IV.10 Pregnancy in renal transplant recipients

Guidelines

A. Renal transplantation restores fertility, and successful pregnancies have been reported in renal transplant women. In women with normal graft function, pregnancy usually has no adverse effect on graft function and survival. Therefore, women of childbearing age who consider pregnancy should receive complete information and support from the transplant team.
(*Evidence level B*)

B. Pregnancy could be considered safe about 2 years after transplantation in women with good renal function, without proteinuria, without arterial hypertension, with no evidence of ongoing rejection and with normal allograft ultrasound.
(*Evidence level B*)

C. Pregnancy after transplantation should be considered a high-risk pregnancy and should be monitored by both an obstetrician and the transplant physician. Pregnancy should be diagnosed as early as possible. The principal risks are infection, proteinuria, anaemia, arterial hypertension and acute rejection for the mother, and prematurity and low birth weight for the foetus.
(*Evidence level B*)

D. Pregnant women and transplanted patients are at increased risk of infections, especially bacterial urinary tract infections and acute pyelonephritis of the graft. Urine cultures should be performed monthly and all asymptomatic infections should be treated. Monitoring of viral infections is also recommended.
(*Evidence level B*)

E. Acute rejection episodes are uncommon but may occur after delivery. Therefore, immunosuppression should be re-adjusted immediately after delivery.
(*Evidence level C*)

F. Because pre-eclampsia develops in 30% of pregnant transplant patients, especially those with prior arterial hypertension, blood pressure, renal function, proteinuria and weight should be monitored every 2–4 weeks, with more attention during the third trimester. Antihypertensive agents should be changed to those tolerated during pregnancy. ACE inhibitors and angiotensin II receptor antagonists are absolutely contra-indicated.
(*Evidence level B*)

G. Immunosuppressive therapy based on cyclosporine or tacrolimus with or without steroids and azathioprine may be continued in renal transplant women during pregnancy. Other drugs, such as mycophenolate mofetil and sirolimus, are not recommended based on current information available. Because of drug transfer into maternal milk, breastfeeding is not recommended.
(*Evidence level C*)

H. Vaginal delivery is recommended, but caesarean section is required in at least 50% of cases. Delivery should occur in a specialized centre. In the puerperium, renal function, proteinuria, blood pressure, cyclosporine/tacrolimus blood levels and fluid balance should be closely monitored.
(*Evidence level C*)

Commentary on Guidelines IV.10: Pregnancy in renal transplant recipients

Guideline A. Following transplantation, fertility is usually restored in renal transplant women within an average of 6 months [1,2]. In recent years, thousands

of successful pregnancies in renal transplant women have been reported [3–8]. Therefore, transplanted women of childbearing age must be informed that they are able to conceive and should receive appropriate contraception.

Davison reported the most important series of pregnancies after renal transplantation: 3382 in 2409 women, showing that 34% finished in therapeutic (20%) or spontaneous abortion (14%), comparable with that of the general population [9]. Notably, of the gestations that continued beyond the first trimester, 94% ended successfully. However, the incidence of pre-term delivery was 50%, and intrauterine growth retardation was seen in at least 20% of pregnancies with neonates of very low birth weight. In general, labour and delivery are uncomplicated and caesarean section is generally reserved for obstetric reasons only.

In many women, GFR increased during pregnancy, as in the general population, and the magnitude of the increase was related to the baseline GFR [10]. During the last trimester, GFR may decline to values before pregnancy. In some patients, renal function may deteriorate with or without proteinuria in the last 3 months. There are several studies from European [2,6] and American [11] units focusing on the question of whether pregnancy has a negative effect on graft function. The majority of the studies suggest that pregnancy itself does not have a deleterious impact on long-term graft function and survival in women with serum creatinine <133 μmol/l (1.5 mg/dl). Only one study from Finland showed that graft function and survival are negatively affected by pregnancy [12]. Therefore, the consensus at present is that pregnancy usually has no effect on renal function and survival. The National Transplantation Pregnancy Registry (NTPR) showed that graft loss within 2 years after delivery was 8, 1.8 and 10% in women treated with cyclosporine, cyclosporine emulsion and tacrolimus, respectively [13].

Proteinuria may appear or increase to abnormal levels in the last 3 months, but normally disappears after delivery [14]. In general, proteinuria has clinical implications only if it is associated with arterial hypertension [15]. Thirty percent of women present arterial hypertension, pre-eclampsia or both [9], and arterial hypertension at conception is associated with adverse perinatal outcome [8]. Foetal outcome is related to renal function at conception. Thus, successful foetal outcome is seen mainly in women with serum creatinine <124 μmol/l (1.4 mg/dl) [8]. As discussed below, immunosuppressive treatment did not induce a high incidence of developmental abnormalities [9,15].

Guideline B. Based on the information above, related guidelines have been recommended before conception in patients after renal transplantation [9,10,15]. The most important criteria are summarized in Table IV.8.

Although some successful pregnancies have been described in women who become pregnant less than 1 year post-transplant, there is a general consensus to advise female recipients to wait ~ 2 years after transplantation before conception. In a recent study, a long interval from transplantation to conception was a significant predictor of successful outcome [16]. Also, the frequency of prematurity is greater when pregnancy is established <2 years post-transplantation [10,15–17].

Table IV.8. Criteria for considering pregnancy in renal transplant recipients

1 Good general health for about 2 years after transplantation
2 Good stable allograft function [serum creatinine <177 μmol/l (2 mg/dl), preferably <133 μmol/l (<1.5 g/dl)]
3 No recent episodes of acute rejection and no evidence of ongoing rejection
4 Normal blood pressure or minimal anti-hypertensive regimen (only one drug)
5 Absence of or minimal proteinuria (<0.50 g/day)
6 Normal allograft ultrasound (absence of pelvicalyceal distension)
7 Recommended immunosuppression:
  Prednisone <15 mg/day
  Azathioprine $\leqslant 2$ mg/kg/day
  Cyclosporine or tacrolimus at therapeutic levels
  MMF and sirolimus are contra-indicated
  MMF and sirolimus should be stopped 6 weeks before conception is attempted

Women must be advised to avoid conception: contraceptive counselling should be given to women of childbearing age immediately after transplantation, because ovulatory cycles may be normal in the first month after transplantation in women with normal graft function.

One to two years after transplantation, renal function will probably be adequate and stable, and immunosuppressive therapy will be administered at maintenance levels. In fact, 90% of successful pregnancies have been described in women with good renal function, i.e. serum creatinine of 133 μmol/l (1.5 mg/dl) or less [9,15]. Also, a low dose of prednisone is associated with good outcome [16].

Normal blood pressure or minimal arterial hypertension is another crucial point. Bar *et al.* found that the absence of pre-existing arterial hypertension was a significant predictive factor for successful outcome [16]. In contrast, the presence of arterial hypertension at conception is associated with an adverse perinatal outcome [14], and the relative risk of pre-eclampsia is at least five times greater in patients with pre-existing arterial hypertension.

The presence in the first trimester of nephrotic-range proteinuria with hypoalbuminaemia—as occurs in primary glomerulonephritis—is associated with spontaneous abortion, prematurity and intrauterine growth retardation [4], and is a significant risk factor for fetal prognosis. In transplanted women, the situation is similar, and nephrotic-range proteinuria may arise due to chronic rejection or recurrent or *de novo* glomerulonephritis. Therefore, proteinuria should be <500 mg/day before pregnancy [9,10,15].

Normal ultrasound without urinary obstruction before pregnancy is recommended. The presence of

hydronephrosis at conception is associated with infections and lithiasis. During pregnancy, hydronephrosis is expected and can worsen pre-existing dilation [10].

At the present time, cyclosporine microemulsion or tacrolimus is used as basic immunosuppression. Successful pregnancies have been reported under both drugs [9,13,15], as discussed below.

Guideline C. The recommended schedule for monitoring and management of pregnant transplanted women is listed in Table IV.9. Care of the pregnant transplant recipient should be given by a nephrologist and/or transplant physician and by an obstetrician specialized in treating women with renal disease [9,10,15]. It is important to diagnose the pregnancy early, and immediate evaluation of the foetus by ultrasound is mandatory.

It is important to emphasize that rubella vaccine should be administered before transplantation in women of childbearing age, because live viral vaccines are contra-indicated after transplantation [10]. In women who meet the criteria in Table IV.8, it is necessary to know before pregnancy the Rh compatibility, different viral serologies, blood glucose and whether they are taking drugs with teratogenic effects, such as ACE inhibitors, angiotensin receptor antagonists, MMF or sirolimus. These drugs should be discontinued before conception is attempted [10]. During pregnancy, foetal surveillance and monitoring of blood pressure, renal function and proteinuria are very important, together with microbiological studies and urine cultures.

Guideline D. Pregnant renal transplant women are at increased risk of infection, especially bacterial infections. Indeed, 40% of such patients have urinary tract infections, and acute pyelonephritis is relatively frequent in patients with chronic pyelonephritis or reflux nephropathy as the cause of end-stage renal disease. Davison recommended monthly screening of urine cultures. In the case of asymptomatic bacteriuria, the patients should be treated for 2 weeks, then prophylactically with antibiotics for the rest of the pregnancy [9].

Hepatitis B infection is a problem in infants of carriers of hepatitis B antigen, because they become carriers in almost 80% of cases [10]. In this situation, the combined administration of hepatitis B immunoglobulin and hepatitis B vaccine is effective at preventing infection in 95% of cases [10,15]. Vertical transmission of hepatitis C is low (< 7%). In newborns from HCV^+ transplant patients, anti-HCV antibodies can disappear within 6 months of delivery [10].

Because pregnancy is only recommended after ~2 years, CMV infection in pregnant renal transplant recipients seems to be low. At 2 years, the risk of CMV infection is less than in the first year post-transplant. However, CMV infection, primary or reactivation, can transmit to the foetus [18]. Congenital CMV infection is associated with perinatal death, microcephalus or mental retardation in 10% of cases, and some children, apparently normal at delivery, can show hearing loss and learning problems. Culturing of amniotic fluid is essential to allow CMV diagnosis in the foetus [19]. The efficacy and safety of treating the mother with ganciclovir or CMV hyperimmunoglobulin to prevent foetal CMV disease are not known. This therapy should be only started after considering the safety of the mother, as ganciclovir can induce birth defects in animals. Hou recommended measuring titres of anti-CMV IgG and IgM every 3 months during pregnancy [10].

Herpes simplex infection can be transmitted from the mother to the child during birth, and caesarean delivery in infected women can attenuate the risk of neonatal herpes 1 or 2 [20]. Therefore, when a positive herpes infection is demonstrated in cervical cultures, caesarean section should be carried out. Acyclovir can be used during pregnancy [21], but when herpes infection is seen before 20 weeks of gestation there is an increased rate of abortion [10].

Congenital toxoplasmosis infection occasionally occurs after reactivation of toxoplasmosis in immunosuppressed patients, and patients with increasing antibody titres should be considered for therapy with sulfadiazine and pyrimethamine or spiramycin. Pregnant renal transplant recipients should be tested for toxoplasmosis every 3 months [10,15].

Guideline E. The incidence of acute rejection is not greater than expected for non-pregnant transplant patients. Thus, the incidence of acute rejection during pregnancy and 3 months after delivery varies between

Table IV.9. Monitoring and management of pregnant transplant women

Pre-transplantation
Rubella vaccine
Pre-pregnancy (in women meeting conception criteria)
Rh compatibility of patients and transplant
Microbiology studies for hepatitis B, C, herpes simplex, CMV, toxoplasmosis and rubella
Normal blood glucose
Discontinue ACE inhibitors or angiotensin receptor antagonists
Discontinue MMF and sirolimus
Monitoring during pregnancy
Daily
Blood pressure monitoring of the patient
Bi-weekly/monthly
Nephrologist and obstetrician visit
Complete blood count, chemistry panel
Serum creatinine and creatinine clearance
Electrolytes and 24 h proteinuria
Cyclosporine or tacrolimus blood levels
Urine culture
Monthly
Ultrasound
Each trimester
IgM to CMV and toxoplasmosis for seronegative women
Last trimester
IgM to herpes simplex for seronegative women
Bi-weekly foetal surveillance
Careful monitoring of blood pressure

Adapted from Hou [10].

9 and 14.5% in the published series [9,10,13,15]. From a report of 230 renal recipients treated with cyclosporine, factors associated with rejection during pregnancy were rejection before pregnancy and high serum creatinine before and during pregnancy [22]. Acute rejection may occur coincidental with changing levels of cyclosporine or tacrolimus. Frequently, it is necessary to increase the dose of both drugs during pregnancy [23].

Rejection is sometimes difficult to diagnose, and ultrasound-guided biopsy may be helpful to diagnose acute pyelonephritis, recurrent glomerulonephritis and severe pre-eclampsia [9,10,15]. Renal biopsy should be performed before starting anti-rejection therapy, and high steroid doses are the first line of treatment [9,10,15]. OKT3 in cortico-resistant acute rejection has also been administered in some cases [23].

It has been suggested that pregnancy is associated with a privileged immunological status that can benefit the kidney allograft [9,15,16]. It has been suggested that acute rejection during the puerperium may be due to a return to a normal immune status or to a 'rebound effect' from the altered gestational immunoresponsiveness [15]. Danovitch recommends increasing the dose of steroids (to 100 mg of hydrocortisone during labour and delivery) to cover the stress of labour and to prevent post-partum acute rejection [15].

Chronic rejection is a problem in pregnant women, as in all transplant recipients. It is unknown whether pregnancy influences the course of chronic rejection. Theoretically, hyperfiltration associated with pregnancy [2,9] could contribute to chronic allograft failure as a non-immunological factor.

Guideline F. Based on the data of the NTPR, Armenti and colleagues showed that maternal drug-treated hypertension is a significant pre-pregnancy factor that increases the risk of low birth weight, especially in patients treated with cyclosporine [5,13,22]. Thus, if arterial hypertension is present at conception, careful monitoring of blood pressure during pregnancy is absolutely mandatory.

Pre-eclampsia is defined as pregnancy-induced arterial hypertension occurring in the third trimester. It is an important complication because the presence of pre-eclampsia has an unfavourable impact on birth weight [8,15,22]. The incidence of pre-eclampsia ranges between 27 and 38% in the NTPR [22] and is 4-fold higher in renal transplant women than in uncomplicated pregnancies [10].

The diagnosis of pre-eclampsia is sometimes difficult, mainly in patients with pre-existing arterial hypertension or chronic rejection in the last trimester presenting as deterioration of renal function and proteinuria. In renal transplant women, the plasma uric acid is not a useful marker for pre-eclampsia, because hyperuricaemia induced by cyclosporine or tacrolimus is present at all stages of pregnancy [15,23,24]. In the case of severe pre-eclampsia (haemolytic uraemia, elevated transaminase and thrombocytopenia—the HELLP syndrome), differential diagnosis should be carried out with severe acute rejection and mainly with haemolytic–uraemic syndrome [10]. Allograft biopsy is required only occasionally for diagnosis.

Adequate treatment of pre-eclampsia is essential. α-Methyldopa is the first-choice drug to control arterial hypertension (10%). It is effective and does not induce any deleterious effect in the foetus [25]. Clonidine and calcium channel blockers could be used as a second line. It is important to note that ACE inhibitors are contra-indicated during pregnancy. They have been associated with oligohydramnios, pulmonary hypoplasia and neonatal death by respiratory failure [26]. In the case of hypertensive emergencies, intravenous hydralazine is the drug of first choice and labetalol is the second [10]. If blood pressure is not controlled in the last months, hypertensive patients should be hospitalized. If there is a progressive difficulty in controlling blood pressure in the hospital, induction of labour is mandatory [15]. There are no effective treatments to prevent pre-eclampsia. Hou recommends treating women with renal insufficiency with 80 mg of aspirin in the second trimester [10].

Guideline G. Prednisone crosses the placenta, but adrenal insufficiency and thymic hyperplasia have been reported only occasionally in the infants of transplanted women [27]. These problems are unlikely when taking low doses of prednisone (5–10 mg/day). Prednisone is considered relatively safe in transplanted women, although high doses of prednisone have been associated with severe maternal infections [10]. In spite of this, patients with rejection should be treated with a high dose of steroids [15].

Azathioprine crosses the placenta but is not converted in the immature foetal liver to 6-mercaptopurine. High doses are teratogenic in animals but, at doses of $\leqslant 2$ mg/kg/day, no anomalies have been described in offspring [28]. Azathioprine can cause transient gaps or breaks in human lymphocyte chromosomes, but it is not known whether it is associated with the development of malignancies or other abnormalities in offspring [10]. Azathioprine has been associated with dose-related myelosuppression in the foetus, but without clinical implications if the mother's blood leukocyte count is $> 7500/\mu l$. Also, dose-related azathioprine liver toxicity has been observed occasionally during pregnancy.

Classical cyclosporine or cyclosporine microemulsion have not been associated with teratogenicity or mutagenicity. However, they are associated with intrauterine growth retardation and small-for-gestational-age babies. The NTPR reported low birth weight (< 2500 g) in 46% and 54% of 456 and 68 pregnancies in transplant women treated with cyclosporine and cyclosporine emulsion, respectively. These values were higher than those observed when prednisone and azathioprine were used: 39% low birth weight [23,29]. Recently, Di Paolo *et al.* reported that continuous exposure to cyclosporine in the uterus

impairs T, B and natural killer cell development and/or maturation in the infants of cyclosporine-treated female kidney transplant recipients [30]. Also, most of its effects are still evident at 1 year; it is unknown whether these data have clinical implications.

About 50% of patients on cyclosporine present arterial hypertension before pregnancy, and this value increases during pregnancy to 62 and 70%, with incidences of pre-eclampsia of 27 and 23% in women treated with cyclosporine and cyclosporine emulsion, respectively [23]. In this way, cyclosporine increases the production of thromboxane and endothelin, which are implicated in the pathogenesis of pre-eclampsia [10]. Also, ~25% of women treated with cyclosporine have serum creatinine >133 μmol/l (1.5 mg/dl) during pregnancy.

Finally, close monitoring of cyclosporine blood levels is a very important issue. The increased distribution volume usually produces low maternal cyclosporine levels [23].

Experience with tacrolimus is limited compared with cyclosporine. However, there are several publications reporting that pregnancy under tacrolimus in transplanted patients (kidney, liver and pancreas–kidney) was successful [31–34]. A recent article from Germany demonstrated live birth in 68%, spontaneous abortion in 12%, induced abortion in 12% and still birth/perinatal death in 3% of 83 pregnancies in transplanted women (53 liver and 22 kidney). Fifty-nine percent of the neonates were delivered prematurely (<37 weeks of gestation) [34]. In 90% of the cases, birth weight was appropriate for the gestational age, and malformations were similar to those induced by other immunosuppressive agents. This experience agrees with data in the NTPR [23]. Therefore, 70% of pregnancies under tacrolimus had a favourable outcome without any important effect on intrauterine growth and without a major incidence of malformations compared with other regimens.

Tacrolimus crosses the placenta, and doses should be increased frequently to maintain adequate blood levels. Related side effects under tacrolimus are hyperkalaemia and renal insufficiency in some series after liver transplantation.

In animals, an increased risk of malformation in newborns of females treated with mycophenolate mofetil (MMF) has been reported. The risk seems to be minor in offspring of men treated with MMF: no structural malformations were observed in 29 liveborns fathered by males treated with MMF at conception. The NTPR reported experience with nine pregnancies, showing no birth defects among five liveborn of females under MMF immunosuppression. However, until more information is available, treatment with MMF during pregnancy is contra-indicated [13] and should be stopped 6 weeks before conception is attempted.

Sirolimus is contra-indicated in pregnancy.

OKT3 crosses the placenta, and the NTPR has reported several cases of women treated with OKT3 for acute rejection during pregnancy, with occasionally good outcome but with spontaneous abortion in others [23]. All liveborn infants develop normally, at least in the short term after delivery. The effect of polyclonal antibodies on the foetus is unknown [10].

Steroids, azathioprine, cyclosporine and tacrolimus are excreted in breast milk in small percentages of the maternal doses. Currently, the clinical implications of the possible effects on the neonate are unknown, and therefore breastfeeding should be contra-indicated.

Guideline H. The time of delivery for renal transplant women and patients with renal insufficiency is usually delayed until the onset of labour if maternal and foetal conditions remain satisfactory [10]. Vaginal delivery is recommended and caesarean section is usually performed only for standard obstetric reasons [9,10,15,35]. Therefore, before conception, X-ray pelvimetry should be done to plan caesarean section if it is necessary.

The incidence of pre-term delivery is 50% because of the presence of pre-eclampsia, renal function deterioration, foetal distress, premature rupture of membranes and premature labour [9]. Intrauterine growth retardation showing small-for-age babies is present in 20% of pregnancies [9,13,15]. In general, successful foetal outcome is related to better renal function at conception. Despite immunosuppressive therapy, there is no increase of foetal abnormalities. Infants born to transplanted women should be monitored by a specialist paediatrician, even if they are healthy [10].

Danovitch recommended administering steroids during labour and delivery to cover the stress of labour and to protect against acute rejection [15]. In the perinatal period, renal function, proteinuria, coagulation, arterial hypertension and fluid balance should be monitored closely. Cyclosporine/tacrolimus blood levels should be determined frequently to adjust the dose of immunosuppressive agents. In the first 3 months after delivery, transplanted women should be followed closely in the renal transplant unit because renal function deterioration or even acute renal failure due to haemolytic–uraemic syndrome is seen occasionally [15].

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