

Case Studies – Individuals

Infertility in a young woman with Type 2 diabetes

Romana Szaboova

Foundation Trainee, Royal Free Hospital, London, UK

Senan Devendra

Consultant Physician in Acute Medicine & Endocrinology, West Hertfordshire Hospitals NHS Trust, UK

Key messages

- Ovulatory dysfunction is the most common female cause of infertility in the UK.
- Polycystic ovarian syndrome is associated with oligo-ovulation and Type 2 diabetes.
- Good glycaemic control is essential before getting pregnant to prevent congenital malformations and miscarriages in young women with Type 2 diabetes.
- Metformin is safe in the first trimester and reduces the rate of miscarriages and gestational diabetes.
- Labetalol, methyl dopa and hydralazine are deemed safer in pregnancy.
- Women should not conceive on statins due their potential teratogenic effects.

Why this matters to me

Polycystic ovarian syndrome (PCOS) is a frequently encountered condition in general practice and can have a significant impact on the quality of life of young women. Apart from addressing ovulatory problems in these women, it is important to remember to screen for other associated conditions such as Type 2 diabetes, hypertension or hypercholesterolaemia. This article outlines the pathophysiology of PCOS and its diagnostic pathways and also summarises the safety of medical management for the metabolic complications in pregnant women. It is important for healthcare professionals to be aware of the latest guidance for treatment of PCOS in order to provide high-standard evidence-based care.

Keywords: hypertension, infertility, PCOS, type 2 diabetes

Case history

A 33-year-old teacher (BMI 28 kg/m²) saw her general practitioner (GP) due to primary infertility. She was previously fit and healthy apart from a history of hirsutism which had been treated by laser therapy in her 20s. As part of her initial diagnostic work-up, she was identified to have Type 2 diabetes and polycystic ovaries on a transvaginal ultrasound scan. Her recent HbA_{1c} was 7.7% (DCCT) (IFCC 60.7 mmol/mol). She was referred to a structured education programme and a dietician. She was also started on metformin and the dose was gradually increased to 2 g/day. Her total cholesterol was 6.2 mmol/l and her blood pressure was 144/86 mmHg. Her case was brought to the Ealing multidisciplinary group meeting for further discussion.

Ways to think about the problem

What is the likely cause of her infertility?

In the UK, approximately one in seven heterosexual couples experience problems conceiving and investigations reveal a cause in 75% of these. The most frequent causes of subfertility are outlined in Table 1. Male causes of subfertility are mainly detected by semen analysis and testing for sexually transmitted infections (STI). In women, the routine investigations would include a transvaginal ultrasound scan, follicle-stimulating hormone (FSH) and Luteinising hormone (LH) levels, day 21 progesterone level, STI checks and, if necessary, more invasive procedures such as an

Table 1 Male and female causes of infertility in the UK.¹

Cause	Frequency (%)
Female factors	
Ovulatory dysfunction (e.g. PCOS, hyperprolactinaemia, advanced age, thyroid disease, primary ovarian insufficiency)	25
Tubal damage	20
Uterine or peritoneal disorders (e.g. endometriosis, fibroids)	10
Male factors	
Abnormal semen production or transport (e.g. genetic defects, surgery, infection, retrograde ejaculation)	30
Combined male and female factors	40
Unexplained fertility	25

hysterosalpingogram or laparoscopy. Fertility problems affecting both the man and the woman are detected in 40% of couples with conception problems.¹

This young woman has infertility associated with Type 2 diabetes, high BMI and polycystic ovaries. The most likely diagnosis would be polycystic ovarian syndrome (PCOS), causing oligo-ovulation and metabolic disturbance.

What is the definition and pathophysiology of PCOS?

PCOS affects 6–7% of women of reproductive age and the cause is thought to be multifactorial. The PCOS Society revised the diagnostic criteria for PCOS in 2006.² PCOS is diagnosed when all of the following criteria apply:

- ovarian dysfunction (oligo-ovulation or polycystic ovaries on an ultrasound scan);
- clinical or biochemical hyperandrogenism;
- other related disorders associated with hyperandrogenism are excluded (e.g. Cushing's syndrome).

PCOS occurs when there is peripheral insulin insensitivity and subsequent hyperinsulinaemia, which together with elevated LH act on ovarian theca cells and lead to increased androgen production. Elevated androgen levels prevent normal follicular maturation, causing infertility. Hyperinsulinaemia often leads to Type 2 diabetes mellitus and metabolic syndrome, increasing the risk of cardiovascular disease. Apart from addressing the fertility problems associated with PCOS, regular screening for cardio-

vascular risk factors is essential, including measurements of blood pressure, waist circumference, BMI and lipid profile.

Would you treat her elevated blood pressure and cholesterol?

If there is persistently elevated blood pressure requiring oral antihypertensive therapy, the pregnancy status of the patient needs to be checked. The standard first line oral antihypertensive medication in a young patient would be an angiotensin-converting enzyme (ACE) inhibitor, but it is avoided in pregnancy because it impairs fetal and neonatal renal function causing oligohydramnios, hypotension and possibly death in utero.³ Diuretics are also avoided because they reduce the placental blood flow. The antihypertensives considered safe in pregnancy are labetalol, methyldopa or hydralazine.³

Hypercholesterolaemia is primarily managed by lifestyle changes including healthy diet and exercise. A referral to a dietician could be beneficial as well. Statins are generally avoided if the patient is trying to get pregnant due to their potential teratogenic effects on the fetus.

Is metformin safe if she becomes pregnant?

Metformin has not been shown to have any major adverse effects on the fetus if it is taken in the first trimester of pregnancy, based on a meta-analysis of eight small studies.⁴ However, no large-scale randomised controlled trials have been performed. The National Institute for Health and Care Excellence

(NICE) recommends that metformin and glibenclamide can be used during pregnancy, but only if the benefit of an improved glycaemic control outweighs the potential risk on the fetus.⁵ For example, in women with PCOS, the use of metformin has been shown to reduce the number of early pregnancy miscarriages and reduces the possibility of gestational diabetes. Other oral hypoglycaemic agents such as sulfonylurea (gliclazide), glitazones (pioglitazone, rosiglitazone), acarbose, sodium-like glucose transporters-2 inhibitors (dapaglifozin, canaglifozin) and meglitinides (repaglinide) should be avoided in pregnancy and instead insulin should be used.⁶

Would you advise her to get pregnant if her HbA_{1c} is above 7.5%?

It is not advisable for this patient to get pregnant with HbA_{1c} of 7.7% due to a higher rate of congenital malformations and an increased risk of first trimester miscarriage associated with poor glycaemic control.^{7,8} NICE guidelines state that the HbA_{1c} level should be below 6.1% for a safe pregnancy to occur. Pregnancy is not recommended if the level is above 10%. Any reduction of HbA_{1c} towards 6.1% would help to reduce the risk of congenital malformations.⁵ A combined approach of weight loss, healthy diet, exercise programme and, if necessary, a hypoglycaemic agent (such as metformin) would help lower her blood sugar levels and improve fertility.

Progress and outcome of the case

After four months on metformin therapy and attempts to reduce her weight by adhering to a strict diet, the patient's HbA_{1c} improved to 6.4%. Her 24-h ambulatory blood pressure revealed a mean systolic pressure of 126 mmHg and diastolic of 78 mmHg, therefore meaning she was not started on any anti-hypertensive medications. She was referred to the local fertility centre for further investigations and management of her infertility.

CONFLICTS OF INTEREST

The authors are not aware of any conflicts of interest.

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ADDRESS FOR CORRESPONDENCE

Senan Devendra
Consultants Office
Level 3 AAU
Watford General Hospital
Watford WD18 0HB
UK
E-mail: ddevendra@nhs.net

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