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Pregnancy after renal transplantation: Case report and literature review

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Abstract

Background: Renal transplantation is one of the main treatments for end-stage renal disease. Therefore, pregnancy after renal transplantation is also considered as a high-risk pregnancy. The five-color risk project management introduced in 2017 in China plays an important role in pregnancy risk assessment and management of pregnant women after renal transplantation. The incidence of pregnant women with a medical history of renal transplantation for pregnancy complications such as preeclampsia and anemia is much higher than normal pregnant women. Although there may not be much difference in treatment methods between renal-transplanted pregnancy and normal pregnancy, it still needs to be treated standardizedly. In addition, with the deepening of research, breast-feeding is no longer taboo for renal-transplanted women.

Case presentation: Three patients with pregnancy after renal transplantation admitted to Renmin Hospital of Wuhan University between 2019 and 2021 were reported in this study. All the three patients were 32 to 33 years old. Their pregnancy week was 34 weeks to 37 weeks. They have complications such as hypertension and anemia and diagnosed as orange color in five-color risk project management. They received medication such as tacrolimus and azathioprine and received cesarean section to end their pregnancy and have a premature baby.

Conclusions: The five-color risk project management were used to evaluate the pregnancy risk of the pregnancy women. Our experience in the treatment of pregnancy after renal transplantation will be helpful for the future clinical management and treatment of pregnancy after renal transplantation.

Keywords: Renal transplantation; Pregnancy; Hypertension; Anemia; Breast-feeding.

Abbreviations: RT: Renal Transplantation; U-TP: 24-Hour Urine Protein; CYC: Cystatin C; CPAP: Continuous Positive Airway Pressure; UA: Uric Acid; eGFR: Estimated Glomerular Filtration Rate; MMF: Mycophenolate; HDP: Hypertensive Disorders of Pregnancy; EPO: Erythropoietin.

Background

Renal Transplantation (RT) is one of the main therapies for end-stage renal disease. In the past, due to the limitation of medical technology and the lack of relevant experience, medical personnel once suggested that women with a medical history of RT should try to avoid pregnancy as much as possible. However, with the increasing number of RTs, doctors have accumulated amount treating experience from a large number of cases for pregnancy after RT. Despite all this, pregnancy after RT still has great risks. Since 2017, a five-color risk project management was introduced in the pregnancy risk assessment and management of pregnant women, especially for those who had high pregnancy risk. Starting from three patients with pregnancy after RT admitted to Renmin Hospital of Wuhan University between 2019 and 2021, we will introduce our experience in the management of pregnancy after renal transplantation and the prospects for the future.

Case presentations

Case 1: A 33-year-old female, admitted to Renmin Hospital of Wuhan University for 35 weeks pregnancy, missed abortion once. Eight years after renal transplantation, the patient was treated with nicardipine hydrochloride for blood-pressure-reduction and tacrolimus for anti-rejection treatment. Physical examination on admission: BP: 152/104 mmhg, no obvious abnormality in gynecological examination. The 24-hour Urine Protein (U-TP) was 1.59 g/24 h. She was diagnosed as "chronic hypertension superimposed with preeclampsia, gestational diabetes mellitus, uterine fibroid, renal transplanted history, 35 weeks pregnant". After 35 weeks and 3 days of gestation, cesarean section and uterine banding were performed, and a baby girl was delivered. The Apgar score of the baby was 9. After birth, she had shortness of breath and poor reaction. The examination showed type I respiratory failure, fetal intrauterine infection, acidosis, hyperkalemia and hypomagnesemia. Discharged after CPAP assisted ventilation, anti-infection and correction of electrolyte disorder, her general condition was stable. The second day after cesarean section, the levels of Cystatin C (CYC) was 1.52 mg/L, serum Uric Acid (UA) was 493.00 mg/L and serum tacrolimus was 7.7 ng/ml. Echocardiography showed the echocardiographic changes of hypertension with a small amount of pericardial effusion. Color Doppler ultrasound showed no abnormality. On the sixth day after operation, the patients were discharged after no obvious abnormality of liver and kidney function.

Case 2: A 33-year-old woman admitted to Renmin Hospital of Wuhan University for 34 weeks pregnancy and artificial abortion once. Five years after renal transplantation, she took tacrolimus +azathioprine +sodium bicarbonate for anti-rejection treatment since the transplantation surgery. Physical examination on admission found her blood pressure is 147/88 mmHg. The examination after admission showed that the patient had mild anemia (red blood cell 3.31 x 10^{12}/L, haemoglobin 103.00 g/L); Serum creatinine was 111.00 μmol/L, Estimated Glomerular Filtration Rate (eGFR) was 56.17 ml/min, and the concentration of serum tacrolimus was normal. She was diagnosed as "Gestational diabetes mellitus, renal insufficiency, preeclampsia, anemia, uterine fibroid, hepatitis B, renal transplanted history, 34 weeks pregnant". The treatment strategy is promoting fetal lung maturating, monitoring fetal heart rate and other symptomatic treatment. Reexamination on the fourth day of admission showed: Serum creatinine was 122.00 μmol/L, serum UA was 537.00 20 mmol/L and eGFR was 50.10 ml/min. On the 7th day after admission, a boy was delivered by cesarean section. The Apgar score was 9. The examination showed the newborn has Respiratory distress syndrome, metabolic acidosis, patent ductus arteriosus, high lactic acid, hypocalcemia, hypomagnesemia, hyperbilirubinemia. Postoperative reexamination showed: serum creatinine was 118.00 μmol/L, serum UA was 518.00 μmol/L, eGFR was 52.16 ml/min and serum tacrolimus was 9.1 ng/ml. Ultrasound showed slight hydronephrosis in the transplanted kidney. The patient was discharged after her condition improved.

Case 3: A 32-year-old female, admitted to Renmin Hospital of Wuhan University for 36 weeks pregnancy. Six years after renal transplantation, the patient was treated with tacrolimus, azathioprine and prednisone for anti-rejection treatment. Physical examination on admission: BP: 145 / 92 mmhg, no obvious abnormality in gynecological examination. The 24-hour Urine Protein (U-TP) was 1.79 g/24 h. She was diagnosed as "preeclampsia, gestational diabetes mellitus, anemia, renal transplanted history, 36 weeks pregnant". After 36 weeks and 1 day of gestation, cesarean section and uterine banding were performed, and a baby girl was delivered. The Apgar score of the baby was 9. After birth, the newborn was diagnosed as nerosary colorectal colitis, gastrointestinal bleeding, neonatal sepsis, paralyzable intestinal obstruction, abnormal coagulation function, patent foramen ovale, hyperbilirubinemia. Postoperative reexamination showed: Serum creatinine was 108.00 μmol/L, eGFR was 59.16 ml/min and serum tacrolimus was 8.1 ng/ml. Ultrasound showed slight hydronephrosis in the transplanted kidney. The patient was discharged after her condition improved.

The characteristics of the three patients as well as the information of their babies were listed in Table 1 and Table 2. Written consent were obtained from the included participants to publish their personal information. In the first trimester of pregnancy, we should first to assess the renal function and establish the perinatal manual after the early pregnancy is determined. Then the pregnant women who were evaluated as higher risk (orange) will enter high-risk clinic project management path; those who were evaluated as general (yellow) risk will enter the general out-patient check-ups. Both obstetrics and transplantation doctors pay attention to the maintenance of pregnancy. In the second trimester of pregnancy, the concentration of anti-transplant drugs is monitored monthly. In addition to routine fetal growth and development assessment, the obstetrics should pay attention to the appearance of other complications such as abnormal blood pressure and serum glucose level as well as anemia. When the pregnant women were evaluated as orange risk, they should be hospitalized and receive a timely treatment. The doctors will balance the fetal maturity and the mother's risk of continuing pregnancy and chose an appropriate time to end pregnancy. The three pregnant women in this article all have chosen cesarean section to terminate pregnancy. Selecting the abdominal wall hole into the abdominal cavity and the method of placing only the left belly hook to avoid the oppression of the right transplanted kidney. We also monitor the blood flow of the transplanted kidney on the day of surgery by ultrasound. On

the second day after surgery, we also monitor the total protein quantification, liver and kidney function as well as serum electrolyte change. After discharge from hospital, the kidney function was followed up by transplanted clinic. The specific flow chart of pregnancy management of kidney transplant patients was shown in Figure 1.

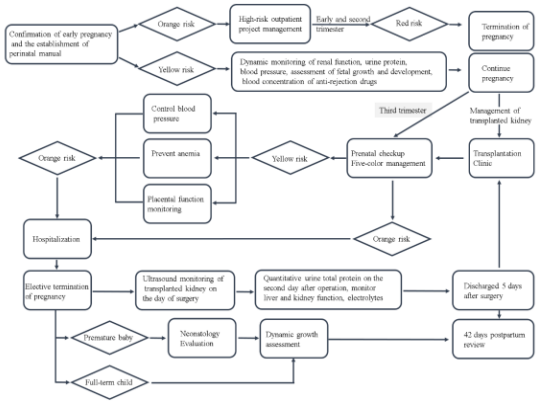

Figure 1: Flow chart of pregnancy management of kidney transplant patients.

Discussion

In 2017, National Health and Family Planning Commission of PRC promulgated the implementation of "Specifications for Pregnancy Risk Assessment and Management" [1], which referred to as "Five Color Management". The pregnant women were divided into five colors including "green (low risk), yellow (general risk), orange (higher risk), red (high risk), and purple (infectious diseases)" according to the severity of the risk [1]. Green color indicates low pregnancy risk, which means the basic condition of the pregnant women was good, and no pregnancy complications were found. Yellow color indicates the risk of pregnancy is medium. The basic condition of pregnant women has certain risk factors, or suffers from complications during pregnancy and childbirth, but the condition is mild and stable. Orange color indicates higher risk of pregnancy. Pregnant women who are ≥40 years old or BMI ≥ 28, or suffer from serious pregnancy complications, which may pose a certain threat to the safety of mothers and babies. Red color indicates high risk of pregnancy, which means pregnant women suffer from severe pregnancy complications and continued pregnancy may endanger the life of the pregnant woman and we should stop pregnancy as soon as possible. Purple color means pregnant women suffer from infectious diseases. This three cases of pregnant women after transplantation, due to kidney disease, current condition is stable and renal function is normal, early pregnancy evaluation is yellow risk (medium risk, code B204). Case 1 suffered severe preeclampsia in the third trimester of pregnancy and evaluated as orange risk (higher risk, code C307). Case 2 and case 3 suffered from diabetes in the second trimester of pregnancy and have no need to use insulin, which also evaluated as yellow risk (medium risk, code B205). During their third trimester of pregnancy, they suffered from mild anemia with their serum hemoglobin was 103 g/L and 99 g/L and also evaluated as yellow risk (medium risk, code B2062). However, as their blood creatinine value exceeding the normal value, the risk level is upgraded to orange (code C204). The three cases of pregnant women terminated pregnancy at the time of the risk level was increased, all of which obtained satisfactory pregnancy endings.

In the clinical work, combined with "five-color management" grading, we summarized the flow chart of outpatient clinic, hospitalization, and postpartum follow-up of pregnancy after Renal Transplantation. In the path shown in the Figure 1, the obstetricians should pay attention to the renal function of the transplanted kidney, monitor and adjust the dose of anti-rejection drugs under the guidance of renal transplant physicians. Moreover, the obstetricians should also pay attention to the growth and development of the fetus, monitor blood pressure, serum glucose and hemoglobin changes and discriminate hypertensive disorder, gestational diabetes mellitus and anemia timely, determine the risk level of pregnancy accurately, which is helpful to take corresponding measures to help those pregnant women after renal transplantation pass the pregnancy period and puerperium safely. The examination items listed in this flow chart are general projects, which will not increase the additional expenditure of pregnant women after renal transplantation.

Edith Helm transplanted a kidney from his identical twin sister in 1956 and delivered a healthy baby boy by caesarean section in 1958 [2]. Since then, people have realized that the medical history of RT is not an absolute contraindication of pregnancy and delivery. On the contrary, renal transplantation can relieve the inhibition of end-stage renal disease on gonadal function. The risk of kidney rejection is not greater during pregnancy except in those sensitized patients [3,4]. Despite that more and more experience and knowledge were accumulated in this field, the possibility of delivering a live baby is 10 times lower comparing with the healthy women [5]. More than 14000 women with a medical history of RT have successfully conceived and delivered science 1958. In 2002, the EBPG Expert Group on Renal Transplantation issued guidelines, indicating that the fertility of renal transplant women can be restored within half a year after transplantation, and pregnancy is not likely to have adverse effects on the function of the transplanted kidney and maternal survival. The guideline suggests that women with transplanted kidney must meet the following conditions before trying to conceive: 1) Pregnancy is 2 years away from the transplantation surgery and the patient has a good health; 2) The function of the transplanted kidney is stable (creatinine<177 mmol/l); 3) No obvious evidence of rejection recently; 4) Blood pressure is normal or can be controlled by only one kind of drug; 5) Proteinuria<0.5 g/day; 6) No obvious abnormality was found by ultrasound of the transplanted kidney (no hydronephrosis and pelvicalyceal distension); 7) Recommended immunosuppressant and dosage: prednisone<15 mg / day, azathioprine ≤ 2 mg / kg / day, and it is suggested to stop mycophenolate (MMF) and sirolimus 6 weeks before pregnancy [6]. In this paper, the pregnancy time of three cases from renal transplantation time were 8 years, 5 years and 6 years, 9 without significant abnormal creatinine during the gestation, in line with the requirements of the guideline. The anti-transplant drugs used during pregnancy are also in line with the recommendations of the guidelines. Tacrolimus was used as immunosuppressant in 3 cases before and during pregnancy, with the normal blood concentration before cesarean section. At the same time, the guideline also pointed out that 7 of 10 pregnancy women would have their own children because tacrolimus can inhibit the immune rejection without causing fetal malformation [5], which indicates the anti-rejection drug used was helpful for successful pregnancy to some extent.

Monitoring of renal function and control of anti-transplant drugs during pregnancy requires the help of transplanted doctors. Obstetricians concentrated on the control of blood pres-

sure and anemia correction. The three cases listed in this article end their pregnancy due to the increase in blood pressure and the occurrence of pregnancy complications. Madej et al. included 37 pregnant women with medical history of RT (45 deliveries) for analysis. 187 pregnant women without a transplanted kidney were selected as the control group. It was found that the prevalence rate of hypertension in the RT group was 77.8% (n=35). Among them, 32 cases had medical history of hypertension before pregnancy, and the incidence rate of preeclampsia was 31.1% (n=14). As for the control group, only 4.3% (n=8) suffered from this pregnancy complication. Only one of them had the medical history of hypertension before pregnancy, and the incidence of preeclampsia also decreased to 0.5% (n=1). In addition, the average age of patients with normal blood pressure in the RT group (28.7 years old) was significantly lower than that of patients with hypertension (30.5 years old), which means that age also plays an important role in the pathogenesis of gestational hypertension, and blood pressure is highly related to the incidence of intrauterine malnutrition [7]. In another study, Jussara et al. retrospectively analyzed 43 cases of pregnancy after RT. In this study, the incidence of preeclampsia reached 65% (n=28), and the incidence rate of anemia reached 60.5% (n=26). It is speculated that this may be related to the decrease of erythropoietin, As the average serum creatinine of the sample population increased with the increase of gestational age (from 98 mmol/L in the second trimester to 127 mmol/L in the third trimester). Although it is still within the recommended range of the guidelines, it has exceeded the range of medical reference ranges. At the same time, the mean value of urine protein also increased from 180 mg/L to 910 mg/L. Serum creatinine and urine protein in late pregnancy were significantly higher than the normal level [8]. This evidence indicated that the physiological changes in the third trimester of pregnancy may aggravate the burden on the kidney, which may be related to the increase of circulating blood volume and the increased uterine pressure on the renal vein. Therefore, the guidelines recommend that pregnancies with renal transplantation should be classified as high-risk pregnancies, and routine blood tests, serum creatinine and proteinuria tests should be carried out every 2-4 weeks during the gestation.

It can be learned from the above two clinical researches that Hypertensive Disorders Of Pregnancy (HDP) and proteinuria are the main complications of pregnancy after RT. HDP includes gestational hypertension, preeclampsia, eclampsia, chronic hypertension with superimposed preeclampsia and pregnancy with chronic hypertension. About 10% of pregnant women will suffer from HDP [9] and HDP also accounts for about 10% of the causes of maternal death. Complications such as gestational hypertension, preeclampsia, and gestational diabetes are quite common during pregnancy after transplantation [10]. According to the guidelines, the probability of preeclampsia in pregnant women with RT history is about 27% - 38%, which is four times higher than that in normal women. This statistical result is basically consistent with the situation observed by Madej et al. but lower than the result observed by jussara et al. It is worth mentioning that due to the use of cyclosporine and tacrolimus, whether there is preeclampsia or not, the serum uric acid level of pregnant women may 10 increase, so it is not recommended to use the uric acid level as an important indicator to judge whether there is preeclampsia in pregnant women. In terms of treatment, ACEI may lead to oligohydramnios and neonatal respiratory dysfunction, so it is not recommended as a hypertension control drug for pregnant women with transplanted kidney. Researches and guideline recommend α- Methyldopa and hydralazine as the first-line drugs for hypertension in women with medical history of RT. Intravenous injection of hydralazine is recommended for the acute stage of hypertension. If the effect of these two drugs is not obvious, it is a good choice to use calcium blocker in stable phase and labetalol in acute phase. In brief, the monitoring of renal function during pregnancy and the regulation of anti-transplant drugs require the help of a transplant doctor. Obstetricians are more concerned about blood pressure control and anemia correction. All three of our patients terminated their pregnancy early because of the increase in blood pressure to the late stage and the emergence of pregnancy complications.

The incidence of anemia after renal transplantation is 20% - 51%, which may be related to the decreased secretion of (EPO) [11]. Due to the increase of blood volume and insufficient intakes of nutrients such as iron, folic acid and vitamins, nearly half of pregnant women will have anemia during pregnancy. These factors might help us understand the increased incidence of anemia in women after kidney transplantation. Just like the 60.5% incidence of anemia observed by jussara et al., case 2 was also found to have mild anemia. The application of iron-supplementary and EPO can effectively alleviate the symptoms and degree of anemia, and also can strengthen the protection of cardiovascular and renal damage caused by anemia [12].

At the same time of the control of blood pressure and anemia, the ultrasonic monitoring of the growth and development of the fetus in the palace is also very important. Fetal complications such as growth restriction, preterm delivery, and delivery by caesarean section were also observed in pregnant women with transplanted kidney [10]. It has been reported that the rate of births with caesarean section after transplantation of 56.9% [13]. In our three cases, all three subjects suffered from caesarean section and preterm delivery. No evidence showed obvious correlations between the use of immunosuppressive drugs and the development of congenital anomalies [14-16]. In our three cases, no baby has congenital anomalies.

Due to the limitation of studies at that time, the guidelines did not advocate breastfeeding. However, the latest evidence showed that the concentration of anti-rejection drugs such as tacrolimus in milk was significantly lower than the amount of tacrolimus passing through the blood placental barrier. Therefore, prednisone, azathioprine, cyclosporine and tacrolimus were considered safe and could be taken during lactation, However, due to the lack of available evidence, breast-feeding should be avoided as far as possible after taking mycophenolic acid products, sirolimus, everolimus and belacep [17]. In our three cases, none of the three mothers choose breastfeeding, which indicated 13 1 that they still worried about the side-effects of the drugs on the baby.

Conclusion

Pregnancy after RT still has great risks. The main complication of pregnancy after RT is HDP, which is also a very common complication in normal pregnancy. It should be noted that in the treatment of anemia during pregnancy, the application of EPO in renal transplanted women may be much better than simple iron supplement. When prednisone, azathioprine, cyclosporine and tacrolimus are used as anti-rejection drugs, breastfeeding should also be considered relatively safe. Obstetricians should control blood pressure, correct anemia and monitor the growth and development of the fetus in the uterus using ultrasound,

evaluate the risk and manage those pregnant women according to the flow chart listed in this article and the five-color management rules, work closely with the pediatrician of the transplantation department to obtain a satisfactory pregnancy outcome.

However, current research is still very limited. With the improvement of renal transplantation technology and postoperative nursing level, the reproductive demand of renal transplanted women will become more and more vigorous. Therefore, it is very meaningful to carry out multi-center and large sample clinical research, update and expand the relevant guidelines based on the research and other studies.

Declarations

Data availability statement: The data that support the findings of this study are not openly available due to patients' data and 4 are available from the corresponding author upon reasonable request.

Conflict of interest statement: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics approval and consent to participate Human studies were performed according to the Declaration of Helsinki and were approved by the human research ethics committees of Renmin Hospital of Wuhan University in Wuhan, China.

Consent for publication: All were agreed to publish this article in written format.

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Authors' contributions: LBL and YM contributes to the data collection. LBL and QL wrote and revised the manuscript. QL and JY are the guarantors of this work. All authors approved the final version of the manuscript.

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