REVIEW ARTICLE

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The challenge of pregnancy after kidney transplantation

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ABSTRACT

Kidney transplantation restores the impairment in fertility of end-stage renal disease patients. The majority of pregnancies after renal transplantation are sucessful, although there are risks for the mother and for the fetus, related to graft function, rejection, hypertensive disturbances, infections, caesarian deliveries, as well as preterm and low birth weight babies. Immunosuppressive drugs and other medication have to be carefully reviewed before this period, and the timing of conception is also an issue of debate.

In this article the author reviews the most recent practices in the medical follow-up of a renal transplanted pregnant woman.

Key words: pregnancy, renal transplantation, risk factors

INTRODUCTION

The first successful pregnancy in a kidney transplant recipient occurred in 1958, in a woman who received a kidney from her twin sister and delivered a healthy baby boy at 40 weeks by caesarian section[1]. Since then, many successful pregnancies have been reported.

Current knowledge of pregnancy in kidney transplant is limited and arises from case reports, single and multicenter studies, and four voluntary registries including the National Transplantation Pregnancy Registry (NTPR) in the United States, the National Transplant Pregnancy Registry in the United Kingdom, the European Dialysis and Transplant Association (EDTA) Registry, and the Australian and New Zealand Dialysis and Transplant Registry[2-5].

Although the majority of pregnancies are successful, renal transplant recipients experience overall higher rates of caesarian sections, preterm (< 37 weeks) deliveries with babies of small gestational age and low birth weight[6]. Risk factors described in association with poor pregnancy outcomes are hypertension, elevated prepregnancy creatinine ≥ 1.4mg/dL, proteinuria, and history of ≥ 2 renal transplants[7]. There was about 6-fold higher likelihood of poor fetal outcome (stillbirth, miscarriage, neonatal death, birth < 32 weeks, and congenital anomalies) in women with high prepregnancy creatinine and high diastolic pressure during second and third trimesters as reported in a study by Bramham et al.[8]. In addition, young age at pregnancy and young age at transplantation are associated with a higher likelihood of successful outcomes of live births[7].

In 2016, 513 kidney transplantations were performed in Portugal, and almost 40% of the recipients were women. We do not have information about pregnancies in our transplanted women; apart from descriptions from some transplant units.

In this article the author reviews the challenges and most recent practices in the medical follow-up of a pregnancy in renal transplanted women.

FERTILITY IN END-STAGE RENAL DISEASE (ESRD)

Women with ESRD have abnormalities in their hypothalamic-pituitary-ovarian (HPO) axis, commonly manifested by amenorrhea, anovulation, decreased libido, vaginal dryness, orgasmic dysfunction, impaired fertility, hot flashes and earlier onset of menopause. Pregnancy is therefore rare in women on dialysis, with very low incidence of conception ranging from 0.9 to 7%. Even after conceiving successfully, there is a high risk of maternal and fetal complications[9]. Nevertheless, the results of pregnancy in dialysis patients have greatly improved over time, with a gain in fetal survival of almost 25% per decade, from 23% in the EDTA report in 1980, to near 50% in the 1998 report by Bagon et al., to over 90% of live babies in the recent Canadian series of patients receiving high efficiency, long-nocturnal dialysis treatments[10-12].

Kidney transplantation allows the HPO axis to normalize and normal levels of circulating sex steroids are typically restored within 6 months, resulting in fertility improvement[9,13]. In a recent meta-analysis from 2011, a total of 4706 pregnancies in 3570 kidney transplant recipients were reported from 2000 to 2010 with a live birth rate consistently between 72% and 80%, a rate that is comparable to the general population[6]. Though, in a large retrospective Italian study, kidney transplant recipients had a 10-fold higher probability of delivering a live child compared to women who conceive on hemodialysis, but a 10-fold lower probability when compared to the general population[14]. This discrepancy in the results is probably because of underreporting bias of early spontaneous miscarriages in voluntary registries.

PREGNANCY AFTER TRANSPLANTATION – CONSEQUENCES FOR THE MOTHER

1. Allograft function

It has been shown that even after compensatory growth in the transplanted kidney, there is a further increase in glomerular filtration rate (GFR) during gestation, and it results in a fall in the serum creatinine level, with return to baseline after delivery. How much the GFR increases depend on renal function before pregnancy; the better the GFR before pregnancy, and the bigger the increment in pregnancy. Although it has been suggested that the resultant hyperfiltration may cause progressive loss of renal function due to sclerosis in glomerulus from the increased pressures and/or plasma flow, glomerular hyperfiltration during pregnancy is transient and not accompanied by permanent renal impairment[15].

In the absence of the abovementioned risk factors, pregnancy itself has no impact on graft function, as reported by Richman *et al.* in a review of registry and single-centre practices and outcomes: kidney transplant recipients with a history of pregnancy compared to nulliparous controls showed no difference in graft function at years 1, 5, and 10 and comparable graft survival rates after 15 years (61.6–67.3% vs 58.1–68.7%)[16].

Conversely, history of drug treated hypertension, prepregnancy creatinine ≥1.4mg/dL and proteinuria >500mg/24h significantly increased the risk for irreversible graft loss as a result of the pregnancy[4,16-18].

2. Acute rejection

Pregnancy is a state of immunological tolerance associated with immunodepressant activity of lymphocytes, which creates tolerance to the fetus and may benefit the renal allograft. On the other hand, the antigenic stimulus provided by the fetus may trigger graft rejection, and rejection may be higher in the postpartum due to return to normal immunosurveillance status[7]. In addition, as a result of changes in blood volume, maintenance of immunosuppressive medication dosing can be difficult and higher dosages are required to maintain graft function[19].

Overall, acute rejection rates are not increased during pregnancies and in the first 3 months postpartum, and vary between 1 and 14.5%[4,20].

Risk factors for rejection include high serum creatinine, rejection before pregnancy, and changing levels of immunosuppressive drugs[21]. Therefore, to avoid graft rejection, immunosuppressive dosing should be maintained at prepregnancy levels through frequent monitoring of serum drug levels[20,22].

Detection of rejection can be difficult because it is frequently associated with a small rise in serum creatinine and could be confounded due to hyperfiltration related decrease in creatinine during pregnancy. If rejection is suspected, an ultrasound-guided allograft

biopsy is safe and recommended. If rejection occurs, it can be treated with corticosteroids[19].

■ 3. Hypertension and preeclampsia

Arterial hypertension and preeclampsia are the two main reasons for the high rate of preterm babies in renal transplant women[23].

Hypertension is common in kidney transplant recipients before and during pregnancy with a reported incidence of 52–73%[6,8,17,23]. It increases the risk of preterm delivery, intrauterine growth retardation (IUGR), and the risk of graft loss[17]. Furthermore, renal transplant patients with hypertension are at increased risk for development of superimposed preeclampsia, with an incidence of 21–38%, 6-fold higher than the general population (4–5%)[6,8,17,23].

Diagnosis of preeclampsia may be difficult because blood pressure commonly rises late in pregnancy; many patients have hyperfiltration related proteinuria, and hyperuricemia and edema are often coexistent in renal transplant patients[19].

Antihypertensive drugs should be initiated if the blood pressure is consistently higher then 140/90mmHg. Alfa and beta-adrenergic blockers, calcium channel blockers and thiazides are the agents of choice. Atenolol is an exception – it should be avoided because of concerns about fetal growth. Angiotensinogen converting enzyme inhibitors are contraindicated due to their association with pulmonary hypoplasia and oligohydramnios in the fetus[24]. Low dose aspirin reduces the risk of preeclampsia in a high-risk population and should be given to all renal transplant recipients[25].

■ 4. Infection

Maternal transplant recipients have a higher risk of infection as a result of the use of immunosuppressive medications. Urinary tract infections (UTI) occur in up to 40%, due to vesicoureteral reflux, mild hydronephrosis after transplant, and pregnancy related dilatation of ureters and renal collecting ducts[7]. Dipstick screening for UTI should be performed at every visit and urine cultures at 4-week intervals. Asymptomatic bacteriuria should be promptly treated with antibiotics for 2 weeks and prophylaxis continued throughout pregnancy[7,20].

Maternal-fetal transmission of infectious agents needs to be considered as a potential risk not only to the mother but also to the fetus. Intrauterine exposure to immunosuppressive agents causes characteristic changes in the immunological profile of infants born from kidney transplant recipients, including lower numbers of CD4+ T cells, activated CD8+ T cells, NK cells and regulatory T cells, as well as a dramatic reduction in B cell numbers[26].

Primary cytomegalovirus (CMV) infection results in 30–39% transmission to the fetus and up to 13% of them being symptomatic at birth[27]. Congenital CMV is associated with hearing loss, learning problems, microcephaly, mental retardation and perinatal death. The presence of maternal immunity does not absolutely protect the fetus, although it reduces the likelihood of transmission. Antiviral medication prophylaxis has not been recommended during pregnancy[7].

Herpes simplex infection (HSV) before 20 weeks of gestation is associated with an increased rate of abortion. A positive HSV cervical culture at term is an indication for caesarean section, aiming to minimize the risk of neonatal herpes. Acyclovir can be safely used in pregnancy[28].

Other infections that may pose additional risks include toxoplasmosis, primary varicella infection, HIV infection and infection with hepatitis B or C virus. It should be noted that women who are not rubella immune should receive the vaccine before transplantation, since live virus vaccines are contraindicated posttransplantation.

■ 5. Caesarian delivery

Most infants are delivered by caesarian section, with a reported incidence as higher as 64%, with the majority being for fetal distress[8]. The presence of the transplanted kidney in the false pelvis does not in itself indicate the need for caesarian section, however, and it should be performed only for obstetric reasons. Vaginal delivery is well tolerated and recommended in uncomplicated pregnancies[22].

■ 6. Gestational diabetes

There are conflicting observations about rates of gestational diabetes, but if any, there seems to be only a slightly increased risk of developing diabetes during pregnancy[6,8].

PREGNANCY AFTER TRANSPLANTATION – CONSEQUENCES FOR THE FETUS

Published registry reports, as well as case and centre reports, consistently point to a high risk for preterm delivery (<37 weeks) (40-60%), low birth weight (<2500g) and IUGR (≤10th percentile of weight for gestational age)[4,17]. The mean gestational age for newborn is 35.6 weeks with mean birth weight of 2420gr[6].

The incidence of preterm delivery has been reported to be 40–60% versus 5–15% in the general population and occurs mostly due to maternal or fetal compromise, rather than spontaneous preterm labor[4]. Bramham et al. reported that renal allograft recipients have a 13-fold higher risk of preterm deliveries, a 12-fold higher risk of low birth weight babies, and a 5-fold high risk of small for gestation babies as compared to the general population[8].

There is no higher risk of perinatal mortality in the absence of risk factors of hypertension, proteinuria, and impaired allograft function[4,8,17].

PREGNANCY AFTER TRANSPLANTATION – IMMUNOSUPPRESSION

All immunosuppressive drugs cross the placenta and have been detected in variable degrees in fetal circulation.

The Food and Drug Administration (FDA) categorizes drugs for pregnancy safety with letters from A through D and X. None of the immunosuppressive drugs are labelled A (no human risk), and the majority fall into category C, where risks and benefits have to be weighed.

1. Calcineurin inhibitors (CNI)

Tacrolimus and cyclosporine blood levels detected in the fetus are about half that of the mother. The rate of congenital malformations after gestational exposure to CNI was not higher than in the general population, so they are considered to be safe in pregnancy. Trough levels may fluctuate due to an increase in metabolic activity of cytochrome P450 3A, alterations in the volume of distribution and changes in drug-binding components in the blood, such as erythrocytes and albumin. Then, CNI trough levels should be carefully monitored, and there may be a 20–25% dose elevation required to achieve stable target trough levels in pregnancy[29].

Cyclosporine increases production of thromboxane and endothelin, which have been implicated in the pathogenesis of preeclampsia. Because of this, some physicians have suggested that the dose be limited to 2–4mg/Kg/day[28].

Tacrolimus is excreted in breast milk, but only 1% of the total weight-adjusted maternal dosage is present in the milk, with even less reaching the infant. The milk-to-blood ratio of tacrolimus level in the mother reportedly varies from 0.08 to 0.23, and it is often undetectable in the infant. Cyclosporine is readily excreted in breast milk, and milk-to-maternal blood ratio can be as high as 1.4, but infant levels are often undetectable[9].

2. Mycophenolic Acid

Mycophenolic acid and mycophenolate mofetil are category D drugs, and are associated with increased risk of spontaneous abortion and congenital malformation. A specific embryopathy pattern under first trimester exposure to mycophenolic acid has been described, characterized by microtia, orofacial clefts, coloboma, hypertelorism, micrognathia, congenital heart defects, agenesis of the corpus callosum, esophageal atresia, and digital hypoplasia[30].

They are contraindicated in pregnancy and should be stopped 6 weeks prior to conception. Mycophenolate is often switched to azathioprine in anticipation of conception[31].

There is no evidence of increased risk of miscarriages or malformations when mycophenolate is taken by the father[32,33]. However, the risk of genotoxicity cannot be ruled out, so the European Medicines Agency (EMA) recommends stopping mycophenolate before conception[34].

Women should be avoiding breastfeeding if they are taking mycophenolate, as clinical data on safety are inadequate.

3. Azathioprine

Azathioprine, which is converted to 6-mercaptopurine, is safe in pregnancy, even though it has been listed

as class D drug. Fetal liver lacks inosinate phosphorylase enzymatic activity, which converts 6-mercaptopurine to its active form thioinosinic acid and therefore the fetus is protected from its adverse effect[35].

Azathioprine is associated with a dose related myelosuppression in fetus but neonatal leukopenia is usually rare if maternal white blood cell count is greater than 7500/mm[336]. Doses ≤ 2mg/Kg/day are recommended[28].

Azathioprine is mostly undetectable in breast milk, and breastfeeding is considered safe[37].

■ 4. Corticosteroids

The placenta metabolizes 90% of the maternal dose of corticosteroids before it reaches the fetus;, therefore only low levels have been detected in fetal circulation. Steroids increase the risk of premature rupture of membranes and maternal hypertension and there are sporadic cases of fetal adrenal insufficiency, thymic hypoplasia and cleft palate usually at doses > 20g/day[7]. The dose of prednisone should be ≤ 15mg/day[28].

Exposure of infants to prednisone in breast milk is at most 0.1% of total maternal dose, and it does not cause adverse effects to infants[38].

■ 5. mTOR inhibitors (mTOR-I)

Safety information about fetal exposure to mTOR-I in humans remains sparse. In animal studies, sirolimus has been linked to increased fetal mortality, growth retardation and delayed ossification of skeletal structures[39].

Sirolimus is a category C drug and it is advisable to discontinue 6 weeks prior to planned conception.

There is insufficient information about sirolimus and everolimus absorption from breast milk, so breastfeeding should be avoided.

■ TIMING OF PREGNANCY AFTER KIDNEY TRANSPLANTATION

The optimal interval between transplantation and pregnancy remains a topic of debate. Patients should be counselled about the risks and challenges, and the time of conception should be individualized based on graft function, patient's age, infections, and comorbidities. Furthermore, patients should be closely monitored during pregnancy by the obstetric and transplant nephrology teams, due to the increased risk of adverse events.

Current guidelines in the United States recommend conceiving only after the first year posttransplantation, whereas the European guidelines recommend delaying pregnancy for a period of 2 years[20,22]. Furthermore, pregnancy is advisable if there is adequate and stable graft function (creatinine < 1.5mg/dL, and no or <500mg/24h protein excretion), stable maintenance immunosuppression, no use of teratogenic medications, no current fetotoxic infections, and no rejection within the past year[22].

There is a higher likelihood of viable fetal outcome when conception is within 2 years of a transplant[6], and it is safe to conceive even after 6 months provided the previous grounds are met[7]. By this time, viral prophylaxis has been completed and the immunosuppressive medication is at its nadir. Waiting longer may have a deleterious effect on pregnancy outcome, because of older mother age and renal function deterioration over time.

However, a recent retrospective study found that pregnancy in the first posttransplant year was independently associated with increased risk of all-cause graft loss [hazard ratio (HR): 1.18] and death-censored graft loss (HR: 1.25), and pregnancy in the second year was associated with increased risk of death-censored graft loss (HR: 1.26), while pregnancy in the third posttransplant year was not associated with an increased risk of death censored graft loss[40].

■ CONCLUSION

All women of childbearing age should be counselled as to the possibility and risks of pregnancy after kidney transplantation. Contraceptive advice should begin immediately after transplantation, because ovulatory cycles may begin soon in women with well functioning grafts[28].

The nephrological management of pregnancies after kidney transplantation entails 3 main responsibilities, namely, advising patients about the risks and optimal timing of pregnancy, managing maintenance

immunosuppression before and during pregnancy, and treatment of renal complications[13]. The experience of obstetric teams is critical for the good pregnancy outcomes.

To learn more about this topic, it is necessary that the Portuguese Transplant community gather and start a national registry, which will help transplant physicians' daily work, benefiting women who want to embark on the challenge of pregnancy after transplantation.

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