

# Successful pregnancy in a patient with Landesman's Group C autosomal dominant polycystic kidney disease

Mobin Mohteshamzadeh, Andrew Coutinho, Ibi Erekosima, Rana Rustom and Christopher F Wong\*

## SUMMARY

**Background** A female with autosomal dominant polycystic kidney disease was followed up over the course of four pregnancies. Her first three pregnancies were unsuccessful. Her fourth pregnancy resulted in a live birth, but at what expense?

**Investigations** The diagnosis of autosomal dominant polycystic kidney disease was confirmed by ultrasound imaging. Physical examination, blood pressure measurement, and urine and blood analyses were performed at each follow-up visit.

**Diagnosis** Deterioration of renal function following multiple complicated pregnancies.

**Management** Attention to blood pressure and proteinuria delayed initiation of dialysis, but effects of the number of pregnancies took their toll. The patient was started on hemodialysis and underwent renal transplantation.

**KEYWORDS** autosomal dominant polycystic kidney disease, chronic kidney disease, hypertension, pregnancy, proteinuria

## CME

### Vanderbilt Continuing Medical Education online

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

### Competing interests

The authors declared no competing interests.

## THE CASE

A 43-year-old white female was referred to a renal clinic with hematuria, loin pain, hypertension and renal insufficiency. Following a routine visit to her general practitioner for contraceptive advice at the age of 22 years, the patient had been diagnosed by renal ultrasound with autosomal dominant polycystic kidney disease (ADPKD) with cysts in the liver and pancreas. She had remained largely asymptomatic for many years and not until she experienced an episode of loin pain and hematuria at the age of 43 years was renal follow-up arranged. This episode resolved spontaneously and renal ultrasound confirmed the previous diagnosis of ADPKD. At that time she was started on antihypertensive medication. The patient's mother also had ADPKD, but the disease could not be traced further back in the family tree. The patient was followed up at the renal clinic over the course of four pregnancies. Physical examination, blood pressure measurements, and urine and blood analyses were performed at each visit.

The patient first became pregnant at the age of 43 years, but the fetus died *in utero* at 30 weeks' gestation. The fetus was found to have had bilateral multicystic dysplastic kidneys. The patient became pregnant again when she was 45 years old, but this second pregnancy was also unsuccessful, with a spontaneous abortion occurring at 19 weeks of gestation. Six months after the second pregnancy, the patient became pregnant a third time, but this pregnancy resulted in a stillbirth at 31 weeks' gestation. The patient's fourth pregnancy at the age of 47 years was successful, however, with a live birth at 34 weeks' gestation.

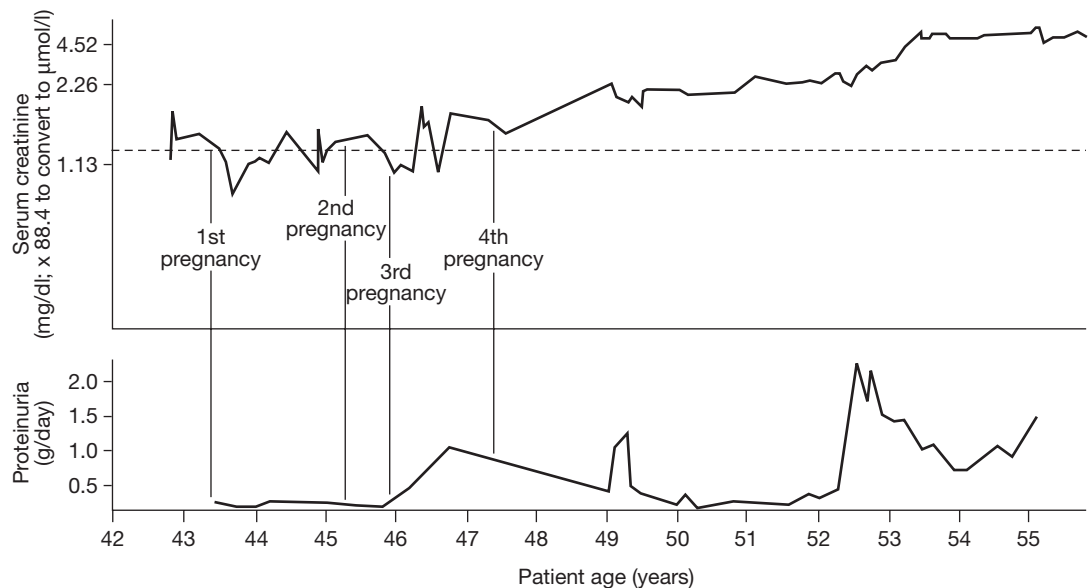
*M Mohteshamzadeh is a Consultant Physician and Nephrologist at the Royal Berkshire NHS Foundation Trust, Reading, A Coutinho is a Senior House Officer and CF Wong is a Consultant Physician and Nephrologist at the Aintree University Hospital Foundation Trust, Liverpool, and I Erekosima is a Staff Grade Nephrologist and R Rustom is a Senior Lecturer and an honorary Consultant Nephrologist at the Royal Liverpool University Hospital, Liverpool, UK.*

### Correspondence

\*Aintree University Hospital Foundation Trust, Lower Lane, Liverpool L9 7AL, UK  
chriswong@doctors.org.uk

Received 9 August 2007 Accepted 6 December 2007 Published online 5 February 2008

www.nature.com/clinicalpractice  
doi:10.1038/ncpneph0748



**Figure 1** Progression of autosomal dominant polycystic kidney disease (as measured by serum creatinine levels) and proteinuria in relation to the patient's age and four pregnancies.

Over the 2 years between her third and fourth pregnancies, the patient's blood pressure became more difficult to control and she developed proteinuria that increased to around 1 g/day. Initially, the patient's blood pressure had been controlled successfully with oral lisinopril titrated to maximum dose and, later, doxazosin; however, methyldopa and labetalol were used for blood pressure control when she became pregnant for the fourth time. The patient's blood pressure ranged from 150/100 mmHg to 175/105 mmHg, and her proteinuria ranged from 0.5 g/day to 1.5 g/day during her fourth pregnancy (Figure 1). The doses of methyldopa and labetalol were titrated to maximum levels in order to control the patient's blood pressure. The patient's renal function continued to deteriorate over the 8 years following her successful pregnancy and, at the age of 55 years, she was started on hemodialysis. When she was 59 years old, the patient received a cadaveric renal transplant, which was still working well at the latest follow-up visit 6 years after transplantation.

#### DISCUSSION OF DIAGNOSIS

ADPKD is an important cause of end-stage renal disease,<sup>1,2</sup> accounting for at least 6–9% of end-stage renal disease cases worldwide. Pregnancy complicated by ADPKD has been well documented in the literature and was first described by Crabtree in 1942.<sup>3</sup>

The literature is conflicting as to whether or not pregnancy exacerbates renal disease,<sup>4,5</sup> or whether renal disease has an adverse effect on pregnancy.<sup>2</sup> The frequency of conception is lower in women with chronic kidney disease (CKD) than in healthy women, and is particularly low in women on dialysis.<sup>6</sup> Among women with serum creatinine levels of 124  $\mu\text{mol/l}$  (1.4 mg/dl) or higher, the risk of accelerated loss of renal function is greater in those who become pregnant than in those who do not.<sup>6</sup> Renal function decline is also faster in pregnant women with ADPKD than in women with ADPKD who do not become pregnant.

ADPKD tends to present between the third and fifth decades of life, by which point many women are past the usual childbearing age. Pregnancy in women with ADPKD is associated with many complications, which vary depending on the severity of the disease.<sup>6–9</sup> Milutinovic *et al.*<sup>7</sup> studied fertility and complications of pregnancy in 137 women at risk of inheriting the *PKD1* gene mutation (associated with ADPKD); 76 of the women (55%) were diagnosed with ADPKD and the other 61 women (45%) acted as controls. The investigators found no significant differences between the two groups in fertility or in the incidences of spontaneous abortion, stillbirth or urinary tract infection. Hypertension (during or unrelated to pregnancy), however, was significantly

more common in women with ADPKD than in controls (32% vs 6%;  $P < 0.01$ ). Only two of the women with ADPKD developed pre-eclampsia. Ectopic pregnancies were reported in two women with ADPKD, but none occurred among controls. Another interesting observation was that an increased number of pregnancies was not associated with an increased incidence of renal failure in women with ADPKD. Other studies have also indicated that a higher number of pregnancies is not associated with a higher risk of renal failure in women with ADPKD.<sup>4</sup>

Gabow *et al.*<sup>10</sup> studied 580 people with ADPKD and 194 unaffected relatives. In total, 170 pregnancies were observed. Renal function did not differ between patients with ADPKD who never became pregnant and those who had experienced a pregnancy. Patients with ADPKD who were older than 41 years and who had three or more pregnancies, however, had worse renal function than those who had experienced fewer than three pregnancies. The study also found that increased left ventricular mass and the presence of hypertension were both associated with faster progression of chronic kidney disease in patients with ADPKD. Furthermore, ADPKD patients with hepatic cysts had significantly more severe renal disease than those without hepatic cysts ( $P < 0.01$ ); when the data were analyzed by gender, the presence of hepatic cysts was associated with worse renal function in females but not in males.

The greater the severity of preconception renal failure, the higher the incidence of complications encountered by both the mother and the child.<sup>11</sup> Indeed, there have been reports of increased fetal mortality and acceleration of renal disease in patients with moderate or severe renal failure during pregnancy.<sup>7,12</sup>

Landesman and Scherr<sup>11</sup> classified pregnant patients with ADPKD into three groups on the basis of the severity of their renal disease (Box 1). The patient presented in this Case Study would be classified as Landesman's Group C, and reports of successful pregnancy in a Group C patient are rare.<sup>9,13,14</sup> This case is different to the others reported in that the patient had three unsuccessful pregnancies before having a successful outcome. With each pregnancy, there was evidence of progression of hypertension, proteinuria and CKD.

During an 8-year period, Chapman *et al.*<sup>15</sup> studied a total of 849 pregnancies, 605 of which

**Box 1** Landesman and Scherr's classifications of pregnant patients with autosomal dominant polycystic kidney disease, based on the degree of severity of their renal disease.

**Group A:** Patients whose kidneys are not recognized as abnormal during pregnancy or who are known to have autosomal dominant polycystic kidney disease but remain asymptomatic throughout pregnancy

**Group B:** Patients who show some degree of blood pressure elevation and have palpable kidneys but normal renal function

**Group C:** Patients in whom renal destruction has reached the point of insufficient kidney function and uremia

occurred in 235 women with ADPKD and 244 of which occurred in 108 women without ADPKD. Only five of the pregnancies in women with ADPKD occurred in individuals with a serum creatinine level of greater than 106  $\mu\text{mol/l}$  ( $>1.2 \text{ mg/dl}$ ) before conception. Women with ADPKD developed a greater number of complications during pregnancy than did women without ADPKD. Complications during pregnancy were particularly common in women with ADPKD who were older than 30 years and in those who had pre-existing hypertension. New or worsening hypertension and pre-eclampsia occurred more frequently in women with ADPKD than in women unaffected by ADPKD. Women with ADPKD who were normotensive before pregnancy but who developed hypertension during pregnancy were found to develop chronic hypertension much earlier in life than those who were normotensive throughout pregnancy. Rates of fetal prematurity and perinatal mortality were higher in pre-eclamptic ADPKD women than in normotensive ADPKD women. Women with ADPKD who had a complication during their first pregnancy were more likely to have further complications in succeeding pregnancies than were women with ADPKD who had experienced an uncomplicated first pregnancy. ADPKD women who had experienced four or more pregnancies had lower creatinine clearances than age-adjusted ADPKD women who had less than four pregnancies. As most women with ADPKD in the study had near-normal renal function before conception, it is not surprising that hypertension was the factor that exerted the most negative effect

on maternal and fetal outcome. More importantly, however, 28 of the 235 women with ADPKD (12%) required renal replacement therapy. Such therapy was initiated a mean of  $22 \pm 2$  years after a woman's last pregnancy, at a mean age of  $52 \pm 2$  years.

Jones and Hayslett<sup>16</sup> demonstrated that pregnancy-related loss of renal function is a common complication in women with moderate or severe CKD. All the women in their study had a serum creatinine level of greater than  $124 \mu\text{mol/l}$  ( $>1.4 \text{ mg/dl}$ ) before pregnancy or at their first antepartum visit. The frequency of maternal complications was two times higher in their study population than that which had been found in a previous study on patients with normal preconception renal function.<sup>13</sup> Both maternal and fetal outcomes are better among women who have renal disease before they become pregnant than in those who are diagnosed during or after pregnancy, possibly because of increased maternal surveillance in those with pre-existing renal disease.<sup>14</sup> Nowadays, the rate of complications from both pregnancy and ADPKD should be lower than it was in previous years, as women with ADPKD have better access to obstetricians and nephrologists, and there is greater maternal surveillance, more advanced technology and better antihypertensive drugs than there was previously.

#### TREATMENT AND MANAGEMENT

The patient presented in this Case Study was determined to have a child and as such her doctors supported her throughout this endeavor. The patient's first pregnancy at the age of 43 years, when she already had mild renal impairment, required increased surveillance with careful attention to blood pressure control. Despite good control of blood pressure, her first three pregnancies failed. The treating physicians then focused on reducing proteinuria and stabilizing the patient's renal function and blood pressure. To their surprise she became pregnant a fourth time. Expectations for a successful pregnancy were not high, and the patient was counseled appropriately. During this time, the patient's blood pressure actually proved more difficult to control than it had done previously and was associated with a rise in creatinine level that failed to improve following successful delivery. The patient's renal function continued to

deteriorate despite attention to blood pressure control and proteinuria. She was started on renal replacement therapy at the age of 55 years.

#### CONCLUSIONS

What can we learn from the case presented here and the current evidence available regarding ADPKD and pregnancy? In the patient described in this Case Study, it is likely that the four pregnancies, with the consequent increased hypertension and proteinuria, directly accelerated progression to stage 5 CKD. Overall, most studies have shown that up to 80% of pregnancies in women with ADPKD are successful. There are increased risks for both the mother and the child during pregnancy, however, particularly for women who were hypertensive before conception or during the first trimester. More importantly, maternal and fetal complications are more likely to occur in pregnant women with ADPKD who have risk factors such as age at conception  $>30$  years, hypertension or an increased number of pregnancies. Moreover, hypertension and an increased number of pregnancies (e.g. more than three) affect CKD progression, although the effect of the latter factor was not consistent between the studies. Apart from the need to have good control of hypertension before conception, it might, therefore, be advisable for patients with ADPKD to have their pregnancies before they are 30 years old and to limit their number of pregnancies to three. Such issues should be discussed during counseling sessions for ADPKD patients who are pregnant or are pursuing pregnancy. In view of the heritable nature of ADPKD and the long-term requirement of renal replacement therapy, such sessions should also explain to the patient the modes of inheritance, natural history, prenatal diagnostics and management options for ADPKD.

The case presented here seems to be unique, as despite the patient's older age, together with her previous three unsuccessful pregnancies and the presence of CKD, hypertension and proteinuria, she was determined to have a child against all odds. Women with a similar history should be made aware that there could be a price to pay if they choose to become pregnant, in that they might require renal replacement therapy much earlier than they would have done otherwise.

## References

- 1 Lowrie EG and Hampers CL (1981) The success of Medicare's end-stage renal-disease program: the case for profits and the private market place. *N Engl J Med* **305**: 434–438
- 2 Parfrey PS *et al.* (1990) The diagnosis and prognosis of autosomal dominant polycystic kidney disease. *N Engl J Med* **323**: 1085–1090
- 3 Crabtree EG (1942) *Urological diseases of pregnancy*. Boston, MA: Little, Brown & Co.
- 4 Hayslett JP (1985) Pregnancy does not exacerbate primary glomerular disease. *Am J Kidney Dis* **6**: 273–277
- 5 Becker GJ *et al.* (1985) Pregnancy exacerbates glomerular disease. *Am J Kidney Dis* **6**: 266–272
- 6 Hou S (1999) Pregnancy in chronic renal insufficiency and end-stage renal disease. *Am J Kidney Dis* **33**: 235–252
- 7 Milutinovic J *et al.* (1983) Fertility and pregnancy complications in women with autosomal dominant polycystic kidney disease. *Obstet Gynecol* **61**: 566–570
- 8 Imbasciati E and Ponticelli C (1991) Pregnancy and renal disease: predictors for fetal and maternal outcome. *Am J Nephrol* **11**: 353–362
- 9 Katz M *et al.* (1979) Severe polycystic kidney disease in pregnancy. *Obstet Gynecol* **53**: 119–124
- 10 Gabow P *et al.* (1992) Factors affecting the progression of renal disease in autosomal dominant polycystic kidney disease. *Kidney Int* **41**: 1311–1319
- 11 Landesman R and Scherr L (1956) Congenital polycystic kidney disease in pregnancy. *Obstet Gynecol* **8**: 673–680
- 12 Packham DK *et al.* (1989) Primary glomerulonephritis and pregnancy. *Q J Med* **71**: 537–553
- 13 Davidson JM *et al.* (1985) Kidney disease and pregnancy: obstetric outcome and long term renal prognosis. *Clin Perinatol* **12**: 497–518
- 14 Katz AI *et al.* (1980) Pregnancy in women with kidney disease. *Kidney Int* **18**: 192–206
- 15 Chapman AB *et al.* (1994) Pregnancy outcome and its relationship to progression of renal failure in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* **5**: 1178–1185
- 16 Jones DC and Hayslett MD (1996) Outcome of pregnancy in women with moderate or severe renal insufficiency. *N Engl J Med* **335**: 226–232

## Competing interests

The authors declared no competing interests.