PCOS and thromboembolism: a complex case

SALLY M. REID MB BS
ROBERT J. NORMAN MD, FRANZCOG, FRCPA, CREI

What are the diagnostic criteria for polycystic ovarian syndrome (PCOS) and should treatment with the oral contraceptive pill continue following a thromboembolism?

Case scenario

Miss KK, a 16-year-old girl, presents four years after menarche with weight gain, severe cystic acne and distressing dark hair growth on her chin, chest and arms. She describes oligomenorrhoea (>35 days between menses) and she is not sexually active. Past medical history includes mild asthma, for which she takes terbutaline. She is emotionally well balanced. There is a significant family history of type 2 diabetes and no family history of thromboembolism or thrombophilia.

On examination, Miss KK has a BMI of 28 kg/m^2 and normal blood pressure. There are no cushingoid features or acanthosis nigricans. The cardiovascular, thyroid and abdominal examinations are unremarkable. She has a Ferriman-Gallwey score (which is a clinical score of hirsutism) of 12. The Table shows the investigation results.

How do we manage this patient?

Miss KK meets all three of the Rotterdam diagnostic criteria for polycystic ovarian syndrome (PCOS) as shown in the box on page 44. This syndrome of multifactorial origin encompasses clinical and/or biochemical hyperandrogenism, hyperinsulinaemia, anovulation and polycystic ovaries. It should be noted that there is concern regarding the overdiagnosis of this syndrome in adolescents because they are physiologically prone to acne and irregular menses. Alternative criteria to the Rotterdam and the US National Institutes of Health criteria for PCOS in adolescents

Figure. Severe cystic acne in a 16-year-old girl.

Key points

- **Polycystic ovarian syndrome (PCOS) encompasses clinical and/or biochemical hyperandrogenism, hyperinsulinaemia, anovulation and polycystic ovaries.**
- **The cornerstone of PCOS management is education on the immediate and future effects of this condition, with an emphasis on the positive benefits of a healthy lifestyle.**
- **The oral contraceptive pill is a safe, effective treatment for patients with acne, hirsutism and menstrual irregularities.**
- **Although use of the oral contraception pill is contraindicated in the setting of acute venous thromboembolism, its later use may be reconsidered after a thorough assessment of the risks and benefits and full informed consent.**

ENDOCRINOLOGY TODAY 2012; 1(1): 43-45

Dr Reid is a Senior Obstetrics and Gynaecology Registrar at the Women's & Children's Hospital, Adelaide. Professor Norman is a Professor in Obstetrics, Gynaecology and Reproductive Medicine and the Director of The Robinson Institute at the University of Adelaide, and a Senior Consultant at the Women's Health Centre, the Royal Adelaide Hospital, Adelaide, SA.

Table. The patient's test results

Investigations	Results (normal ranges)
Pelvic ultrasound (transabdominal)	>12 follicles of <9 mm peripherally in both ovaries Endometrial thickness 9 mm
Follicle stimulating hormone	4.9 IU/L (4–10 IU/L follicular/luteal)
Luteinising hormone	7 IU/L (1–12 IU/L follicular/luteal)
Oestradiol	188 pmol/L (150–600 pmol/L follicular/ 150–850 pmol/L luteal)
17-hydroxyprogesterone (early morning, follicular)	3 nmol/L (0.2–4.4 nmol/L follicular/ 0.5–11.3 nmol/L luteal)
Androgens Total testosterone Calculated free testosterone Sex hormone binding globulin Free androgen index Dehydroepiandrosterone sulfate (DHEAS)	 2.0 nmol/L (0–1.8 nmol/L) 41 pmol/L (1–34 pmol/L) 19 nmol/L (30–110 nmol/L) 10.7% (0.4–6%) 9.9 nmol/L (2–11 nmol/L)
Thyroid stimulating hormone	1.5 mIU/L (0.5–5 mIU/L)
Prolactin	284 mIU/L (85–500 mIU/L)
Fasting plasma glucose	5.4 mmol/L (<7.8 mmol/L)
Lipid profile, fasting Total cholesterol Triglycerides High-density lipoprotein cholesterol Low-density lipoprotein cholesterol (calculated)	 3.7 mmol/L (<5.5 mmol/L) 0.7 mmol/L (0.3–2.0 mmol/L) 1.6 mmol/L (1.0–2.2 mmol/L) 1.8 mmol/L (<3.7 mmol/L)

have been proposed, but as yet there has been no consensus.[1]

The importance of lifestyle management for PCOS should be emphasised to Miss KK. In particular, healthy food choices and aerobic exercise for at least 150 minutes per week should be recommended.[2] Exercise improves insulin sensitivity, increases ovulation and allows weight loss.

The oral contraceptive pill (OCP) is a safe, effective therapy for women with PCOS, providing both symptomatic and menstrual control. Contraindications such as migraine with aura and severe liver disease should be excluded. Cyproterone acetate, an antiandrogenic progestogen, is a particularly effective form of treatment for acne and hirsutism.[3]

In addition, topical therapies for acne can be recommended and it would be prudent to refer Miss KK to a dermatologist. Management of hirsutism takes up to six months because of the hair growth cycle, but if hormonal treatment is suboptimal, treatment with electrolysis or laser hair removal could be considered.

Case scenario continued

Miss KK's androgenic symptoms improve greatly after commencing the OCP (ethinyloestradiol and cyproterone acetate). At 18 years of age she has a regular menstrual cycle and has maintained a healthy weight. She exercises for an hour every day and her diet is well balanced, having a regular breakfast, healthy snacks and avoiding soft drinks and fruit juice.

A month later, however, Miss KK sustains a fractured left femur in a car accident. Two weeks after her surgery, she presents with severe pain in her left leg. Duplex ultrasound reveals an occlusive thrombus within the popliteal vein.

How should this complication be managed?

Miss KK is commenced on appropriate anticoagulation for six months and the OCP is ceased. Clearly, Miss KK's thrombosis has occurred in the context of a transient risk factor and hormonal provocation of thrombosis would usually occur within the first

year of use of the OCP. Regardless, most clinicians would recommend cessation of the OCP in the setting of a thromboembolism.

The risk of venous thromboembolism with a standard dose OCP (e.g. 30 to 35 µg ethinyloestradiol plus levonorgestrel) has been estimated at 15 per 100,000 patient-years.[4] Cyproterone acetate is associated with a higher incidence of thromboembolism compared with levonorgestrel.[5] This rate, however, is comparable with the risk of thromboembolism during pregnancy and it should be noted that the absolute risk of this event during pregnancy is still low at about 60 per 100,000 patient-years.

A thrombophilia screen should be recommended for Miss KK and alternative treatments for PCOS sought. The insulin-sensitising medication metformin has been widely studied and has quite a reassuring safety profile. By decreasing insulin resistance, metformin reduces ovarian androgen production. Metabolic health improves, although beneficial clinical outcomes in the features of PCOS are modest at best. In particular, control of menses and hirsuitism is often suboptimal with the use of metformin. Obviously metformin is not a contraceptive and it is prescribed off-label for PCOS, which the patient should be made aware of. Some people will develop vitamin B_{12} deficiency while taking long-term metformin and this parameter should ideally be intermittently monitored (e.g. at baseline and every one to two years).

Diagnostic criteria for PCOS

Rotterdam diagnostic criteria

Requires two of the following:

- Oligoanovulation or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries and exclusion of other aetiologies, such as hypothyroidism, hyperprolactinaemia, congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome

US National Institutes of Health diagnostic criteria

Requires both of the following:

- Oligo-anovulation or anovulation
- Clinical and/or biochemical signs of hyperandrogenism, and exclusion of other aetiologies, such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome

Case scenario continued

For the next two years, Miss KK maintains a healthy weight while taking metformin (1 g twice daily, slow release) with minimal gastrointestinal side effects. She now presents, however, with annoying irregular bleeding, hirsutism despite laser therapy and moderate-to-severe cystic acne. She is using erythromycin gel and has tried two courses of oral isotretinoin, but her acne has recurred and is having quite an impact on her self-esteem. She has not experienced a recurrence of her deep vein thrombosis and her thrombophilia screen was unremarkable, with the exception of being heterozygous for the methylenetetrahydrofolate reductase (MTHFR) *gene mutation (C>T). She is very keen to recommence the OCP, both for contraception and symptom control.*

Could use of the OCP be reconsidered?

In this situation, hormonal treatment has provided Miss KK with the greatest improvement in her symptoms. There are other pharmacological options for hirsutism, such as spironolactone, but these are relatively ineffective and the OCP offers a comprehensive solution to her clinical presentation.

It would be important to initiate a risk/benefit discussion, exclude other risk factors for thromboembolism and seek the opinion of a physician or haematologist. In the case of Miss KK, her deep vein thrombosis was most likely the result of a transient risk factor (her fracture/immobility) and the risk of recurrence would be very low. The clinical impact and management of her *MTHFR* gene variation remains controversial and the association with arterial thromboembolism is more widely accepted compared with venous thromboembolism. Adequate folate intake should be ensured.

Using the lowest dose of oestrogen would be judicious, as clinically all low-dose formulations produce a similar improvement in androgenic symptoms when compared with higher-dose formulations.[6] Some concern has been expressed about use of the OCP aggravating insulin resistance in women with PCOS.[7]

Conclusion

This case illustrates that optimal management of PCOS is holistic and that it is essential to individualise treatment. Although use of the OCP is contraindicated in the setting of acute venous thromboembolism, its later use may be re-considered after a thorough assessment of the risks and benefits. Close monitoring, patient awareness of reportable symptoms and full consent is recommended. **ET**

References

1. Sultan C, Paris F. Clinical expression of polycystic ovary syndrome in adolescent girls. Fertil Steril. 2006; 86, Suppl 1: S6.
2. Teede H, Misso M, Deeks A, et al. Assessment and management of polycystic ovarian syndrome: summary of an evidence-based guideline. Med J Aust 2011; 195(6): S65.
3. Franks S, Layton A, Glasier A. Cyproterone acetate/ethinylestradiol for acne and hirsutism: time to revise prescribing policy. Hum Reprod 2008; 23: 231-232.
4. Bochner F. Australian Medicines Handbook (AMH) Adelaide: Newstyle Printing; 2008.
5. Martinez F, Ramirez I, Perez-Campos E, Latorre K, Lete I. Venous and pulmonary thromboembolism and combined hormonal contraceptives. Systematic review and meta-analysis. Eur J Contracept Reprod Health Care 2012; 17: 7-29.
6. Speroff L, Fritz MA. Clinical Gynecologic Endocrinology and Infertility. 8th edition. Philadelphia: Lippincott Williams & Wilkins; 2011.
7. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovarian syndrome. Lancet 2007; 370: 685-697.

COMPETING INTERESTS: None. The views expressed are purely those of the authors.