Clinical Case Report

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# Successful management of twin pregnancy in a woman with advanced chronic kidney disease

## A case report

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**Abstract**

**Rationale:** Twin pregnancy in women with chronic kidney disease (CKD) is very rare but poses a great risk to both mother and children. In developing countries like China, advanced CKD twin pregnancies are often terminated. Here, we report a successful case and reviewed related cases, hope to facilitate further study.

**Patient concerns:** A 29-year-old woman with a twin pregnancy showed serum creatinine (Scr) 100 μmol/L (CKD2) at conception. During her 12th week, Scr reached 263 μmol/L (CKD4) with urine protein 3+ and hypertension.

**Diagnoses:** Due to her pregnancy, renal biopsy was not considered. Lab tests showed deterioration of renal function and ultrasound detections showed small kidney size.

**Interventions:** The patient was given basic drug therapy to control her blood pressure and supplemental nutrition without hemodialysis.

**Outcomes:** The patient delivered 2 healthy babies weighting 0.9 and 0.7 kg by cesarean section at the 28th week, but has been under maintenance hemodialysis since then.

**Lessons:** Despite low birth weight and preterm delivery, successful twin pregnancies in some patients with CKD could be realized under early multidisciplinary intervention, but this poses great risks for mothers and twins, especially for patients with advanced CKD and those on hemodialysis.

**Abbreviations:** ADKPD = autosomal domain polycystic disease, ALB = albumin, BP = blood pressure, CKD = chronic kidney disease, eGFR = estimated glomerular filtrate rate, Hb = hemoglobin, HELLP syndrome = hemolysis, elevated liver enzymes, and low platelet syndrome, IVF-ET = assisted fertilization, LN = lupus nephritis, PE = preeclampsia, Scr = serum creatinine, vitro fertilization, and embryo transfer.

**Keywords:** chronic kidney disease, hemodialysis, preeclampsia, twin pregnancy

### 1. Introduction

Pregnancy with chronic kidney disease (CKD) accounts for about 3% of pregnancy in some developed countries.[1] Not only CKD progressing largely threats fertility and baby survival, but the burden of pregnancy can also accelerate disease progression, especially in advanced CKD stages. Therefore, pregnancy in patients with CKD poses great risk, and generally pregnancy is terminated despite a desire of having baby in developing countries like China. When CKD combined with twin pregnancy, reports are even more sporadic and rough, hard to trace detailed information like maternal prognosis, complications, and treatment, which largely hinders further studies. Even healthy twins have much higher risk of severe complication than singletons, including intrauterine death, low birth weight, and preterm delivery, and CKD in the mother only renders this more dangerous. Here, we report a successful delivery of twins by a mother with advanced CKD in China. Despite scarce information and heterogeneous cases, we also made literature review and extracted findings that merit discussion, and we hope to facilitate further study.

### 2. Case presentation

A 29-year-old woman with twin pregnancy (via assisted fertilization, vitro fertilization, and embryo transfer [IVF-ET]) was admitted in Department of Obstetrics because of significant edema, hypertension, and renal failure. Before pregnancy, this woman was diagnosed as chronic glomerular nephritis, with mild renal insufficiency (Serum creatinine [Scr] 100 μmol/L, NR 35–71). The estimated glomerular filtrate rate (eGFR) was 60.44 mL/(min 1.73 $m^2$) (CKD 2, NR > 90) and the only therapy was nifedipine for blood pressure (BP) control. Her 1st visit to department of nephrology was in 12th week of pregnancy. Laboratory test showed Scr raised (263 μmol/L, NR 35–71),

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eGFR 19.8 mL/(min 1.73 $m^2$) (CKD 4, NR > 90), urinary protein level (3+, NR 0), and occult blood (27/HP, NR 0) in urinalysis, spot urinary protein to creatinine ratio (0.498 g/mmol/Cr, NR < 0.3) serum albumin (ALB; 33.5 g/L, NR > 40), and hemoglobin (Hb; 93 g/L, NR > 100). Antineutrophil cytoplasm antibody, antiglomerular basement membrane antibody, anticardiolipin antibody, and thyroid function were negative. Since then she visited departments of obstetrics and nephrology every 2 weeks. Polysaccharide iron complex 150 mg/d and folic acid were used for anemia therapy. BP was well controlled with nifedipine, urine protein level had no change with prednisone 30 mg/d for 3 months. Prednisone was reduced to 25 mg/d in the 4th month.

Till 24th week, Scr raised slowly from 263 to 386 μmol/L (NR 35–71), without any other complications. In 26th week, the Scr experienced a sharp increase to 528 μmol/L (NR 35–71) and refractory hypertension occurred. In 28th week, the BP raised to 190/120 mm Hg (NR < 140/90). Blood tests showed Scr 773 μmol/L (NR 35–71), blood urea nitrogen 24.71 mmol/L (NR 2.8–7.2), ALB 31 g/L, blood phosphorus ion 2.05 mmol/L (NR 0.96–1.61), blood calcium ion 2.06 mmol/L (NR 2.25–2.75), blood potassium ion 5.6 mmol/L (NR 3.5–5.5), and Hb 61 g/L (NR > 100). Urine volume did not decrease. In case of preeclampsia (PE), pregnancy was terminated by cesarean section. Two live born babies with very low weights (0.9 and 0.7 kg, respectively) were delivered and admitted in newborn baby intensive care unit (ICU) for 3 months.

Mother suffered from poor nutrition level (Hb76 g/L [NR > 100], ALB 23.6 g/L [NR > 40]) and was immediately transferred to department of nephrology. There she received systematic treatment including hemodialysis treatment, antiinfectious, and other support treatments such as blood and ALB transfusion. Ultrasound detection showed kidney to be small in size (length 8.7 and 8.5 cm of left and right kidneys, respectively, NR 10.5–11.5). Unfortunately, renal function did not return to normal, and she was under maintenance dialysis twice a week from then. Two babies in their 1 year old both had bodyweights of 8 kg and in good development, including hearing and renal function.

## 3. Discussion

Other literatures involved CKD twin pregnancy are listed in Table 1. However, those cases did not have the definite baby outcome.

Despite potential to damage fertility and the heavier renal burden that they can pose, twin pregnancies in patients with CKD still emerge in various stages of CKD including hemodialysis and renal transplant. Prognosis factors, like mothers' BP , proteinuria, CKD stages, sufficient hemodialysis, baby weight, and gestation,

**Table 1**

**Twin pregnancy cases in patients with CKD in review.**

| Author | year | Patient number | Mother primary disease | Mother CKD stage | Baby survival/gestation week | Adverse outcome |
|---|---|---|---|---|---|---|
| Brunini et al[2] | 2018 | 2 | Alport syndrome | CKD 1<br>CKD4 | SS/33 wk<br>BS /29 wk | PE<br>PE, progress to HD |
| Attini et al[3] | 2016 | 2 | – | CKD 1<br>CKD 1 | BS/36 wk<br>BS/35 wk | – |
| Farr et al[4] | 2014 | 1 | – | PT (CKD 1T) | BS/30 wk | Progress to CKD 3 |
| Gizzo et al[5] | 2014 | 1 | – | PT (CKD 2T) | BS/31 wk | – |
| Croft et al[6] | 2014 | 1 | ANCA-associated vasculitis | CKD 1 | BS/31 wk | – |
| Piccoli et al[7] | 2014 | 1 | Interstitial | HD | SS/29 wk | – |
| Gramkow et al[8] | 2014 | 1 | LN | CKD 4<br>HD since 24 wk | BS*/29 wk | PE |
| Piccoli et al[9] | 2013 | 17 | – | PT (CKD 3T): 1<br>CKD 1–2: 16 | /<br>14 BS*(4):/27–37 wk<br>2 SS:/32 wk | miscarriage at 8w |
| Wyld et al[10] | 2013 | 15 | – | PT | BS: 12 | 1 pair stillbirth<br>2 pairs neonatal death |
| Kennedy et al[11] | 2011 | 2 | – | PT | SS: 1/30 wk | –<br>1 miscarried 10 wk |
| Cheung and Bhandari[12] | 2009 | 1 | – | PT CKD 3T | BS/32 wk | – |
| Furman et al[13] | 1999 | 2 | – | PT CKD 1T<br>PT CKD 2T | BS/36 wk<br>BS/33 wk | PE<br>PE |
| Skhiri et al[14] | 2005 | 1 | – | PT CKD 1T | BS/– | – |
| Loeffler et al[15] | 2005 | 1 | ADPKD | ADPKD (without dialysis) | BS*/26 wk | Superimposed PE |
| Vyas et al[16] | 1999 | 1 | – | PT | SS/32 wk | – |
| Hsien et al[17] | 1991 | 1 | – | HD | – | Intrauterine death of both at 29th wk |
| Haugen et al[18] | 1991 | 1 | – | PT | BS | – |
| Burrows et al[19] | 1988 | 1 | – | PT | BS/35 wk | – |
| Vega et al[20] | 1988 | 1 | – | HD then transplant at 20th wk | – | Neonatal death of babies 25th wk |
| Grunebaum and Minkoff[21] | 1987 | 1 | LN | CKD 4 | BS/33 wk | – |
| Wei | This case | 1 | CGN | CKD 3 | BS/28 wk | Superimposed PE progressed to HD after delivery |

ADKPD = autosomal domain polycystic disease, ANCA = antineutrophil cytoplasm antibody-associated small vessel vasculitis, BD = both dead, BS = both survived, CGN = chronic glomerulonephritis, CKD = chronic kidney disease, HD = hemodialysis, LN = lupus nephritis, PE = preeclampsia, PT = posttransplant, SS = single survived,– = not mentioned, *(number) = number of assisted fertilization,.

have been reported repeatedly in many singleton CKD pregnancies. The risks posed by twin pregnancy still need to be considered with caution because of the bias in existing published case reports and the small sample sizes in case series.

In these cases, CKD stages of mothers before pregnancy are not always parallel with babies' survival. One mother with lupus nephritis (LN) had both babies survive despite being CKD 4.[8] One twin born to a mother with diabetes died during the neonatal period after surgery for a vascular abnormality even though her condition was only CKD 1.[9] A best practice guideline from Italy notes that diabetic nephropathy is associated with perinatal death and infant malformation.[22] Of note, although dialysis support can help babies survive, their outcomes are still worse than those of transplanted mothers in CKD 1T (with normal renal function).[23] This trend was also observed in our reviewed cases.

For singleton pregnancies, babies born to patients with CKD 1 tended to have better outcomes than those born to transplanted patients with eGFR > 90 mL/min, but this advantage disappeared for CKD 2 to 5. Although proteinuria was not analyzed, CKD 2 to 5 and hypertension were found to be risk factors related to preterm and early preterm deliveries according to a multivariate analysis, but renal transplantation was not.[24] Many questions remain for twin pregnancies because the sample size is small and we were not able to analyze some stages of CKD for transplanted patients in our review.

In the case of CKD twin pregnancy, 16 mothers at CKD 1 and 2 mentioned earlier maintained their original CKD stage after twin delivery,[9] indicating that the risk of disease progression for patients with CKD 1 and 2 with twin pregnancies might be low, which is consistent with the singleton study of IgA nephropathy pregnancies.[25]

For those patients who unfortunately have advanced CKD like the present case, the stress of renal function deterioration and baby survival often make them prone to terminate their pregnancy. In such high-risk groups, multidisciplinary support, including hemodialysis, can be an emergency choice and has been shown to work in some cases.

Using hemodialysis to clean waste is a traditional consideration in advanced CKD pregnancy. In accordance with this guidance, an LN patient with CKD 4 started dialysis during the 24th week and delivered twin babies at the 28th week, successfully avoiding the risk inherent in polyhydramnios and toxin accumulation for babies.[8] For patients with maintenance dialysis, the total hours spent on dialysis in a week can strongly affect preterm delivery and small size for gestational age, which may exclude of uremic toxins. One study demonstrated that the live birth rate reaches 85% when the patient underwent hemodialysis for 36 hours per week or more.[26] Intensive dialysis is a universal rule for maintenance dialysis population. In reviewed twin cases, dialysis time was 24 hours per week for 1 patient and 28 hours per week for the other, a very common time, as in singleton pregnancies. These 2 patients experienced both intrauterine fetal death and the survival of only 1 baby postnatally, respectively. Despite the heterogeneity of patients and bias in the reports, twins might necessitate more dialysis time than singletons and so improve baby outcome due to the extra burden posted by 2 fetuses. Currently, there is no accepted optimal time to start dialysis in advanced CKD pregnancies, even for singletons, but a lower threshold is adapted by many clinicians (usually serum urea above 20 mmol/L). Decisions must be balanced based on careful monitoring of laboratory and ultrasound examinations. In China, due to limited experience, pregnancy management guidelines for CKD do not recommend dialysis for pregnant patients.[27]

With drug therapy only, our fortunate patient encountered rising creatine largely caused by renal insufficiency but did not had complications as, infection, oliguria, heart failure, or electrolyte disturbance all of which necessitate immediate hospitalization or hemodialysis, only with uncontrolled hypertension in last stage. The fetuses were alive despite their very low weight. Early detection of renal insufficiency and interference with careful and frequent multidisciplinary monitoring was crucial to this successful delivery.

Comparable stable BP may play an important role as suggested before, because hypertension is a risk factor of early preterm delivery. The recommend BP target according to China's guideline is 130 to 140/80 to 90 mm Hg.[27] Another unsuccessful singleton delivery of a CKD 1 mother may indicate the importance of early interference, especially BP control.[28] That mother did not undergo regular monitoring of her BP and was not aware she had CKD. It was until 28th week did she found intrauterine death of fetus with her BP 220/130 mm Hg and electrolyte imbalance, even her Scr was only 160 μmol/L which returned to normal level a year later. Another case by Grunebaum and Minkoff[21] also demonstrate possibility of baby survive in advanced CKD without dialysis.

The fetal risks are mainly related to prematurity, and these risks increased as CKD progressed. Achieving longer gestation is very important for CKD pregnancy. Better renal function led to longer gestation, as demonstrated in those cases reviewed. The early preterm delivery of our case was not an exception, especially when PE rather than other conditions that could be improved by dialysis occurred. Multiple pregnancies and hypertension were considered risk factors for PE, even in healthy mothers. Certain primary diseases, such as LN and autosomal domain polycystic disease (ADKPD), are more susceptible to PE.[8,22] Distinguishing CKD progress from PE via a noninvasive method was nearly impossible clinically, but it was very important for elongating gestation in the case of emergency. Not only did they share the same domain symptoms as hypertension, proteinuria, and increasing creatinine levels, but the use of biomarkers and ultrasound in early detection were still limited, especially in cases involving twins.

One of the pathophysiologic changes of PE is damaged uteroplacental flow followed by angiogenic and antiangiogenic ratio alteration, which finally causes endothelia damage. Ultrasound to detect uteroplacental flow combined with blood test of Fms-like tyrosine kinase 1 (sFlt-1)/placental growth factor (PIGF) ratio showed promise, and the latter is especially recognized by the New England Journal of Medicine. The use of Flt-1/PIGF diagnosis standards for singletons is not appropriate for twins because twins have a different receiver operating characteristic cut point from singletons.[29] Aspirin at low dose shows promising preventive properties with robust clinical evidence, to the point of a 25% reduction in risk in high-risk groups, as established in clinical practice. The recommended dose is 75 mg/d from the 12th week of gestation to delivery. China consensus recommends aspirin (50–100 mg/d) until the 28th week.[27] One innovative report showed that removal of sFlt-1 through dextran sulfate apheresis can also elongate gestation despite PE.[30] Further studies of aspirin in advanced CKD pregnancy are needed. Since sFlt-1/PIGF and ultrasound both have their limits in clinical practice and might not always be available, currently diagnosis of PE in patients with CKD is still

mainly based on doctors' own interpretations, using such signs as worsened hypertension, proteinuria, and hemolysis, elevated liver enzymes, and low platelet syndrome (HELLP syndrome).

Of note, 7 of the 55 cases mentioned assisted fertilization. With the progress of assisted fertilization and the newborn ICU, more "planned" twins from patients with CKD, even advanced CKD might pose more challenges for doctors in renal, obstetric, and newborn ICU divisions. While the high risk of mother/baby complications, such as low birth weight, PE, and preterm delivery, infant survival still improved even among dialysis, and transplant patients.

Our case and literature review suggest CKD mothers undergoing twin pregnancies are not incapable of giving birth to healthy babies if under the multidisciplinary care of doctors in renal, obstetric, and newborn ICU divisions, even babies with very low weights. However, great risks are involved for both mother and twins, especially in cases of patients with advanced CKD and hemodialysis. More studies are needed to improve management for twin pregnancies in patients with CKD.

## Author contributions

**Supervision:** Li Zhou, Qiang Yao, Ping Fu.
**Writing – original draft:** Yan Wang.
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