Pregnancy after organ transplantation

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Submitted: 2008-09-22 Accepted: 2008-10-29 Published online: 2009-02-28

Key words: **kidney transplantation; liver transplantation; solid organ transplantation; pregnancy complications; delivery; cesarean section; immunosuppression**

Neuroendocrinol Lett 2009; **30**(1): 6–10 **PMID:** 19300385 NEL300109R04

REVIEW

Abstract

Ovarian function with regular menstrual cycles is usually restored in women of reproductive age after solid organ transplantation. The number of pregnancies reported in these patients increases gradually. Pregnancy is always considered high risk, and not properly planned may lead to serious complications. The best for the patient is to conceive in a period of good general health and good stable graft function, after appropriate preparation and not later than five years after transplantation. Immunosuppressive regimen should be modified before conception. Sirolimus and mycophenolate mofetil should be excluded. The blood levels of immunosuppressive agents should be regularly controlled during the whole pregnancy. The rate of successful pregnancies is approximately 95% in graft recipients. Increased incidence of preterm labor, anemia and intrauterine growth restriction is observed compared with general population. Organ transplantation itself is not an indication for cesarean section and vaginal delivery is recommended as the best for the patient, the graft and the newborn. Breast feeding is believed to be contraindicated in women on immunosuppressive therapy, however no adverse effects were reported in children of graft recipients who decided to breast feed. The rate of congenital malformations in newborns is approximately 3–4% and does not differ from the rate seen in general population. The rate of perinatal deaths decreased beneath 0.8% in recent reports. Jaundice, hyperglycemia and hyperkalemia, observed more frequently in newborns of graft recipients, are mild and in most cases do not have any clinical implications.

INTRODUCTION

The group of allograft recipients constitutes of patient from various age ranges. The significant part of women, approximately 12% of kidney recipients and 75% of liver recipients, is of reproductive age. Improvement of general health and restoration of endocrine function are observed soon after successful transplantation. Ovarian function with regular menstrual cycles is usually restored in renal transplanted women within an average of six months [18] and in liver recipients within nineten months [7]. Ovulatory cycles are reported in approximately 40% of patients, however, 40% rate of disturbed lutheal function is observed [23,24]. Normal function of the graft together with the significantly improved general health and life quality is associated with the natural need for motherhood in women of childbearing age.

The first successful pregnancy in a woman after organ transplantation (renal transplantation) was noted as early as in 1958 [20]. In 1967 Board [3]

Abbreviations & Units:

PAP smear – Pappanicolau smear
l – liter
dl – deciliter
g – gram
mg – milligram
kg – kilogram
μmol – micromol
HBV – Hepatitis B Virus
HCV – Hepatitis C Virus
CMV – Cytomegalovirus
HSV – Herpes Simplex Virus
HPV – Human Papilloma Virus
FDA – Food &Drug Administration
WBC – White Blood Count
CsA – Cyclosporine A
Aza – Azathioprine
Tac – Tacrolimus
MMF – mycophenolan mofetil
NTPR – The National Transplantation Pregnancy Registry
EDTA – European Dialysis and Transplantation Association
Ig – Immunoglobulin
VDRL – Venereal Disease Research Laboratory test
Rh – Rhesus factor

and Kauffman [15] described first vaginal deliveries in graft recipients under immunosuppressive therapy. First woman after liver transplantation delivered in 1978. Great majority of information regarding pregnancies in transplanted women, associated complications and outcomes comes from The National Transplantation Pregnancy Registry (NTPR) established at Thomas Jefferson School of Medicine in Philadelphia in 1991, data of European Dialysis and Transplantation Association (EDTA) and reports from different transplant centers. The data of live births, spontaneous and therapeutic abortions, stillbirths and ectopic pregnancies are collected. The analyses of approximately 7500 pregnancies in 6200 graft recipients (mainly renal graft recipients) since 1990 indicate for over 95% rate of successful pregnancies and increase in the risk of preterm labor and intrauterine growth restriction compared with general population [1,2]. Chances for uneventful course of pregnancy and healthy newborn are much higher in patients with stable graft function at the time of conception [9,28].

Organ transplantation in pregnant woman is performed extremely rare as well as conception in the early post-transplant period is rarely reported [7]. At that time high level of immunosuppressive agents is required, what is associated with the increased incidence of intrauterine growth restriction, acute graft rejection and severe infections [9]. Moreover some immunosuppressive agents may induce developmental abnormalities. After numerous congenital malformations had been observed in offspring of women treated with mycophenolan mofetil (MMF), in 2002 European Best Practice Group recommended eliminating that agent from immunosuppressive regimen at least six weeks before planned conception [9,16]. Most data regarding the course and outcome of pregnancy, the effect of pregnancy on both the recipient and the graft come from observational studies of women after renal transplantation. In order to decrease the risk of the adverse outcomes in renal graft recipients in 2002 EDTA created and published guidelines recommended before conception in patients considering pregnancy [9]:

1. Good general health for about two years after transplantation
2. Good stable graft function: serum creatinine < 2 mg/dl (177 μmol/l), preferably < 1.5 mg/dl (133 μmol/l)
3. No recent episodes of acute rejection and no evidence of ongoing rejection
4. Normal blood pressure or mild arterial hypertension with minimal anti-hypertensive regimen (only one drug)
5. Absence of or minimal proteinuria (<0.5 g/day)
6. Normal allograft ultrasound
7. Recommended immunosuppressive regimen: Prednisone <15 mg/day, Azathiophrine ≤ 2 mg/kg/day, Cyclosporine or tacrolimus in therapeutic levels. Mycophenolan mofetil and sirolimus are contra-indicated.

MANAGEMENT OF GRAFT RECIPIENT BEFORE CONCEPTION

Care of the pregnant graft recipient during the course of pregnancy, labor and puerperium should be given by the team of specialists including a transplant physician, an obstetrician and a neonatologist. All patient should be informed that the pregnancy is always considered high risk, and not properly planned may lead to serious complications, including both heath-threatening and life-threatening states. The best for the patient is to conceive in a period of good general health and good stable graft function, after appropriate preparation and not later than five years after transplantation in order to diminish the risk of chronic graft rejection [3,23].

Microbiological studies for viral infections (HBV, HCV, CMV, rubella) and toxoplasmosis should be performed. Rubella vaccine should be administered prior to transplantation in all seronegative women of reproductive age. Hepatitis B vaccine is also recommended unless the patient is already immunized. At least six weeks before conception is attempted immunosuppressive regimen should be modified. Sirolimus and mycophenolate mofetil should be excluded in order to avoid their reported teratogenic effects [8,27]. Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists can not be used in the treatment of arterial hypertension. Blood glucose levels should be monitored and in case of any abnormalities in all diabetic patients the kind and doses of insulin need to be modified to

achieve normal glucose control. No foci of infections should be found and negative urine culture should be achieved before conception [28].

MANAGEMENT DURING PREGNANCY

Early detection of pregnancy is of great importance. During the whole pregnancy patients are administered immunosuppressive therapy and blood levels of immunosuppressive agents should be regularly controlled (at least monthly). Steroids, widely used in immunosuppressive treatment (class B according to FDA) crosses the placenta and achieves 1:10 of the maternal level in fetal circulation. Adrenal insufficiency and thymic hyperplasia have been observed in the infants, however such complications are not reported if the doses of steroids are<15 mg/day. The high rate of severe maternal infections is associated with the doses of steroids over 20 mg/day. The increased incidence of premature rupture of the membranes has been also observed [31]. Azathioprine (class D according to FDA) crosses the placenta, but in 64–93% in the form of inactive metabolite. Tests on animals proved the teratogenic effect of Aza in doses > 6 mg/kg/day. In case of WBC lower than 7500/mm^3 in pregnant women treated with Aza, myelosuppression with leucopenia has been observed in newborns [22]. Cyclosporine A (class C according to FDA) is administered in higher doses in pregnancy and its blood levels should be regularly monitored. Although no CsA placental transfer or only minimal transfer is observed, lesion of fetal renal tubules has been reported in animals [29]. The increased risk of gestational diabetes, arterial hypertension, renal lesion and low birth weight of the neonates is noted in pregnant women treated with CsA. The reported higher rate of preeclamsia is believed to be associated with the induced increase in tromboxan and endothelin production. In reflect of the above data some authors suggest to decrease the doses of CsA to 2–4 mg/kg/day in all pregnant women [17, 21]. Tacrolimus (class C according to FDA) is administered in lower doses in pregnancy, but regular controls of its blood levels are also necessary [10,14].

Untill the 20th week of gestation obstetrician and transplant physician visits should be performed every four weeks and bi-weekly thereafter. Complete blood count, urinalysis and the urine culture, serum creatinine, creatinine clearance, electrolytes and the daily proteinuria should be obtained on every visit. Sonographic examination of the fetal intrauterine growth is performed monthly. In all seronegative patients measuring tires of IgG and IgM to CMV and toxoplasmosis should be repeated in each trimester and additionally test for HSV need to be performed in the last trimester. The microscopic inspection of vaginal discharge is obligatory in each trimester. Likewise all pregnant women, graft recipients should have PAP smear obtained and VDRL and Rh immunization tested. The vaginal and anal swab should be cultured for Group B Streptoccocci in the third trimester. Every-day control of blood pressure and body weight is obligatory. All pregnant transplanted women should be referred for hospitalization to specialized multidisciplinary centers [4, 9,17,28].

DELIVERY

Vaginal delivery is recommended as the best for the patient, the graft and the newborn (the limited blood loss and lower risk of infections). Organ transplantation itself is not an indication for cesarean section. Majority of cesarean sections in graft recipients is performed for obstetrical indications or severe deterioration of maternal condition [13,26]. According to literature cesarean sections are performed in approximately 46–55% of renal recipients, 35% of liver recipients, 57% of renal-pancreas recipients, 30% of heart recipients and 38% of lung recipients [1,2,5,6,12,19]. If the operative procedures are performed, staff must strictly follow all sanitary regulations, doses of steroids should be increased and prophylactic antibiotics, most likely cephalosporin and metronidazole, administered.

PUERPERIUM

Breast feeding is believed to be contraindicated in women on immunosuppressive therapy and the lactation is inhibited after labor. Cyclosporine A is secreted into breast milk where reaches 1:10 of maternal serum level. Such concentrations may significantly influence the newborn. Other immunosuppressive agents are also contraindicated during lactation [10,11]. In NTPR there are data, however, about 32 immunosuppressed graft recipients who breast fed 37 children within the period from several days to two years. No adverse effects were reported in those children [1,2].

On the first day of puerperium the doses of immunosuppressive agents are usually increased due to the post-partum regression of physiological pregnancy-associated immunotolerance. The blood levels of immunosuppressant agents (CsA, Tac) should be determined on the third day of puerperium and the doses readjusted when necessary. In renal recipients 50% increase of the steroid dose is advised during the first two weeks of puerperium in order to cover the stress of labor and protect against postpartum graft rejection [9,21].

MOST COMMON COMPLICATIONS OF PREGNANCY

Abortion

According to data from NTPR spontaneous abortion is observed in 20%–24% of pregnancies in renal transplanted women on tacrolimus-based or CsA-based

immunosuppressive regimens. In the group of recipients treated with MMF or/and rapamycine 62.5% of pregnancies finish in spontaneous abortion. The incidence of abortion in liver recipients on CsA, Aza, Tac and steroids is approximately 19%. The rate of still birth in graft recipients is estimated to be 1–3% [1,2,5, 26].

Hypertension

Among women after renal transplantation, 62–72% of patients treated with CsA and 58% of women receiving Tac present arterial hypertension. It is observed in 35% of pregnant liver graft recipients and in up to 75% of patients after renal-pancreas transplantation. The rates of pregnancy induced hypertension (PIH) are estimated to be approximately 30% in renal recipients, 23% in liver recipients and 34% in renal-pancreas recipients [1,2,17,26]. α-Methyldopa and hydralazine are most frequently used anti-hypertensive agents in pregnant patients. In late pregnancy beta-blockers (atenolol, metoprolol) may be also administered. Their use in early pregnancy, however, may be associated with intrauterine growth retardation. Non-selective beta-blockers should not be administered due to the risk of premature uterine contractions. Labetalol is rarely used in particularly severe cases but there are no data in literature regarding its safety for the fetus. Calcium channel blockers administered in the first trimester may lead to congenital malformations and should be discontinued before conception is attempted. A number of adverse effects, mainly renal dysfunction or failure and intrauterine death, may appear in women using angiotensin-converting enzyme inhibitors in the second and third trimester. No data indicate for their negative effects in the first trimester, however, those agents are contraindicated in pregnant patients. Diuretic agents should not be administered during pregnancy due to their negative impact on plasma volume and placental blood flow [9,28].

Premature labor

Premature labor occurs in 52–54% of renal recipients and 78% of renal-pancreas recipients. 36% of women after liver transplantation deliver prematurely [1, 5, 14, 26].

Congenital malformations

The rate of congenital malformations in graft recipients is approximately 3–4% and does not differ from the rate seen in general population [1].

Anemia

Anemia, frequently observed complication in pregnant graft recipients, can be deteriorated by myelosuppression associated with immunosuppressive therapy. Erythropoietin deficiency, associated with renal failure, is observed not only in renal transplanted patients and is accompanied with lower anemia-induced erythropoietin secretion. The stores of iron, folic acids and vitamins should be supplemented, myelotoxic agents eliminated and in most severe cases treatment with erythropoietin administered [9].

Infections

Urinary tract infection is most commonly seen infectious complication of pregnancy in transplanted women (40%). Functional and anatomic changes of the urinary tract, urinary retention and immunosuppressive treatment predispose pregnant patients to urinary tract infections. In case of positive urine culture, antibiotics according to antibiogram are administered and prophylactic treatment is recommended for the rest of the pregnancy. Pregnant immunocompromised graft recipients are also at increased risk of viral infections: CMV, HSV, HPV, HBV (highest risk of vertical transmission) and HCV and of toxoplasmosis [4,31,32].

COMPLICATIONS IN CHILDREN OF GRAFT RECIPIENTS

Some complications, like jaundice, hyperglycemia and hyperkalemia, are observed more frequently in newborns of graft recipients compared to those of healthy mothers. In most cases the disturbances are mild and do not have any clinical implications. Sometimes transient adrenal insufficiency is reported in newborns of patients treated with high doses of steroids. During the first year diminished production of antibodies is observed in most children. Some authors have noted retarded mental and psychomotor development as well as the lack of concentration in children of graft recipients. The study groups were too limited, however, to draw final conclusions. The rate of perinatal deaths was 2% in the 80-ties of the twentieth century and decreased beneath 0.8% in recent reports [1,2,26].

THE IMPACT OF PREGNANCY ON THE GRAFT FUNCTION

According to NTPR data pregnancy in patients with stable graft function does not increase the risk of rejection [1,2, 25]. In 12% of women deterioration of graft function is observed either in the course of pregnancy or after the delivery. Acute rejection appears in 9% of renal recipients, 10% of liver recipients, 10% of renal-pancreas recipients, 20% of heart recipients and up to 36% of lung recipients. No case of graft loss has been observed in 33 women after heart transplantation within the two-year observational period.

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