Acta Scientiarum

http://www.uem.br/acta
ISSN printed: 1679-9291
ISSN on-line: 1807-8648
Doi: 10.4025/actascihealthsci.v34ispec.10554

Pregnancy after kidney transplantation: when is the best time?

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ABSTRACT. The authors report a case of a patient underwent kidney transplantation that went through an unplanned pregnancy, at 41 years old, as well as the implications for both mother and fetus.

Keywords: Transplantation, Pregnancy, Prenatal care.

Gravidez após transplante renal: qual o momento ideal?

RESUMO. Os autores relatam o caso de uma paciente submetida à transplante renal que evoluiu com uma gravidez não planejada, aos 41 anos de idade, bem como suas implicações para o binômio mãe e feto.

Palavras-chave: Transplante, Gravidez, Cuidado pré-natal.

Introduction

Women with chronic kidney disease often present infertility, but the completion of successful kidney transplantation determines the return of fertility, which usually occurs after the sixth month of the intervention (KIM et al., 2008). Although having satisfactory evolution, there is impairment of maternal and fetal prognosis due to clinical complications like preeclampsia, chronic hypertension, anemia, urinary tract infection, early amniorrhexis, preterm labor, and intrauterine growth restriction (ARAÚJO et al, 2006; BRUNO; BARROS, 1988; MCKAY; JOSEPHSON, 2005; MCKAY; JOSEPHSON, 2008).

Initially, the pregnancy was not recommended to transplanted women, due to complications associated with and to the effects of immunosuppressive therapy. However, in 1958 occurred the first successful pregnancy in this group, and currently it is believed that these patients have lower risks when well monitored (DAVIDSON, 1991; TOURAINE et al, 1997; MILHEIRAS et al., 2005).

Determining the risks of pregnancy requires knowledge about some aspects such as, for example, gestational age, maternal health, transmission of infections, and the risks associated with exposure to immunosuppressive agents during organogenesis and maturation (MCKAY; JOSEPHSON, 2008).The prenatal control of the pregnant renal transplant patients should be multidisciplinary, emphasizing the control of blood pressure, renal function, infectious episodes, and fetal well-being (MILHEIRAS et al., 2005; MCKAY; JOSEPHSON, 2005). In this context, despite some controversies the ideal is that pregnancy occurs in a stable patient with good graft function and minimum dose of immunosuppressants. In practice, it is recommended that the serum creatinine levels be below 1.5 mg dL^{-1}, with minimum proteinuria, no rejection episodes in the last year, immunosuppressants at maintenance dose and with an interval over two years between the transplantation and gestation (DAVIDSON, 1991; TOURAINE et al, 1997; MILHEIRAS et al., 2005, MCKAY; JOSEPHSON, 2005; KDIGO, 2009).

However in some cases, despite these recommendations, the patient becomes pregnant at an inappropriate time, delaying to start the prenatal care, which could result in higher maternal and fetal complications. The authors report the case of a 41 years-patient, renal transplant, with hypothyroidism and chronic hypertension, which evolved in prenatal high risk, after renal transplantation, of an unplanned pregnancy.

This case report was approved by the Discipline of Obstetrics of the Federal University of Juiz de Fora and Ethics Committee of the Maternity Therezinha de Jesus.

Material and methods

Case report

ADM, 41 years, G3P2A0, referred to the high-risk prenatal due to chronic hypertension, hypothyroidism and renal transplantation performed five years ago. She had been taking azathioprine (100 mg day^{-1}), cyclosporine (250 mg day^{-1}), ferrous sulfate (120 mg day^{-1}), methyldopa (1 g day^{-1}), and levothyroxine (25 mcg day^{-1}). The hypotensive regimen prior to the pregnancy diagnosis was hydrochlorothiazide (12.5mg)

and enalapril (40mg day^{-1}). At the time of conception, the patient had creatinine 1.0 mg dL^{-1}, with creatinine clearance 79.7ml min^{-1} 1.73m^{-2}, and proteinuria 319mg 24h^{-1}. The immunosuppressive regimen was kept.

The laboratorial exams followed the criteria of the Brazilian Federation of Gynecology and Obstetrics (FEBRASGO, 2010) and are described in Table 1. Besides that, the Service of Nephrology of the UFJF accompanied the patient with fortnightly clinical assessments and monthly laboratorial tests (blood count, platelet count, serum creatinine, protein / creatinine ratio in urine sample, type I urine test and urine culture). She had initiated the prenatal care with 13 weeks of gestation, without complaints, hemodynamically stable and with exams of the first trimester, required by other service. She had anemia (Hb = 9.8) and urinary infection by *E. coli*, which was treated with cephalexin (2g day^{-1}). No ultrasound was performed in the first trimester of pregnancy.

During the evolution, the patient had three episodes of urinary infection treated with nitrofurantoin (400 mg day^{-1}), cephalexin (2 g day^{-1}) and cefuroxime (1 g day^{-1}), which led to the prophylaxis with macrodantin (100 mg day^{-1}). After the prophylaxis start, on the 22nd week, the patient had no further episodes of urinary infection. Furthermore, there was also a need for increasing the thyroid medication (125 mcg day^{-1}) in order to maintain the levels of TSH within safe values.

The patient developed a rise in blood pressure, requiring the increase of methyldopa (2 g day^{-1}), association with nifedipine (40 mg day^{-1}) and propranolol (40 mg day^{-1}), as in Figure 1 that shows the evolution of blood pressure and the antihypertensive medication administered.

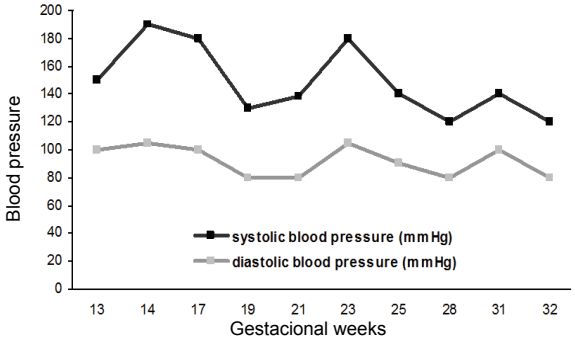

Figure 1. Evolution of blood pressure and association with gestational age (weeks). 1 - Aldomet 2 g day^{-1} + Nifedipine40 mg day^{-1}; 2 - Aldomet 2 g day^{-1} + Nifedipine 40 mg day^{-1} + Propranolol 40 mg day^{-1}. Source: Authors

Renal function remained stable, with creatinine and proteinuria around the baseline. The levels of cyclosporine (immunosuppressant) have not been significantly changed (Table 1).

Table 1. Laboratorial propaedeutics, according to second and third trimestres of gestation.

	Laboratorial propaedeutics conducted during prenatal care			
	Tests	First trimester	Second trimester	Third trimester
Routine Prenatal tests	Hemoglobin (mg dL^{-1})	9.8	8.3	9.4
	Hematocrit (%)	28.4	24.0	29.0
	Fasting glucose (mg dL^{-1})	88.0	90.0	78.0
	50 g of dextrose	xxx	92	xxx
	ABO and Rh	A +	xxx	xxx
	VDRL	NR*	NR*	NR*
	Serology for Toxoplasmosis	IgM negative IgG negative	IgM negative IgG negative	IgG negative IgG negative
	Serology for rubella	IgM negative IgG positive	xxx	xxx
	Serology for CMV	IgM negative IgG positive	xxx	xxx
	Anti-HCV	Negative	xxx	Negative
	Anti-HIV	Negative	xxx	Negative
	Urine routine	Altered; >20 pyocytes/field	Altered; > 20 pyocytes/Field	Pyocytes: 2/field; Nitrite negative
	Urine culture (UFC mL^{-1})	Positive; *E. coli* > 100,000	Positive; *E. coli* > 100,000	Negative
Testing for hypertension and renal function control	Urea (mg dL^{-1})	43	42	43
	Creatinine (mg dL^{-1})	1.0	1.0	1.0
	Uric acid (mg dL^{-1})	5.8	5.9	5.9
	24 hour-proteinuria	319	320	320
	K+ (mEq L^{-1})	3.8	4.3	4.3
	Ca++ (mEq L^{-1})	10.8	10.0	10.0
	Na+ (mEq L^{-1})	136	145	145
	Phosphorus (mEq L^{-1})	4.0	3.3	3.3
	TGO/TGP mg dL^{-1}	27/17	10/15	31/17
	Dosage of cyclosporine	195	203	189
Control tests for hypothyroidism	Free T4	1.0	0.8	0.9
	TSH	4.3	7.5	2.3
Control tests for anemia	Serum iron	124	90	90
	Ferritin	46	19	19

*NR= non reagent. Source: Authors

Nevertheless, it was found a decreased uterine progression after the beginning of the third trimester, characterizing a intrauterine growth restriction. It was indicated the induction of fetal lung maturity by means of betamethasone (12 mg day^{-1}) for two consecutive days and the termination

of pregnancy at 32 weeks of gestation after the diagnosis of change in the U/C ratio to the doppler. The Figure 2 presents the uterine growth development, and the Table 2 shows the description of the laboratorial exams during the three trimesters of pregnancy.

The newborn male was admitted to the neonatal intensive care unit and discharged with 1,995 g, in good condition.

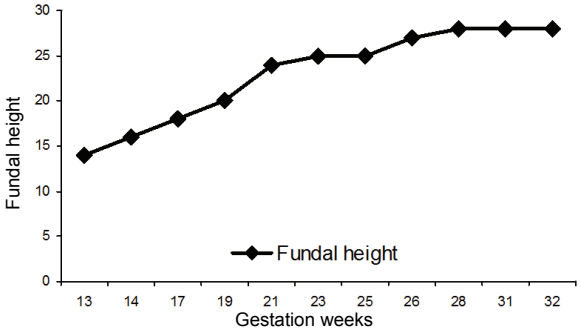

Figure 2. Association between the fundal height (axis y) and gestacion weeks (axis x). Source: Authors

Table 2. Ultrasound data of the first, second and third trimesters.

Ultrasound in gestational trimesters			
	First Trimester	Second Trimester	Third Trimester
Obstetric Ultrasound	Not performed	• Pregnancy topical, with good development. Gestational age of 13:5 days, with normal nuchal translucency of 1.7 mm – CCN= 72.9 mm; • Pregnancy single and topical, with good progress, with 19/20 weeks of development, normal amniotic fluid, anterior placenta, level I. Normal morphology by ultrasound; • Pregnancy single and topical, with 24/25 weeks, normal amniotic fluid, fetal hartbeat 130, and placenta body level I, weight: 700 g, normal morphology.	• Doppler of uterine arteries with bilateral notch. The rest without normality; • US with gestation of 31/32 weeks, doppler with U/C ratio higher than 1, consistent with centralization of flow. Reduced amniotic fluid.

Discussion

This case report is about a 41-year-old patient, renal transplant five years ago, in prenatal care, after unplanned pregnancy. Clinical data has evidenced uncontrolled high blood pressure and laboratory tests showed minimum proteinuria (319 mg dL^{-1}), with creatinine below 1.5 g dL^{-1}, five years of renal transplant, and immunosuppressant at maintenance dose. Despite being an unplanned pregnancy, clinical and laboratorial data were of low risk for a pregnancy, given the transplantation condition. These observations are consistent with authors who argue that the pregnancy should be delayed for 18-24 months for the stabilization of graft function, of the maintenance dose of immunosuppressive therapy and complete recovery after surgery (MILHEIRAS et al., 2005, MCKAY; JOSEPHSON, 2005; KDIGO, 2009). Considering only the patient's age (41 years) the obstetric risk was already greater than usual because of the possibility of fetal malformation, gestational diabetes, and preeclampsia, in addition to increased fetal mortality and morbidity (CECATTI et al, 1998; AZEVEDO et al, 2002; ANDRADE et al, 2004). But fortunately this fact did not change the pregnancy course in this patient.

The transplanted patient has higher risk for infection, thus the maternal-fetal transmission of infectious agents should be considered as a potential risk to mother and fetus. The infection by cytomegalovirus (CMV) is serious because is associated with loss of hearing and vision, mental retardation, and can be transmitted via placenta during delivery or breastfeeding. Other infections that can cause additional risks to immunosuppressed patients include the toxoplasmosis, syphilis, HIV and hepatitis B or C. The prenatal serological screening for these infections was negative (DEL MAR COLON; HIBBARD, 2007). The patient had three episodes of urinary infection, classified as asymptomatic bacteriuria, which could be treated with antibiotics at home. The infection was cleared after established the antibiotics prophylaxis, and in the third trimester of pregnancy there was no urinary infection. This evolution is considered excellent, taking into account that this patient had besides the pregnancy, two factors of risk for urinary infection: use of immunosuppressive drugs and hypothyroidism.

The patient was taking azathioprine and cyclosporine at maintenance doses, since the transplantation occurred five years ago. immunosuppression regimen was determined by the characteristic of the kidney donor who had the best possible match, in other words, had the same HLA (Human Leukocyte Antigens). Most gestations in renal transplant patients occurred under the use of these medications, which is considered the lowest risk combination (KDIGO, 2009). For this reason, the regimen was not changed. It is believed that azathioprine when administered to mothers can be found in the fetal blood, in the form of inactive metabolites, but at high doses (6 mg kg^{-1}) which are

no longer used, is teratogenic in animals. Moreover, the low weight at birth, prematurity, jaundice, and the respiratory distress syndrome are probably related to its use (LESSAN-PEZESHKI, et al., 2001). On the other hand, the azathioprine has been safely used in pregnant transplanted patients, so it is considered an acceptable immunosuppressant in clinical practice (MCKAY; JOSEPHSON, 2005; KDIGO, 2009).

Cyclosporine has little or no transplacental passage in rodents. In human, there are conflicting reports about the transference of cyclosporine through human placenta and some studies showed that its administration was associated with low weight at birth, higher incidence of maternal diabetes, hypertension, renal graft dysfunction and preeclampsia, once the production of thromboxane and endothelin is increased through the action of cyclosporine (BACKMAN et al, 1988; MASON et al, 1985; MURIRHEAD et al, 1992; LINDHEIMER; KATZ, 1992; LESSAN-PEZESHKI, 2001).

A recent study performed with 12 pregnant renal transplant patient verified complications in nine patients, such as urinary tract infection, preeclampsia, placental abruption, spontaneous abortions, intrauterine growth restriction, respiratory distress syndrome, and prematurity (DI LORETO et al, 2010). Bouattar et al (2009) identified 10 gestations in 7 transplant patients. The time between the transplantation and the beginning of pregnancy was 33.4$\pm$23.2 months, and all patients took cyclosporine, with no difference between serum creatinine levels before and after pregnancy. The complications registered were preeclampsia, hypertension, urinary tract infection, anemia, and two cases of neonatal death. In this case, the blood pressure was controlled with antihypertensive medication, there was no superimposed preeclampsia, and the uterine growth was satisfactory until early third trimester, when fetal growth has stopped. The termination of pregnancy was not caused by maternal hypertension, but by fetal distress, event reported in several studies (CORNELLA et al, 2009).

After renal transplantation, the hypothalamic-pituitary function usually improves, so pregnancy is a relatively common event (GASSEN et al, 2009). In this way, pre-conception advice should be done for all patients, exposing the possible risks of a pregnancy after transplantation, and when is the ideal time for a pregnancy (GUAZELLI et al, 2008; KDIGO, 2009)). On the other hand, the contraceptive advice is essential for all women of childbearing age, pre- and post-transplant, especially older ones (WATNICK; RUEDA, 2008). For this end, specific contraceptive methods should be individualized to the needs of the patient, since the risks of a pregnancy post-transplant are added up to the risks of pregnancy at an advanced age.

Conclusion

In summary, the pregnancy after renal transplantation is possible, and should be assisted by a multidisciplinary staff, considering the time of transplant, renal function, immunosuppressant medication in maintenance dose, and good control of blood pressure.

The contraceptive advice is of paramount importance to these patients, especial those without plans for new gestation and after 35 years old, once the risks of a pregnancy post-transplant are added up to the risks of pregnancy at an advanced age.

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Received on June 30, 2010.
Accepted on April 27, 2011