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## Polycystic Ovary Syndrome: Not Only a Gynaecological Disease

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### INTRODUCTION

Polycystic ovary syndrome (PCOS), first described by Stein and Leventhal in 1935, is now recognized as one of the most common gynaecological endocrine disorders in women of reproductive age. The overall prevalence is reported to be 6% to 8% in the general population, but the prevalence can be as high as 70% to 80% in women with oligo-amenorrhoea and 60% to 70% in women with anovulatory infertility.<sup>1</sup> Never-

theless, the diagnosis is frequently missed, and affected women are often treated symptomatically for 'irregular menses' without revelation of their underlying endocrine problem. The early diagnosis of PCOS is of paramount importance as accumulating evidence suggests that it is not only a gynaecological disease, but also equally important as a metabolic disorder.<sup>2</sup> It is therefore important for healthcare providers to understand the pathogenesis, diagnosis and treatment of the syndrome.

### CLINICAL HETEROGENEITY AND DIAGNOSTIC CONTROVERSY

PCOS is well recognized as a complex heterogeneous disorder characterized by a wide spectrum of clinical manifestations, including menstrual irregularities, anovulatory infertility, hyperandrogenic features and obesity. Until now, there has been no universally accepted definition of PCOS because of its clinical heterogeneity. The two most commonly accepted diagnostic criteria in clinical practice are listed in Table 1, and are based on the expert consensus at the 1990 National Institutes of Health-sponsored Conference on PCOS (NIH criteria) and the 2003 Rotterdam PCOS Consensus Workshop (Rotterdam criteria).<sup>3,4</sup> The old NIH criteria include both oligo-amenorrhoea/chronic anovulation and clinical/biochemical hyperandrogenism as the main diagnostic features, but have been criticized for not including the polycystic ovary morphology in the definition. The Rotterdam criteria broadened the definition and have been shown to identify more women with PCOS. In this new definition, a diagnosis of PCOS can be reached when at least two of these three elements are present: oligo-amenorrhoea/chronic anovulation; clinical/biochemical hyperandrogenism; and ultrasound appearance of polycystic ovaries. Both definitions require

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that other causes of hyperandrogenism and menstrual irregularities, such as Cushing's syndrome, nonclassical adrenal hyperplasia, androgen-secreting tumour, hypothyroidism and hyperprolactinaemia, have been excluded.

## MULTIFACTORIAL PATHOGENESIS

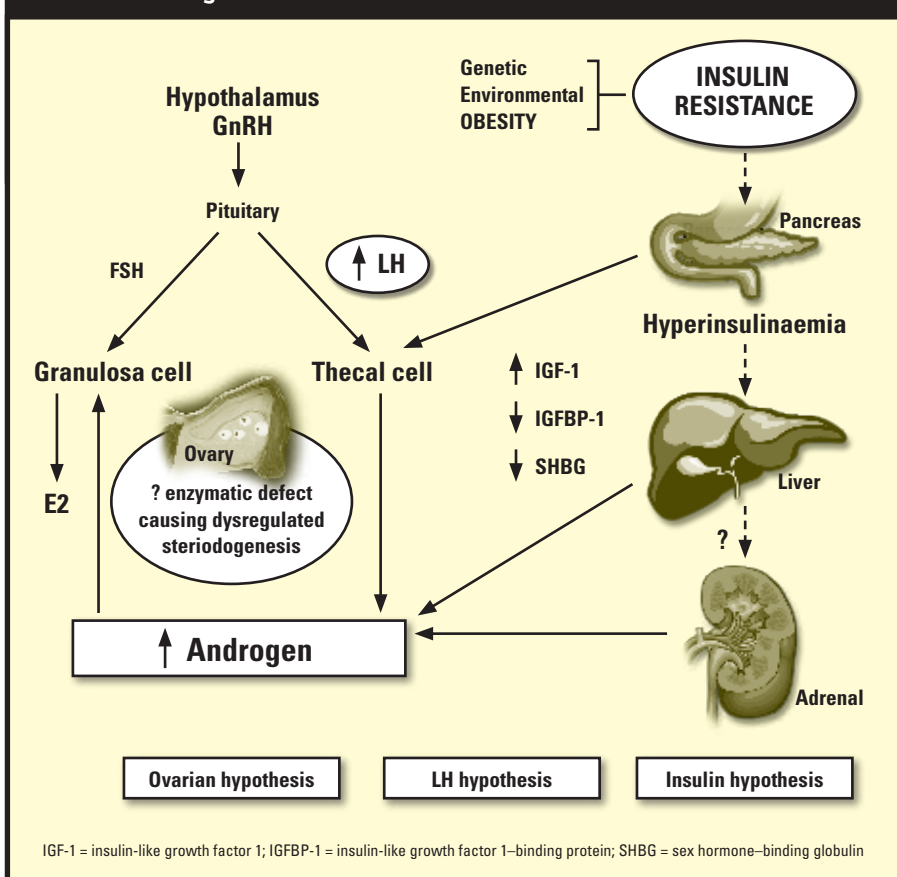
The pathogenesis of PCOS is still unclear but is thought to be multifactorial, consisting of endocrine, metabolic, genetic and envi-

ronmental factors. The syndrome's heterogeneity reinforces its multifactorial nature. Familial segregation of cases suggests a genetic component in this syndrome, but most of those genes have yet to be identified.<sup>5</sup> Despite its diverse phenotypes, hyperandrogenism and polycystic ovary morphology have been regarded as the two main cardinal features of PCOS.<sup>4</sup> It has been suggested that PCOS should primarily be regarded as a disorder of excessive androgen biosynthesis, use and metabolism. Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of androgen. Hyperandrogenism, however, may mediate through different mechanisms as illustrated in Figure 1. Three major pathophysiological pathways have been described, but they are not mutually exclusive. These include: (1) dysregulation of ovarian steroidogenesis (ovarian hypothesis); (2) disordered gonadotropin release (luteinizing hormone [LH] hypothesis); and (3) insulin resistance (insulin hypothesis).<sup>6</sup> Primary enzymatic defects of ovarian steroidogenesis have been found, which drive excessive androgen production. Hypersecretion of luteinizing hormone (LH) can also lead to an increase in androgen production by the ovarian thecal cells. Hyperinsulinaemia, besides stimulating excessive ovarian androgen production, also decreases liver production of sex hormone-binding globulin (SHBG), leading to an increase in the level of free androgen. Different pathophysiological mechanisms may predominate in different subjects, thus accounting for its clinical heterogeneity. Ethnicity also has a great impact on the presentation of PCOS, which is presumably related to the differences in genetic and environment factors.

**Table 1. The different diagnostic criteria for PCOS**

	1990 NIH criteria	2003 Rotterdam criteria
<b>Criteria</b>	<ul style="list-style-type: none"> <li>• Oligo-amenorrhoea/chronic anovulation</li> <li>• Clinical and/or biochemical hyperandrogenism</li> </ul>	<ul style="list-style-type: none"> <li>• Oligo-amenorrhoea/chronic anovulation</li> <li>• Clinical and/or biochemical hyperandrogenism</li> <li>• Ultrasound features of polycystic ovaries</li> </ul>
<b>Requirements</b>	Both criteria required after exclusion of other aetiologies	2 out of 3 criteria required after exclusion of other aetiologies

**Figure 1. The three major pathophysiological hypotheses to explain the clinical findings of PCOS**



## CLINICAL FEATURES AND COMPLICATIONS

### Reproductive Dysfunctions

The common clinical features of PCOS are summarized in Table 2. Anovulatory infertility is frequently the initial reason the patient presents for medical help. Although menstrual disturbance in terms of oligo-amenorrhoea is another common feature, this symptom is frequently neglected despite the long-term risk of development of endometrial hyperplasia and cancer due to chronic unopposed oestrogen stimulation.<sup>7</sup> It is also suggested that women with PCOS have an increased risk of miscarriage, gestational diabetes, pre-eclampsia and preterm labour.<sup>8</sup> The reasons for the adverse pregnancy outcomes are unclear, but hypersecretion of LH, hyperandrogenaemia and hyperinsulinaemia have all been postulated.

### Endocrine Abnormalities

Women with PCOS may have varying degrees and manifestations of androgen excess. The frequent manifestations are hirsutism, acne, and male-pattern hair loss. Among these, hirsutism is the commonest symptom and affects up to 70% of women with PCOS, although significant ethnic variation is present. The chin, upper lip, chest, lower abdomen and thighs are the common sites of excessive hair growth. Nevertheless, it is important to exclude other endocrine causes of hyperandrogenism, particularly in the presence of clinical virilization (eg, deepening of voice, breast atrophy, clitoromegaly) or markedly elevated serum androgen levels, given that hyperandrogenism may occasionally be a sign of a more serious medical problem and serum

<b>(A) Reproductive dysfunctions</b>
- Oligo-amenorrhoea
- Anovulatory infertility
- Pregnancy loss
<b>(B) Endocrine abnormalities</b>
- Hyperandrogenism
- Excessive luteinizing hormone secretion
<b>(C) Metabolic disturbances</b>
- Obesity
- Hypertension
- Disturbances of insulin and glucose metabolism
- Atherogenic lipid profile
- Dysfibrinolysis
<b>(D) Long-term complications</b>
- Endometrial hyperplasia/endometrial cancer
- Type 2 diabetes
- Possible atherogenic cardiovascular diseases

androgen levels are only modestly elevated in PCOS.

Another common endocrine abnormality associated with PCOS is excessive LH secretion, although serum follicular stimulating hormone (FSH) is usually normal. This may give rise to an elevated LH to FSH ratio in some patients, mostly in lean PCOS women.<sup>9</sup> However, it should be noted that measurements of LH are not always reliable because of the pulsatile nature of gonadotrophin secretion.

### Metabolic and Cardiovascular Risks

The recognition of insulin resistance as one of the major contributing factors to PCOS has led researchers to discover many of the cardiometabolic risk factors associated with PCOS.<sup>10,11</sup> These include central obesity, hypertension, glucose intolerance and atherogenic dyslipidaemia. Many of these are also key components of the metabolic syndrome. Meta-

bolic syndrome, which consists of a constellation of cardiovascular risk factors associated with insulin resistance, is a diagnostic entity which carries significant implications as it confers a five-fold increase in the risk of type 2 diabetes and a two-fold increase in the risk of atherosclerotic cardiovascular disease.<sup>12,13</sup> According to the 2005 modified Adult Treatment Panel III criteria proposed by the American Heart Association and the National Heart, Lung, and Blood Institute,<sup>13</sup> the diagnosis of metabolic syndrome requires three or more of the following abnormalities: (1) central obesity with waist circumference >80 cm in Asian women<sup>14</sup>; (2) elevated systolic and/or diastolic blood pressure >130/85 mm Hg; (3) increased fasting triglycerides >1.7 mmol/L; (4) reduced high-density lipoprotein cholesterol (HDL-C) <1.3 mmol/L; and (5) impaired fasting glucose >5.6 mmol/L. Although debate still continues regarding the clinical utility of establishing a diagnosis of metabolic syndrome and

whether the diagnosis confers risk that is above and beyond that conferred by its individual components, it is believed that establishing a diagnosis of metabolic syndrome would contribute towards the assessment of global cardiometabolic risk. The author has recently completed a cross-sectional study to evaluate the cardiometabolic risk factors in 295 Hong Kong Chinese women with PCOS whose mean age was 30 years. The prevalence of metabolic syndrome in this cohort was 24.9% despite their relatively young age, which was a five-fold increase in risk compared with women without PCOS even after controlling for age and BMI.<sup>15</sup>

The high prevalence of metabolic disturbances and the consequent increase in the long-term risk of type 2 diabetes and cardiovascular diseases indicates that PCOS should be considered as a general health problem. In a recent systemic review, it was estimated that the prevalence of impaired glucose tolerance (prediabetes) and type 2 diabetes was as high as 31% to 35% and 7.5% to 10%, respectively, in women with PCOS by their fourth decade,<sup>16</sup> and the risks were significantly higher at all ages and all weights even in young or lean subjects with PCOS. Although controversy still exists regarding the link to primary cardiovascular events such as stroke and myocardial infarction, due to the lack of long-term prospective studies, women with PCOS were shown to have increased carotid intima media thickness and coronary artery calcification, the two major surrogate markers for atherosclerotic cardiovascular disease.<sup>7</sup>

Obesity, which is found in approximately half of the women with PCOS, is itself an important cardiometabolic risk factor. However, it is important to note that although

metabolic derangements occur more often in obese PCOS women, non-obese subjects with PCOS also have features of insulin resistance which usually take the form of increased triglycerides and reduced HDL-C levels. This is consistent with the finding that women with PCOS, both lean and obese, were more insulin-resistant than their unaffected counterparts who were matched for BMI.<sup>17,18</sup> Lean PCOS women seem to have an intrinsic form of insulin resistance specific to the syndrome involving postbinding defects in insulin receptor signalling,<sup>19</sup> while obese PCOS women not only suffer from the insulin resistance intrinsic to PCOS, but also that associated with increased adiposity.<sup>20</sup>

## PATIENT EVALUATION

### Clinical Features

Healthcare providers should have a high index of suspicion when evaluating women with the above clinical features. The history should include a detailed inquiry on reproductive history, menstrual pattern, medical and drug history, symptoms of androgen excess, coexisting cardiovascular risk factors such as tobacco and alcohol use, physical inactivity, and family history of diabetes. The use of anti-epileptic drugs such as valproate should be explored as this has been shown to be associated with PCOS.<sup>21</sup> Clinical hyperandrogenism and acanthosis nigricans (a sign of insulin resistance) should be sought on examination. It is well recognized that despite hyperandrogenism being the most prominent diagnostic component of PCOS, reliable assessment of hyperandrogenism is difficult. Ferriman-Gallwey scoring is the method generally used to evaluate clinical hirsutism, but is limited by

the subjective variability and is affected by cosmetic treatments. Features of virilization and Cushing's syndrome should be looked for and excluded. Anthropometrical measurements including body weight (kg), body height (m), waist circumference and blood pressure assessment should be performed. Waist circumference is measured midway between the top of the iliac crest and the lower rib margin. Body mass index (BMI = kg/m<sup>2</sup>) and waist circumference should be used to assess obesity and central obesity using appropriate ethnic-specific definitions.<sup>14</sup>

### Ultrasound Features

Ultrasound examination is mandatory in women with suspicious features of PCOS as it is part of the diagnostic component. In a recent ASRM/ESHRE consensus meeting, the ultrasound appearances of polycystic ovary have been standardized as either the presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter, and/or increased ovarian volume of >10 mL.<sup>22</sup> Only one ovary with this appearance is sufficient to fulfil the definition. However, there are still some practical limitations. Firstly, detection of the ultrasound appearance of polycystic ovaries requires expertise and is sometimes operator-dependent. Secondly, transvaginal ultrasound scan is usually the method of choice, but is practically difficult in patients without previous sexual experience. Transabdominal ultrasound scan has poorer resolution, especially in obese subjects, and is a less sensitive method for evaluation.

### Biochemical Features

Laboratory assessment in women with PCOS should initially include appropriate endocrine

tests to achieve the diagnosis and to exclude other endocrine problems. Biochemical hyperandrogenaemia should be sought but may be limited by the inaccuracy and variability in the measurement of circulating androgen levels, particularly if total testosterone is the only measure. The free testosterone index, calculated by total testosterone divided by SHBG, is considered to be a more reliable marker for hyperandrogenaemia, but is not routinely performed because of the high cost of measuring SHBG. Other hormonal tests should include serum LH and FSH measurement performed at the early follicular phase of the menstrual cycle, as well as prolactin and thyroid function tests to exclude other causes of menstrual irregularities. Measurements of dehydroepiandrosterone sulphate and 17-hydroxyprogesterone, or even a low-dose dexamethasone test may occasionally be indicated if other causes of hyperandrogenaemia are suspected. Ovulatory assessment such as mid-luteal progesterone measurement is sometimes required in patients seeking infertility treatment. Monitoring of liver function is also suggested because of the association of nonalcoholic fatty liver with PCOS.<sup>23</sup>

Given the enormous evidence of increased metabolic risk, an oral glucose tolerance test (OGTT) and fasting lipid profiles – including serum concentrations of total cholesterol (TC), triglycerides (TG), HDL-C and low-density lipoprotein cholesterol (LDL-C) – should be performed in all women with PCOS, irrespective of age and weight. Although fasting glucose alone has been suggested as a more convenient method to assess glucose abnormalities, it has been shown to underestimate diabetes prevalence and cardiovascular risk when compared to the use of

**Table 3. Different treatment options for PCOS and their clinical indications**

	Ovulation induction	Menstrual irregularities	Hyperandrogenism	Hyperinsulinaemia
Clomiphene	✓			
Oral contraceptives		✓	✓	? Adverse effects
Cyclical progestogens		✓		
Antiandrogens			✓	
Insulin sensitizers	✓	? ✓	? ✓	✓

OGTT, particularly among obese subjects.<sup>24,25</sup> Controversy also continues regarding the clinical utility of assessing insulin resistance, as there is still no consensus on which is the best method for measurement and what is the ethnic-specific normal value. The hyperinsulinaemic-euglycaemic clamp technique is currently the gold standard for measuring insulin sensitivity, but is of little clinical use as it is labour-intensive, time-consuming and expensive. Homeostatic measurements such as fasting glucose to insulin ratio and insulin sensitivity indices derived from OGTT are potential surrogate markers for future office-based assessment of insulin resistance in women with PCOS.<sup>26</sup>

## TREATMENT

The various treatment options for PCOS are summarized in Table 3. Traditionally, treatment of PCOS is tailored to the presenting complaints of the patient, and usually focuses on short-term symptom control such as relief of menstrual disturbance or androgen excess, or treatment of infertility. With increasing awareness of its long-term health consequences, it is evident that evaluation and therapy for PCOS should go beyond the

target of short-term symptom control to the early screening and long-term prevention of cardiovascular risks.

## Lifestyle Interventions

Lifestyle interventions are universally recommended, and these should include advice on diet, exercise, weight reduction and smoking cessation. Obesity, through its associated adiposity and insulin resistance, exacerbates the metabolic risks and has profound effects on the clinical manifestations of PCOS. Weight reduction in obese PCOS women will not only improve quality of life, but also correct hyperinsulinaemia and improve fertility as well as lipid and androgen profiles.<sup>27</sup> Although long-term adherence may be a challenge, these women should be made aware that lifestyle modifications are the mainstay in reducing cardiometabolic risks and preventing serious health consequences.

## Treatment of Menstrual Disturbances and Prevention of Endometrial Hyperplasia

Oligo-amenorrhoea is a common feature in PCOS but is often neglected in women with no fertility desire. Regular induction of withdrawal bleeding with either oral

contraceptives or cyclical progestogens is, however, advisable to protect the endometrium from development of endometrial hyperplasia and cancer due to chronic unopposed oestrogen stimulation. Oral contraceptive therapy is currently the mainstay of treatment as it can be used not only for menstrual regulation, but also for amelioration of hirsutism and acne through its androgen-lowering effect. However, there is much debate on whether oral contraceptives may decrease insulin sensitivity, induce glucose intolerance and aggravate metabolic derangements in women with PCOS who are already at high metabolic risk.<sup>28</sup> Alternatively, in oligo-amenorrhoeic women with PCOS who already have clinical manifestation of metabolic disturbances such as obesity or glucose intolerance, cyclical progestogen therapy or a progestogen implant can also provide cycle control and endometrial protection, although they have no therapeutic effect on hyperandrogenic symptoms.

### Treatment of Androgen Excess

Besides local cosmetic measures, oral contraceptive therapy is commonly used to suppress LH and androgen levels in women with PCOS with resultant improvement in hyperandrogenic symptoms. The most common choice of contraceptive pill is one that contains cyproterone acetate (a synthetic progestogen with antiandrogen effects), such as Diane®. In addition to oral contraceptives, antiandrogens such as spironolactone and flutamide are sometimes required for a substantial improvement in hirsutism. These drugs can only be used in women with adequate contraception owing to their potential teratogenicity.

### Ovulation Induction for Treatment of Anovulatory Infertility

Apart from weight reduction in obese patients, antioestrogen therapy such as clomiphene is the first-line treatment for ovulation induction in women with PCOS and anovulatory infertility. The starting dose of clomiphene is 50 mg per day for 5 days from day 3 to day 7 (or day 5 to day 9) of each cycle. The dosage can be increased in monthly increments up to 150 mg per day if the woman does not respond to lower doses. A possible association of antioestrogens and ovarian cancer has been described for the long-term user. Therefore, clomiphene should be prescribed at the minimum effective dose, and early referral to specialist infertility centres should be considered if patients are still anovulatory at the maximum dosage (clomiphene resistance) or if there is failure to conceive after 6 to 12 ovulatory cycles (clomiphene failure).

The alternatives for PCOS women with failed clomiphene treatment are metformin, laparoscopic ovarian drilling or gonadotrophins. Insulin sensitizers such as metformin are a new class of drugs utilized in the treatment of PCOS and have promising results both in the short-term aiding of infertility treatment and, possibly, in the reduction of long-term cardiometabolic risks. The use of metformin as a cotreatment with clomiphene has been shown to improve ovulation in women with clomiphene-resistant PCOS.<sup>29</sup> However, clomiphene is still superior to metformin as first-choice treatment for therapy-naïve PCOS patients in achieving a live birth despite the higher risk of a multiple pregnancy.<sup>30</sup> Alternatively, laparoscopic ovarian drilling, either alone

or in conjunction with clomiphene, is also shown to be effective in inducing ovulation in 50% to 90% of women with PCOS.<sup>31,32</sup> Its beneficial effects, however, may only be short term, and the potential ovarian damage associated with the procedure has yet to be evaluated. Ovulation induction with gonadotrophins also provides a good cumulative chance of pregnancy for up to six cycles, but the patient should be warned of the higher risk of ovarian hyperstimulation and a multiple pregnancy.

### Insulin Sensitizers

Medical therapies which address insulin resistance in PCOS were extensively studied in the past decade, and the preliminary results are promising, particularly when used as an adjunctive therapy for ovulation induction in PCOS women with anovulatory infertility. Insulin sensitizers such as metformin help women with PCOS to normalize insulin and glucose, induce ovulation, and to a lesser extent, may improve menstrual irregularities and ameliorate androgenic symptoms. Metformin also improves the unfavourable metabolic profile of women with PCOS, and may reduce their long-term cardiometabolic risks. The detailed discussion of the use of insulin sensitizers in the management of PCOS is beyond the scope of this article. These studies have been summarized in several reviews and meta-analyses.<sup>29,33,34</sup> Although further research is still needed to clarify their clinical indications and specific target subgroups, identification of patients who are at increased risk of the metabolic sequelae of PCOS may allow better selection of patients who are most likely to respond to treatment with insulin-sensitizing drugs. In addition, studies to date have only

addressed the short-term efficacy of insulin sensitizers in PCOS, and evidence for their long-term safety and efficacy in nondiabetic PCOS patients is still lacking. Well-designed long-term prospective studies in this area are urgently needed.

## CONCLUSION

The diagnosis of PCOS has life-long implications with increased risk of metabolic syndrome, type 2 diabetes mellitus, and

possibly cardiovascular disease. Evaluation and therapy for PCOS should, therefore, not only focus on its endocrine abnormalities or reproductive dysfunctions, but also on the comorbidities associated with its metabolic consequences. Women diagnosed with PCOS should be offered regular screening for cardiometabolic risks, which should comprise of anthropometric and blood pressure measurements, fasting lipids and oral glucose tolerance test. They should be given advice on the importance of weight reduction

and lifestyle modifications on diet, exercise and smoking cessation. Structured multidisciplinary approaches to this common, multifaceted condition are required in order to prevent and reduce its long-term health risks.

## About the Author

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CME Article:

## Polycystic Ovary Syndrome: Not Only a Gynaecological Disease

Answer True or False to the questions below.

	True	False
1. Women presenting with oligo-amenorrhoea should be asked about the signs and symptoms of androgen excess and have a pelvic ultrasound examination.	<input type="radio"/>	<input type="radio"/>
2. Oligo-amenorrhoea associated with PCOS is often neglected despite the risk of long-term development of endometrial hyperplasia and cancer.	<input type="radio"/>	<input type="radio"/>
3. Serum luteinizing hormone is always raised in women with PCOS.	<input type="radio"/>	<input type="radio"/>
4. Biochemical evidence of hyperandrogenaemia and elevated luteinizing hormone are both required for the diagnosis of PCOS.	<input type="radio"/>	<input type="radio"/>
5. The key underlying abnormality that leads to long-term health risk in PCOS appears to be insulin resistance.	<input type="radio"/>	<input type="radio"/>
6. Women with PCOS are predisposed to many cardiometabolic risk factors, including central obesity, hypertension and lipid and glucose abnormalities, which subject them to an increased risk of metabolic syndrome and the long-term risk of developing type 2 diabetes and cardiovascular diseases.	<input type="radio"/>	<input type="radio"/>
7. Thromboembolism is a recognized complication of PCOS.	<input type="radio"/>	<input type="radio"/>
8. Although the presence of obesity exacerbates the insulin resistance state associated with PCOS, even lean subjects with PCOS have features of insulin resistance compared to BMI-matched controls.	<input type="radio"/>	<input type="radio"/>
9. In addition to the reduction of metabolic risks, weight reduction in obese PCOS women has been shown to normalize reproductive outcomes and hyperandrogenism.	<input type="radio"/>	<input type="radio"/>
10. Insulin sensitizers such as metformin may be used as a cotreatment with clomiphene to improve ovulation in women with clomiphene-resistant PCOS.	<input type="radio"/>	<input type="radio"/>

T	T	T	F	T	T	F	F	T	T
1	2	3	4	5	6	7	8	9	10
<b>ANSWERS</b>									

This *JPOG* article has been accredited for CME by the Hong Kong College of Obstetricians and Gynaecologists.

## Instructions

1. For each true/false question, please indicate your answer by ticking (✓) the appropriate box on the answer sheet. Erase/whiteout mistakes fully.
2. **Post your answer sheet to:** the Secretariat, Hong Kong College of Obstetricians & Gynaecologists, Room 805, Hong Kong Academy of Medicine Jockey Club Building, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong.
3. Your answer must reach The Secretariat by **31 July 2008**.

CME Points: 1.0 1 Point

## Polycystic Ovary Syndrome: Not Only a Gynaecological Disease

May/Jun 2008 Vol. 34 No. 3

	True	False
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Name in BLOCK CAPITALS: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

### CME Answers for *JPOG* Mar/Apr 2008

**HKCOG CME Article:**  
Antepartum Haemorrhage of Unexplained Origin –  
Can it be Explained?

ANSWERS									
1	2	3	4	5	6	7	8	9	10
T	T	T	F	T	F	F	F	T	F