Pregnancy after renal transplantation: points to consider

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Introduction

Women with chronic renal failure suffer from loss of libido, anovulatory vaginal bleeding or amenorrhea and high prolactin levels [1]. On dialysis most experience decreased libido and reduced ability to reach orgasm [2–4]. Conception is rare for women on dialysis. It occurs at a rate of no more than one in every 200 patients [5].

Fertility is usually restored in women with renal transplants. Pregnancy is then common, occurring in 12% of women at childbearing age in one series [6]. Pregnancy success rate exceeds 90% after the first trimester. The recovery of fertility is less common in women who undergo transplantation close to the end of their childbearing years [3]. The first reported
successful pregnancy occurred in a recipient of a kidney transplant from an identical twin sister performed in 1958 [7]. Since then, there have been hundreds of successful pregnancies reported in renal transplant recipients [8].

**Effect of pregnancy on graft function**

Pregnancy causes an increase in the glomerular filtration rate. In theory, this could lead to hyperfiltration and glomerulosclerosis. However, the hyperfiltration of pregnancy is related to increased plasma flow, with no concomitant increase in intraglomerular pressure [9].

In cyclosporin-treated patients, graft dysfunction after pregnancy was seen in patients with higher mean serum creatinine levels and lower mean cyclosporin doses prior to conception [10]. Overall, in the majority of recipients studied, pregnancy does not appear to cause excessive or irreversible problems with graft function if the function of transplant organ is stable prior to pregnancy [11].

**Immunosuppressive drugs in pregnancy**

Currently, we have limited information regarding the toxicities and teratogenic potentials of these agents, although our knowledge has recently increased as more women maintained on immunosuppressive therapy for solid organ transplants have opted to become pregnant.

**Glucocorticoids**

The most commonly used glucocorticoids are the short acting agents; prednisone, prednisolone and methyl prednisolone. Radiolabelled prednisone and prednisolone can cross the placenta, but maternal- to- cord blood ratios are approximately 10:1 [12]. Adrenal insufficiency and thymic hypoplasia have occasionally been described in the infants of transplant recipients, but these problems are unlikely if the dose of prednisone has been decreased to 15 mg [13]. Cases of cleft palate or mental retardation have also been described in humans after *in utero* corticosteroid exposure [14]. Steroids may be implicated in the increased frequency of premature rupture of membranes of transplant recipients. They can also aggravate hypertension in the mother. Doses of prednisone greater than 20 mg/day have been associated with serious maternal infection. Treatment of rejection with steroids, if necessary, is not contraindicated, however, during pregnancy.

**Azathioprine**

Azathioprine is used during pregnancy in many transplant recipients. Radioactive labelling studies in humans have shown that 64–93% of azathioprine administered to mothers appears in fetal blood as inactive metabolites [15]. In the adult, azathioprine is metabolized to 6-mercaptopurine. The immature fetal liver lacks the enzyme inosinate pyrophosphorylase needed for conversion, and the fetus is relatively protected from the effects of the drug. In high doses (6 mg/kg), azathioprine is teratogenic in animals. In human studies low birth weights, prematurity, jaundice, respiratory distress syndrome and aspiration have been reported in kidney transplant recipients. Azathioprine has been associated with a dose-related myelosuppression in the fetus, but leukopenia is not usually a problem in the neonate if the maternal white blood count is maintained at values higher than 7500/mm³ [16].

**Cyclosporin**

There is little or no transplacental passage of cyclosporin in rodents [17]. In comparison, there are conflicting reports on the transfer of cyclosporin across the human placenta. Studies in pregnant rats have generally shown no effect of cyclosporin on organogenesis, although some renal proximal tubular cell damage can occur [18]. Human data showed that administration of cyclosporin was associated with low birth weights and a higher incidence of maternal diabetes, hypertension and renal allograft dysfunction. Cyclosporin metabolism appears to be increased during pregnancy and higher doses may be required to maintain plasma levels in the therapeutic range [19]. Some of the pregnancies in cyclosporin-treated women were complicated by pre-eclampsia. Cyclosporine increases production of thromboxane and endothelin, which have both been implicated in the pathogenesis of pre-eclampsia. Because of this, some physicians have suggested that the dose be limited to 2–4 mg/kg per day [20].

**Tacrolimus**

There is a paucity of data concerning the effect of tacrolimus on pregnancy. Among 100 pregnancies in 84 women treated with tacrolimus, of whom 27% were renal transplant recipients, 68 progressed to a live birth, with 60% of deliveries being premature [21]. As with cyclosporin, patients taking tacrolimus require frequent monitoring of renal function and drug levels. During pregnancy, the hepatic cytochrome P450 enzymes may be inhibited, which can lead to increased serum level of tacrolimus. The dose may therefore have to be significantly reduced to prevent toxicity (sometimes by as much as 60%).

**Mycophenolate mofetil**

There is concern based on animal studies that the risk of birth defect or abortion is increased in pregnant women exposed to MMF. Nevertheless, one recent report showed successful use of MMF during...
placenta. Because precise data are limited at the moment we do not recommend its use [11,22].

**OKT3 and polyclonal antibodies**

OKT3 is an immunoglobulin G (IgG) that crosses the placenta. The National Transplantation Pregnancy Registry (NTPR) has reported on treatment of five women with OKT3 during pregnancy, with four surviving infants [23]. The effect of polyclonal antibodies on the developing fetus is not known, but the IgG component would be expected to cross the placenta.

**Management guidelines**

All women of childbearing age should be counselled concerning the possibility and risks of pregnancy after kidney transplantation. Women who are not rubella immune should receive the rubella vaccine before transplantation, because live virus vaccines are contraindicated post-transplantation [3]. Women are usually advised to wait at least 1 year after living related donor transplantation and 2 years after cadaver transplantation. However, waiting 5 or more years may result in impaired renal function post-partum that fails to recover, because of gradually deteriorating renal function secondary to chronic rejection.

Contraceptive counselling should begin immediately after transplantation, because ovulatory cycles may begin within 1–2 months of transplantation in women with well functioning grafts. Low dose oestrogen–progestosterone oral contraceptive preparations are advised. The risk of infection from the use of intrauterine devices is increased in immunocompromised patients. The efficacy of IUDs may be reduced because of the anti-inflammatory properties of immunosuppressive agents.

Criteria that should be ideally met before conception are shown in Table 1.

**Management of hypertension**

Women with mild to moderate hypertension should be watched closely, warned about signs of early pre-eclampsia and delivered at 37 weeks of gestation.

**Table 1. Criteria for transplant recipients contemplating pregnancy**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Reference</th>
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<tbody>
<tr>
<td>At least 1 year post-transplantation</td>
<td>3, 11, 20</td>
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<tr>
<td>Stable renal function with creatinine &lt;2 mg/dl</td>
<td>3, 11, 20</td>
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<tr>
<td>No recent episodes of acute rejection</td>
<td>3, 11, 20</td>
</tr>
<tr>
<td>BP ≤140/90 mmHg on medications</td>
<td>3, 11, 20</td>
</tr>
<tr>
<td>Proteinuria ≤500 mg/day</td>
<td>3, 11, 20</td>
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<tr>
<td>Prednisone ≤15 mg/day</td>
<td>3, 11, 20</td>
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<tr>
<td>Azathioprine ≤2 mg/kg/day</td>
<td>3, 11, 20</td>
</tr>
<tr>
<td>Cyclosporin ≤4 mg/kg/day</td>
<td>3, 11, 20</td>
</tr>
<tr>
<td>Normal allograft ultrasound</td>
<td>3, 11, 20</td>
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</tbody>
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This list is drafted mainly from references 3, 11 and 20.

**Antihypertensive drugs used in pregnancy**

- Methyldopa. Its safety and efficacy are supported by the results of several randomized trials and by a 7.5 years follow-up study of children born to mothers treated with α-methyldopa.

- Beta Blockers. Cardiovascular beta blockers, especially atenolol and metoprolol, appear to be safe and efficacious in late pregnancy; but fetal growth retardation has been noted when treatment was started in early or midgestation [24]. Non-selective beta blockers should not be used because of the risk of uterine contractions.

- Hydralazine. Hydralazine is safe and used frequently as adjunctive therapy with α-methyldopa and beta blockers.

- Calcium channel blockers. Nifedipine, nicardipine and verapamil have been used in severe hypertension of pregnancy. They do not appear to be associated with any increase in congenital anomalies when used in the first trimester [3]. Calcium channel blockers may potentiate the hypotensive effects and neuromuscular blockade of magnesium and the interaction should be kept in mind when the drugs are used in women with a possibility of developing pre-eclampsia [25].

- Labetalol. Labetalol appears to be as effective as methyldopa, but there is little follow up information on children born to mothers treated with this drug.

- ACE inhibitors. Exposure to ACE inhibitors during the second and third trimester may be associated with serious adverse fetal effects. Most of these problems relate to disturbances of fetal and neonatal renal function, such as oligohydramnios, neonatal anuria, renal failure and death [26]. The fetal outcome is generally good in women who present in early pregnancy while taking an ACE inhibitor if the drug is stopped. Continued administration of an ACE inhibitor during pregnancy is contraindicated [27].

- Diuretics. The use of thiazide diuretics has been approved in women with chronic hypertension if prescribed before gestation, however, the recommendation is against their use in pre-eclamptic women, who often manifest decreased intravascular volumes and poor placental perfusion.

**Management of infection**

- Bacterial

Urinary tract infections are the most common bacterial infections and occur in up to 40% of pregnant transplant recipients. They are particularly common in patients who develop end-stage renal disease due to pyelonephritis. These women should have monthly screening urine cultures [28], if asymptomatic bacteriuria is present; the patient should be treated for
2 weeks and may be treated with suppressive doses of antibiotics for the rest of the pregnancy. If there is a need for invasive procedures such as fetal monitoring with scalp electrodes or intrauterine pressure monitoring, prophylactic antibiotics are recommended. The selection of antibiotics should consider potential fetal toxicity. Penicillins which do not interact with eukaryote metabolism are the preferred antibiotic agents.

**Viral**

Cytomegalovirus (CMV) remains the most frequent cause of viral infection post-transplantation; however, if the patient waits the recommended time after transplantation to become pregnant, she has passed the peak time of risk for CMV infection.

Infection of the fetus can be diagnosed by culturing the amniotic fluid. Ganciclovir has caused birth defects in animals when administered at twice the human dose [3].

Herpes simplex virus (HSV) infection 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. This can minimize the risk for neonatal herpes. Acyclovir can be safely used in pregnancy [29].

An infant born to an HBSAg-positive mother should be given hepatitis B immunoglobulin within 12 h of birth and HBV vaccine at another site within 48 h followed by a booster injection at 1 and 6 months.

The combination of immunoglobulin and vaccine offers protection for more than 90% of infants. Vertical transmission is believed to be low (<7%) with hepatitis C unless the patient is also infected with the human immunodeficiency virus.

**Labour and delivery**

Vaginal delivery is recommended in most transplant recipient women. Caesarean section should be performed only for standard obstetric reasons. Care must be taken to avoid fluid overload and infection. At the time of delivery, instrumentation should be minimized. Patients with renal insufficiency may be particularly at risk of water retention secondary to oxytocin.

In the perinatal period, the steroid dose should be augmented to cover the stress of labour and to prevent post-partum rejection. Hydrocortisone, 100 mg every 6 h, should be given during labour and delivery. Breastfeeding is discouraged for patients taking any immunosuppressive drugs. Cyclosporin measurement in maternal blood and breast milk revealed a mean breast milk/maternal blood level ratio of 0.84 [30]. These levels can be toxic to a newborn. Similar recommendations exist for tacrolimus or other immunosuppressive agents.

**Conclusion**

Pregnancy does not appear to have generally any adverse effect on the long-term survival of renal allotrafts. Because the outcomes of pregnancy in transplanted women are so different from those in women on intermittent dialysis, it is advisable to treat end-stage renal disease patients with transplantation and wait until renal function has been stable for 1–2 years before undertaking a planned pregnancy. Such planned pregnancies offer to the mother and fetus the best chance of a favourable outcome.

**References**


