and follicle loss, lower levels of inhibin B are present as well as an increase in follicle-stimulating hormone (FSH).[55] Despite these improvements in the reproductive system, metabolic risks remain a problem. These risks are related to obesity rather than menstrual cycle patterns. There is a trend for insulin resistance and hyperinsulinaemia to worsen over time, even in the presence of declining androgen levels.[56]

Conclusion

The importance of lifestyle modification, with weight loss as the mainstay of therapy, cannot be over-emphasised. Emotional support and the effectiveness of group therapy are of the utmost importance. Lifestyle modification remains the initial treatment of women with PCOS, with proven benefits in terms of fertility and metabolic risk reduction.

The mere diagnosis of PCOS in women, regardless of whether pregnancy is desired or not, is not sufficient. Any woman at any age with PCOS should be appropriately managed, informed and assessed for metabolic risks.

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Table IV. Guidelines for non-invasive lifestyle modifications[51]

Effective weight loss and long-term results – National Institute of Health Guidelines

- Sensible diet and changing eating habits for the long term
- Effective physical activity programme sustainable for the long term
- Behaviour modification, reduction of stress, improving well-being
- Combination of dietary and behaviour therapy and increased physical activity
- Social support by physician, family, spouse and peers
- Smoking cessation and reduction of alcohol consumption
- Avoidance of crash diets and short-term weight loss
- Minor roles for drugs involved in weight loss
- Avoidance of aggressive surgical approaches for the majority
- Adaption of weight loss programme to meet individual's needs
- Long-term observation, monitoring and encouragement of patients who have been successful

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polycystic.indd 53 8/28/09 9:06:49 AM