CASE REPORT

21st century obstetrics: a 50-year-old nullip—walk in the park?

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SUMMARY

We discuss the case of a 50-year-old nulliparous woman who conceived after *in vitro* fertilisation. She had multiple medical comorbidities and presented an obstetric and medical challenge. She was carefully managed through pregnancy and had a successful outcome. In this report, we explore the medical complexity, as well as ethical and logistic issues involved.

BACKGROUND

Sustained advances in all realms of medicine into the 21st century have been accompanied by rising life expectancy in those with multiple comorbidities, advanced maternal age and widespread availability of assisted reproductive technology.¹ This has been paralleled by the pandemic of obesity, and closely linked with it, diabetes and related morbidity.² A combination of these factors produces a new genre of patients posing obstetric challenges not faced by our predecessors. We present a case that illustrates the complexity we are likely to encounter more often as we progress through this century. Furthermore, this case highlights important ethical and logistic issues alongside the medical implications.

CASE PRESENTATION

The patient was a 50-year-old gravida 2, para 0, with one previous first-trimester miscarriage 20 years ago. She had conceived after her 11th attempt of *in vitro* fertilisation (IVF) following egg donation abroad and returned to the UK for antenatal care. Having been diagnosed with type 1 diabetes mellitus at 11 years of age, the patient had a long period of suboptimal glycaemic control, partially contributed to by her body mass index (BMI). At 40 years of age, she developed macroscopic proteinuria and systemic hypertension, with a trend towards declining renal function in the years prior to conception. Preconception, the patient was on ACE inhibitors for control of hypertension. She was diagnosed with background retinopathy at 46 years of age and developed several ophthalmic complications secondary to poor glycaemic control including granulomatous uveitis, cataract and proliferative retinopathy, all of which were treated. At the start of pregnancy, she had stable R3 retinopathy in the right eye and R1 retinopathy in the left eye. Few years prior to conception, the patient also developed neuropathy which manifested as a chilling sensation through her spine. She was on pregabalin prior to pregnancy for symptom control. In her

mid-40s, while she was still anxious to conceive, the patient had a BMI of 36 kg/m² and underwent sleeve gastrectomy. While this helped her with weight reduction and blood sugar control, it resulted in significant worsening of her retinopathy about which she was counselled preoperatively. She had contracted hepatitis B at 11 years of age and was now a chronic hepatitis B carrier.

At the start of pregnancy, the patient had a BMI of 25.5 kg/m². Her antihypertensive medication was changed to labetalol and nifedipine. The pregabalin was stopped and she was given a higher dose of folic acid.

INVESTIGATIONS

The patient had a glycated haemoglobin of 36.6 mmol/mol (normal range 20–42) in the first trimester. Other results at booking were a serum creatinine of 89 µmol/L (normal range 49–92), glomerular filtration rate (GFR) of 61 mL/min (normal range >90) and urine protein creatinine ratio (PCR) of 30 mg/mmol (normal range 0–30). Ultrasound done at 12 weeks was normal as were serum screening for Down's syndrome and the anomaly scan at 20 weeks. A fetal echocardiogram done at 22 weeks did not reveal any abnormality. Serial fetal growth scans were done from 24 weeks' gestation.

DIFFERENTIAL DIAGNOSIS

In the background of pre-existing hypertension and nephropathy, it was difficult to make a diagnosis of superimposed pre-eclampsia which this patient was likely to develop and would significantly affect management.

TREATMENT

This patient received multidisciplinary care from the start of pregnancy. She was managed by a team involving an obstetrician, endocrinologist, nephrologist, diabetic nurse/midwife, hepatologist, ophthalmologist and haematologist with subsequent involvement of the anaesthetist and neonatologist. She was counselled about the risks of deteriorating retinopathy and renal function including long-term need for dialysis or renal transplant. She was commenced on antenatal thromboprophylaxis with low-molecular-weight heparin in view of her age, nephropathy and comorbidities with the plan to continue it for 6 weeks postnatally. Aspirin was considered, but the patient had severe gastritis following the bariatric surgery possibly

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compounded by a degree of autonomic neuropathy and could not tolerate it. Her glycaemic control was difficult and she developed several episodes of hypoglycaemia and hyperglycaemia in the first half of pregnancy which required close monitoring and titration of insulin dose. She also developed a systolic hypertension of 200 mm Hg at 16 weeks' gestation for which she required intravenous labetalol and care in the high dependency unit. Blood pressure was subsequently controlled with a combination of nifedipine and labetalol. She developed herpes zoster at 26 weeks' gestation and was managed with aciclovir. Apart from these episodes when she required inpatient monitoring, she was managed in an outpatient setting with antenatal clinic appointments fortnightly until 24 weeks' gestation and more frequently thereafter, being seen by relevant specialties. Additional midwifery input provided social and emotional support required in her circumstances. While at this stage, one might expect the neuropathy to be an insignificant problem, this was most troublesome to the patient. She was constantly in pain with what she described as a chilling sensation through the spine. Her indubitable desire for a successful pregnancy forced her to avoid pregabalin during pregnancy, which had provided her some relief in the past.

Maternal indications for delivery in this case were decided as worsening proteinuria and/or renal function, abnormality in liver function or symptoms of impending eclampsia, all of which would be indicative of superimposed pre-eclampsia or falling insulin requirements which may be considered a surrogate marker for declining placental function. Fetal determinants for delivery were evidence of fetal growth restriction, abnormal Doppler findings, with a lower threshold for delivery in case of abnormally accelerated growth or polyhydramnios.

OUTCOME AND FOLLOW-UP

At 27 weeks' gestation, her insulin requirements dropped significantly and ultrasound showed polyhydramnios. The patient was admitted and given antenatal steroids to reduce neonatal morbidity should early delivery be required. The fetal growth was otherwise normal. As glycaemic control improved subsequently, it was decided to continue with close surveillance to avoid the risks of prematurity. At 32 weeks, the patient developed worsening proteinuria (PCR 260 mg/mmol), rising serum creatinine (106 µmol/L—from previous of 60–70 µmol/L) and declining estimated GFR. The fetal Doppler showed increased resistance through the umbilical artery. A decision for delivery was taken in view of developing pre-eclampsia and fetal compromise balancing the risks of prematurity against possible stillbirth.

A well-for-gestational-age baby boy weighing 1635 g was delivered by a scheduled Caesarean at 32 weeks' gestation. The baby was admitted to the neonatal unit for 4 weeks but did well postnatally. The patient herself had an uneventful recovery with no further deterioration of renal function postnatally. Subsequent home and hospital assessments of mother and baby confirmed good bonding.

DISCUSSION

This case is an exemplar of the rising complexity the obstetrician is likely to face more often with advances in medical science. The MBRRACE-UK reports³ have consistently highlighted medical comorbidity as one of the crucial factors contributing to maternal death. The labyrinth of comorbidities in this patient made her a challenge from the start.

Furthermore, the case supports the importance of preconceptional care in reducing morbidity which was pivotal in her case.

Studies have shown that while diet and exercise play a small role, bariatric surgery may be the only intervention producing a significant and lasting weight reduction in those with a BMI over 35.⁴ This patient may have successfully conceived through assisted reproduction despite obesity, which would have significantly worsened outcome. In addition, she had received appropriate counselling and treatment with respect to the complications she had developed from diabetes.

A recent meta-analysis⁵ showed that pregnancies in women with chronic kidney disease (CKD) were at greater risk of pre-eclampsia (OR 10.36), premature delivery (OR 5.72), low birth weight (OR 4.85) and Caesarean section (OR 2.67). Our patient had all of the above complications. Subgroup analysis revealed that patients with diabetic nephropathy had significantly lower OR of pre-eclampsia and premature delivery compared with women with non-diabetic nephropathy.⁵ Despite this, there was no detectable difference in renal events comparing women who had CKD against those with CKD and were pregnant at 5-year median follow-up even when controlling for blood pressure, baseline creatinine, proteinuria and follow-up time.⁵ There are no large prospective cohort studies to suggest that pregnancy accelerates diabetic nephropathy in women with known diabetes.⁶ Heterogeneity in nephropathy definitions and small numbers included in studies on patients with type 1 diabetes, diabetic nephropathy and pregnancy suggest that conclusions drawn may be tenuous.⁵ However, there is an established increase in adverse pregnancy-related outcomes including preterm delivery and perinatal mortality in those with type 1 diabetic nephropathy in pregnancy compared with those without diabetic nephropathy.⁷

The Bateman Obstetric Comorbidity Score⁸ developed from data of over 850 000 pregnancies in American women between 2000 and 2007 was shown to positively correlate well with maternal end-organ damage or death and maternal intensive care unit (ICU) admission up to 30 days postpartum. The score contains multiple variables including maternal age, multiple gestation, previous Caesarean section, placenta praevia and 17 other comorbidities. The score was externally validated on 5995 Canadian pregnancies between 2007 and 2008 and showed moderate discriminative ability (area under the curve 0.58–0.70) and good calibration (Brier Score 0.01–0.10).⁹ This score in our case was 8, which would indicate a 6.5% risk of end-organ damage or death (vs 0.7% at score 0) and 1.5% risk of maternal ICU admission (vs 0.2% at score 0) up to 30 days postpartum. The score could be used when booking pregnancies to refer patients to appropriate specialist services or tertiary care centres.¹⁰ Furthermore, the use of this score could be used as a comparative research tool.¹⁰

Apart from the medical issues, the case exposes important ethical considerations and resource implications. The pull of women to seek IVF abroad may be in part due to locally varied but limited access to publicly funded reproductive technology in the UK. Intensive multidisciplinary antenatal, intrapartum and postnatal inputs were crucial in helping the woman to cope with the dynamics of pregnancy and the postpartum period that may be perceivably more challenging as compared with her younger counterparts. While national guidelines do not allow funding for assisted reproductive technology in such patients, the ethics of subsequent care and the resulting resource implications on management of pregnancy in such patients are debatable. There is a lack of data to suggest that medical tourism abroad for IVF saves money for native healthcare systems.¹¹ Furthermore, there is suggestion that private reproductive companies abroad may compromise rights of women from low socioeconomic backgrounds, to become egg donors, for example.¹¹ Cheaper reproductive technologies abroad feed into

partially informed consumerism which are often prioritised over a patient's health interests.¹² In addition, it could be argued that the return of health tourists to their native country releases foreign medical teams from their duty of care.¹²

The impact of very advanced maternal age associated with multiple morbidity on the psychological development of the child and issues of care until adulthood could be considerable both to the individual and the healthcare system. Research in this area is currently deficient and could be expected to evolve as such cases become more common. Interestingly, increasing maternal age up to 40 years has been linked with improved cognition and language development at 10–11 years¹³ and 4–5 years¹⁴ of child age, respectively.

Women are free to choose their reproductive destiny and it is our duty to respect patient autonomy. However, changing maternal demographics and the shifting paradigm of modern reproductive choices is likely to pose a substantial cost burden to nationally funded healthcare systems like the National Health Service and may call for changes in healthcare policies in situations such as these as they become more common in the foreseeable future.

Learning points

- ▶ The case highlights the role of intensive antenatal multidisciplinary care in patients with multiple comorbidities.
- ▶ Preconceptional counselling provides a vital role in improving outcomes in cases of obstetric multimorbidity.
- ▶ The Bateman Obstetric Comorbidity Score could be used to identify specialist care needs and improve obstetric multimorbidity research.
- ▶ Regulation change within nationally funded healthcare systems needs to be considered as health tourism can pose significant financial burden on already stretched resources.

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three authors revised the manuscript critically. All authors listed on the manuscript have seen and approved the submitted letter and take full responsibility for the manuscript.

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