# TRANSPLANTATION RÉNALE / KIDNEY TRANSPLANTATION
## PREGNANCY AND RENAL TRANSPLANTATION

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**ABSTRACT** • Pregnancy is common nowadays in kidney transplant female patients because of medical and surgical advances. However, pregnancy is a high risk one in these patients. Fertility is rapidly restored after the transplantation; thus, contraception is a good option in the first year. Adding to that, pregnancy can endanger the allograft function in the presence of hypertension, a moderate to severe kidney disease and proteinuria. Medical complications are more prevalent in kidney transplant population, such as infections, gestational hypertension and diabetes and anemia. Low birth weight infants and premature delivery are two other major concerns in this population. Acute rejection of the allograft is another major complication that can be avoided with close monitoring of the graft and convenient immunosuppression. Immunosuppressive drugs must be continued during pregnancy except for mycophenolic acid and sirolimus that can be teratogen. Delivery of kidney transplant patients should be vaginal and spontaneous. Cesarean section should be reserved for obstetrical indications. Prophylactic antibiotics should be administered for every invasive procedure. Patients treated with corticosteroids can breastfeed their babies. Kidney donating women can have a safe pregnancy but with a slight risk of gestational diabetes and hypertension. In summary, a multidisciplinary medical team should follow pregnant kidney transplant patients in a tertiary center. International and national registries are a must to collect data concerning this particular high-risk population in order to solve unanswered questions.

Keywords: kidney, transplant, pregnancy, high risk, immunosuppression, complications

**RÉSUMÉ** • La grossesse chez les patientes ayant eu une greffe rénale est devenue commune de nos jours, grâce aux avancées médicales et chirurgicales. Cependant, la grossesse de ces patientes est à haut risque. La fertilité est rapidement rétablie après la transplantation rénale ; d'où la contraception est une bonne option durant la première année suivant la greffe. De plus, la grossesse peut détériorer la fonction du greffon, surtout si la patiente présente une hypertension artérielle, un dysfonctionnement rénal modéré à sévère, et/ou une protéinurie. Les complications médicales sont plus fréquentes chez les greffées rénales, comme les infections, l'hypertension gravidique, le diabète et l'anémie. Les retards de croissance intra-utérins et la prématurité sont deux autres complications prévalentes chez ces patientes. Le rejet aigu de la greffe est une complication majeure potentielle ; elle peut être évitée en surveillant de près la fonction rénale et par le biais d'une bonne immunosuppression. Les immunosuppresseurs doivent être continués pendant la grossesse sauf l'acide mycophénolique et le sirolimus pouvant être tératogènes. L'accouchement des patientes transplantées doit être par voie basse et spontané. La césarienne est réservée aux patientes ayant des complications obstétricales. Une antibiothérapie prophylactique est indiquée lors des gestes invasifs. Les patientes sous corticostéroïdes peuvent allaiter. Quant aux patientes donneuses du greffon, elles peuvent avoir une grossesse sans réserve en sachant que le diabète et l'hypertension gravidiques sont un peu plus fréquents chez elles. En résumé, les patientes greffées rénales doivent être suivies pendant leur grossesse par une équipe médicale multidisciplinaire et dans un centre tertiaire. Des registres nationaux et internationaux sont recommandés pour la collecte des données concernant cette population particulière, afin de trouver des réponses aux questions non résolues.

## INTRODUCTION

The first reported successful pregnancy in a kidney transplant (KT) recipient occurred in a kidney recipient from an identical twin sister in 1958 [1]. Since that event, more than 14000 pregnancies in KT patients have been reported worldwide [2].

The number of patients receiving an organ transplant and the incidence of pregnancy in the kidney transplant patient population has increased over the past decade. Advances in surgical techniques and immunosuppressive therapy have improved the survival and quality of life in organ transplant patients. Thus, the number of women within the reproductive age group with organ transplants has also increased. This development demands a heightened awareness of the factors relevant to organ transplantation and pregnancy [3].

Currently, over half of the approximately 100 000 women in the United States living after KT are of childbearing age.

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It has been suggested that KT recipients might be more susceptible to pregnancy complications than their healthy counterparts [4]. KT recipients commonly have comorbidities, such as cardiovascular disease and diabetes, that can put both their pregnancy and their allograft at risk [4]. In addition, previous abdominal surgery, long-term exposure to risky pharmacological agents and advanced maternal age are other factors that can lead to an increased risk of pregnancy complications [4].

Unfortunately, till now, pregnancy complications and their risk factors in KT patients have not been studied in a generalized manner, nor the effect of pregnancy on the allograft and the optimal interval between pregnancy and transplantation.

Current knowledge of pregnancy-related outcomes after KT is limited to a few existing registries, namely a National Transplantation Pregnancy Registry (NTPR) in the United States (founded in 1991), a registry in the United Kingdom (established in 1997 and since discontinued) and one in Australia/New Zealand. The data collected included maternal outcomes, medical and obstetric complications as well as patient and graft survival after pregnancy. These registries also collect, via detailed questionnaires, extensive information on fetal outcomes. As of 2008, post-transplant pregnancies reported to NTPR exceeded 1200, whereas the results from over 800 gestations have been recorded in the UK database [5-6].

Data from these registries only represent one-third of the available information on reported pregnancy outcomes in KT recipients. About two-thirds of the clinically available information on post-KT pregnancy comes from retrospective single-center cohort studies from across the world.

In this article, we summarize current evidence and recommendations for the medical and obstetrical management of the pregnant kidney transplant recipient, based on a review of the medical literature, expert opinion, and European and American guidelines.

### FERTILITY, CONCEPTION AND COUNSELING IN RENAL TRANSPLANT RECIPIENTS

Pregnancy is relatively uncommon in patients with end-stage renal disease (ESRD) since they suffer from hypothalamo-pituitary axis and ovarian dysfunction, anovulatory vaginal bleeding, amenorrhea, high prolactin levels, and loss of libido. Fertility rates in ESRD patients are nearly 10 times lower than their healthy counterparts [7]. As renal function improves following kidney transplantation, endocrine functions generally improve which leads to normal menses and ovulatory cycles; thus fertility resumes in most women few months following KT [8].

However, irregular bleeding remain a major problem in KT patients, since only 49% patients report normal menstruation after KT [9].

About one in fifty patients having functioning grafts become pregnant, according to a report from the National Transplantation Pregnancy Registry in 2004 [10]. Gill *et*

*al*. reported a pregnancy rate of 33 per thousand in female patients aged 15-45 years, between 1990 and 2003 in the United States [11].

Since pregnancy in KT patients is considered a high-risk pregnancy, counseling should be offered to these women.

Counseling should include information regarding options for contraception, optimal timing for pregnancy, known pregnancy and fertility rates, maternal and fetal outcomes, risk of immunosuppression on the fetus, risk of deterioration in renal allograft function, and medical complications that may arise as a result of the pregnancy. They should be informed as well, that many questions have no answers till now and some of our knowledge is controversial.

### CONTRACEPTION

Women of childbearing age having a kidney transplant should be aware of the pregnancy possibilities. Contraception must be initiated very early after kidney transplant, because ovulatory cycles can begin one to two months after transplant in functioning grafts.

Contraception can consist of low dose oral contraceptives (estrogen-progesterone) and barrier methods (diaphragms, condoms, cervical sponges with spermicidal agents). Intrauterine contraceptive devices should be avoided because of potential risk for infections [12]. In complicated patients (acute or chronic patients), barrier methods (condoms, spermicide, and diaphragm) and progesterone-based hormonal contraception are safest [13].

### RENAL ADAPTATION TO PREGNANCY IN TRANSPLANT RECIPIENTS

Moderate-to-severe chronic kidney disease (CKD) is a risk factor for pregnancy-associated complications and neonatal morbidity independent of transplantation.

Women with CKD can be divided into three categories based on serum creatinine (SCR) levels: mild functional impairment (SCR < 1.4 mg/dl), moderate functional impairment (SCR between 1.4 and 2.4 mg/dl) and severe impairment (SCR > 2.4 mg/dl) [14]. There is a direct relationship between the degree of renal impairment and physiological adaptation to pregnancy. Women with severe reductions exhibit little or no increase in glomerular filtration rate (GFR) throughout pregnancy [15]. In addition, women who begin pregnancy with a SCR above 2.0 mg/dl are at substantial risk to experience an accelerated decline in renal function during or after pregnancy and have an increased likelihood of preterm delivery with more than 40% risk of preeclampsia [16].

Renal allografts adapt to pregnancy in the normal fashion. However, the increment in function is abrogated when compared with native kidneys and dependent on pre-pregnancy SCR. The expected reduction in GFR seen in the third trimester compared with prepregnancy levels is twice that observed in nontransplant pregnancies [17].

## PREGNANCY ISSUES
## AFTER KIDNEY TRANSPLANTATION

Pregnancy in kidney transplant recipients presents high risk of complications.

First, these patients experience a high risk of infections especially bacterial infections. Indeed, 40% of these patients have urinary tract infections, and acute pyelonephritis is relatively frequent. A monthly urine culture screening is recommended, and if a symptomatic bacteriuria is diagnosed, the patient should have antibiotics for two weeks, then prophylactically during all the pregnancy [18].

Cytomegalovirus (CMV) infection is also an issue in KT patients. However, since pregnancy is recommended two years after KT, CMV infection incidence is very low. CMV infection, primary or reactivation can transmit to the fetus, causing congenital anomalies [19]. That's why Hou recommends measuring titers of anti-CMV IgG and IgM, once every trimester [20]. Pregnant KT recipients should be tested, as well, for toxoplasmosis every three months because toxoplasmosis could be reactivated in immunosuppressed patients, and then should be treated with sulfadiazine and pyrimithamine or spiramycin [20-21].

It should be noted that rubella vaccine should be administered before KT in women of childbearing age, because live viral vaccines are contraindicated after transplantation [20]. Other infections that are of concern include herpes simplex virus, hepatitis B, hepatitis C, and human immunodeficiency virus. In non-immune patients, hepatitis B vaccination can be given prior to a pregnancy [22].

Beside infections, hypertension and preeclampsia are highly prevalent in KT recipients. A meta-analysis done by Deshpande et al. found a 54,2% rate of hypertension in KT recipients and 27% of preeclampsia (v/s 3.8% in the US population) [23]. The rate of preeclampsia reported by the NTPR among patients on maintenance cyclosporine A (CSA) or tacrolimus was approximately 29% [24]. The UK Transplant Pregnancy Registry reports the incidence of preeclampsia as high as 36% [6].

Three commonly reported prepregnancy factors were described in association with adverse pregnancy outcomes: hypertension, elevated serum creatinine (SCr) and proteinuria [23].

Hypertension should be managed aggressively. Alphamethyldopa is considered the drug of choice because of its well-documented safety and lack of teratogenicity. Second-line agents include nifedipine, labetalol, hydralazine, and hydrochlorothiazide. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists are absolutely contraindicated because of their known teratogenic effects on the fetus [25-28]. In severe hypertension, intravenous antihypertensive agents should be administered to prevent ecclampsia: labetolol and/or hydralazine [28]. Deshpande et al. found as well 8% rate of gestational diabetes in these patients, which is much higher than in the US population (3.9%); it was high in all the populations as well. Miscarriage rate wasn't higher than in the rest of the population (14%) [23].

Anemia is also more frequent in KT pregnant recipients because of underlying kidney disease and suboptimal erythropoietin production, as well as myelosuppressive and even hemolytic effects of medication. A complete blood count should be monitored every 2-4 weeks and reversible causes should be investigated. In most cases, treatment consists of administering oral or intravenous iron [29]. Erythrocyte-stimulating agents appear to be safe and useful in these patients because erythropoiesis is reduced [30].

## NEONATAL OUTCOMES
## AFTER KIDNEY TRANSPLANTATION

The NTPR and the UK Transplant Pregnancy Registry report live birth rates of 75-80% [6, 31]. KT pregnant recipients have an increased prevalence of preterm delivery (37 gestational weeks) and low-birth weight infants (< 2500 g). Over 50% of the babies born to RTRs are delivered at less than 37 weeks of gestation [4, 32]. A large Canadian series [33] supports this finding with a 44% rate of preterm deliveries.

The major risk factors associated with preterm delivery included a SCR above 150 $\mu$mol/l (1.7 mg/dl) before pregnancy and preexisting maternal hypertension [6]. In fact, preterm delivery and low-birth weight infants are correlated to the degree of graft function. Children of mothers with better graft function had higher birth weights, and lower rates of premature delivery [34]. Kidney transplant recipients with biopsy-proven acute rejection episodes during pregnancy were more likely to deliver infants with very low birth weights (< 1500 g) [36].

One should note that preterm delivery is rarely spontaneous and is usually a result of elective cesarean delivery owing to maternal complications, namely hypertension/preeclampsia and deteriorating renal function [6].

A causal link between immunosuppressive drugs and intrauterine growth retardation has not been established yet.

Delivery of the fetus should occur in a specialized center. In the absence of complications, spontaneous labor can be allowed to occur up to 38- to 40-week gestation [36]. Vaginal delivery is preferred and cesarean delivery performed only for obstetric indications [25-26]. Stress-dose steroids during delivery have been recommended for patients on chronic maintenance steroids. Prophylactic antibiotics should be given for any invasive procedures, including amniotomy and episiotomy [4].

## INFLUENCE OF PREGNANCY ON ALLOGRAFT
## REJECTION AND LONG-TERM GRAFT OUTCOME

The impact of pregnancy on allograft function remains controversial [37]. Studies suggested that pregnancy does not have a deleterious effect upon the allograft [10,

38-39], as long as there is good baseline graft function and maternal hypertension is absent [6, 25, 39-42].

The overall risk of graft rejection during pregnancy reported by NTPR in patients receiving calcineurin inhibitors is 2-4% [35].

A preliminary report from NTPR suggests that women with suboptimal renal function (SCR > 1.5 mg/dl) are more likely to have acute rejection episodes during pregnancy. It has been suggested, as well, that an acute rejection during pregnancy confers a poorer graft survival within the first two years after pregnancy [43].

In other published series, the incidence of acute rejection during pregnancy and three months after delivery varies between 9 and 14.5% [18,20-21,44].

No difference was noted in outcomes between living donor and deceased donor kidney recipients [31]. The UK registry, in a matched case-control study of 139 patients, did not show any evidence for increased renal allograft loss after pregnancy [6]. Similarly, a study from the Australian and New Zealand Dialysis and Transplant Registry was reassuring as for allograft function during and after pregnancy [41].

Despite all these reassuring data, graft function must be monitored closely during pregnancy and in the postpartum period by measuring serum and urine urea nitrogen and creatinine, and urine protein excretion every 2 to 4 weeks and more frequently in the third trimester. Any graft dysfunction should be investigated. Differential diagnoses include acute rejection, preeclampsia, volume depletion, drug toxicity, infection, obstruction, and recurrent disease. A renal biopsy under ultrasound guidance is usually necessary to establish an exact diagnosis. [4, 36].

Risk factors for rejection include a high serum creatinine and changing immunosuppressive drug levels during pregnancy. Steroids are the first-line treatment and are considered safe [26,42].

The long-term effects of pregnancy on renal graft is less clear but one of the few studies done on this subject suggests that pregnancy does not adversely affect the long-term survival of the renal graft as well as the patient [40].

OPTIMAL TRANSPLANT TO CONCEPTION TIME
AND ALLOGRAFT SURVIVAL

Although successful pregnancies have been described in women who become pregnant less than one year post-transplant, there is a general consensus to advise female recipients to wait ≈ 2 years after transplantation until conception [25]. It is suggested that the interval between transplantation and pregnancy can affect both graft survival as well as maternal-fetal outcomes [27, 42, 45]. For example, some studies suggested that prematurity is more frequent when pregnancy is established < 2 years post-transplantation [20-21,45].

The recent American Society of Transplantation consensus summary guidelines regarding the timing of pregnancy are currently: a minimum period of one year after transplantation, no acute rejection episodes in the previous year and adequate graft function defined by a SCR below 1.5 mg/dl and no/or minimal proteinuria (less than 500 mg/24 h) [26]. Normal ultrasound without urinary obstruction is recommended as well prior to conception.

IMMUNOSUPPRESSIVE MEDICATIONS
DURING PREGNANCY

The first successful pregnancy in a kidney transplant patient in the setting of immunosuppression (azathioprine and prednisolone) was reported by Hume and colleagues in 1967 [46]. All immunosuppressants used to prevent rejection of transplanted organs cross the maternal-placental interface [47]; however, due to the position of the liver between fetal inferior vena cava and the umbilical vein, all pharmacologic substances that pass the placenta are filtered by the liver before entering the fetal circulation [48].

Immunosuppressive agents must be continued during pregnancy to prevent renal allograft rejection [25-26, 49].

Effects of these medications on the fetus are difficult to determine because of the lack of controlled trials on drug safety in pregnancy [49]. Evidence is therefore largely based on case reporting and data collected by registries such as the National Transplantation Pregnancy Registry.

Birth defects are the major concern about immunosuppressive medications.

The NTPR has evaluated 2000 pregnancy outcomes in female transplant recipients. The incidence of birth defects in the live born was found to be similar to the general population, except for pregnancies with mycophenolic acid (MPA) exposure. Its use was associated with a 23% incidence of birth defects. Long-term follow-up of their offspring has provided reassurance after 20 years of observation [50].

*Corticosteroid* treatment benefits in KT pregnant recipients outweigh its risk. There is no actual evidence that its use increases the risk of congenital anomalies. It may be associated with adrenal suppression in the neonates; nevertheless, it rapidly resolves and has no clinical importance [51-52].

As for *azathioprine*, it is considered as category D (teratogen) for pregnant women because of evidence of skeletal, visceral, and hematologic abnormalities in rodent fetuses [53-54] as well as observations of human fetal immunosuppression and malformations [55]. However, no specific pattern of structural birth defect can be attributed to this drug [56-57]. Therefore, it isn't recommended to discontinue azathioprine during pregnancy [25-26], but it can cause low birth-weight infants and premature birth specially when associated with corticoids [51-52].

*Calcineurin inhibitors* (cyclosporine and tacrolimus)

can be continued during pregnancy.

*Cyclosporine* use is associated with premature birth and low birth weight [51]. It does not appear to have major teratogen effects on humans. Pregnant women exposed to calcineurin inhibitors have an incidence of birth defects of 4-5% in their offspring without a pattern of malformations. This incidence is comparable to the general population [32].

*Tacrolimus,* another calcineurin inhibitor, also was associated with fetal toxicity and fetal growth delay in mice [58]. Outcomes of tacrolimus use do not seem different from those of cyclosporine use [10].

***Mycophenolic acid (MPA)*** products have been reported to cause various deformities such as hypoplastic nails, shortened fifth fingers, and ear and facial deformities [31, 59-60]. The NTPR has reported 11 structural birth defects of 48 live births (22.9%) in pregnant KT patients exposed to MPA [31]. MPA is associated as well with an increased rate of fetal loss according to a Roche Laboratories study [61].

***Sirolimus***, a relatively new agent, was found teratogen in animal studies with no actual evidence in humans. Adding to this, NTPR reported a high incidence of spontaneous abortion and prematurity in women exposed to sirolimus in their early pregnancy [59].

Thus, MPA and sirolimus are to be avoided in pregnancy. They must be discontinued at least six weeks prior to conception, and replaced by other agents; contraceptive methods have to be used during this period [25-26, 42].

Table I resumes the classification of the different immunosuppressive agents according to the US Food and Drug Administration (FDA).

### BREASTFEEDING
### ON IMMUNOSUPPRESSIVE DRUGS

Calcineurin inhibitors and prednisone cross into the breast milk, at different levels. Currently, the American Association of Pediatrics allows breastfeeding for women treated by corticoids, but inhibits it for women taking cyclosporine. As for tacrolimus and azathioprine, no recommendations exist as for their use while breastfeeding [62-63].

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**TABLE I**

Available at: http://www.fda.gov/drugs/drugsafety

| Drugs | FDA safety classification |
|---|---|
| Corticosteroids (prednisolone, methylprednisolone) | B. No evidence of risk in humans |
| Azathioprine | D. Positive evidence of risk |
| Cyclosporine | C. Risks cannot be ruled out |
| Tacrolimus | C. Risks cannot be ruled out |
| Mycophenolate mofetil | D. Positive evidence of risk |
| Sirolimus | C. Risks cannot be ruled out |

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### PREGNANCY OUTCOMES AFTER KIDNEY DONATION

Pregnancy after kidney donation has been reported to have outcomes similar to the general population. However, two recent studies showed that the probability of these donors to develop gestational hypertension, gestational diabetes and preeclampsia appears to be substantially increased when compared with their earlier pregnancy [64-65]. Fetal outcomes were good. Thus, women donating their kidney must be told about the slight increase of their health risk.

### DELIVERY MANAGEMENT

Delivery should occur in a specialized center. Non-stress test or biophysical profile should be done weekly starting from 30 weeks. In uncomplicated pregnancies, spontaneous labor and vaginal delivery are privileged [36]. Cesarean section is performed in case of obstetrical complications [25-26]. Special attention should be paid to the graft and the course of its ureter. Prophylactic antibiotics are administered in cesarean delivery, amniotomy and episiotomy to prevent infections [4]. Stress-dose steroids during delivery have been recommended for patients on chronic maintenance steroids [4].

### CONCLUSION

In summary, pregnancy in kidney transplant patients is possible but entails obstetrical, neonatal and allograft rejection risks. Pregnancy should be planned carefully and closely monitored by the surgeon, nephrologist, obstetrician, pediatrician and nutritionist. Conception is allowed when the graft function is good. Fetal and maternal outcomes are more or less safe, however it becomes more complicated in older women and in the presence of diabetes and hypertension that are prevalent in this population.

These high-risk pregnancies should be monitored in specialized centers. Aggressive management and follow-up are a must.

Long-term observation of the offspring is mandatory to detect immunosuppressive drugs and kidney transplant effects.

### REFERENCES

1. Murray JE, Reid DE, Harrison JH, Merrill JP. Successful pregnancies after human renal transplantation. N Engl J Med 1963; 269: 341-3.
2. Davison JM, Baylis C. Renal disorders. In: De Swiet editor. Medical Disorders in Obstetric Practice, 4th edition. Blakwell Publishing, 2002: 198-266.
3. Hirachan Padam PS, Chhetri Ramesh, Joshi Aditya, Kharel Tirtha. Renal transplantation and pregnancy. Arab Journal of Nephrology and Transplantation 2012 Jan; 5 (1): 41-6.
4. Davison JM, Bailey DJ. Pregnancy following renal transplantation. J Obstet Gynaecol Res 2003; 29: 227-33.

5. Armenti VT, Daller JA, Constantinescu S et al. Report from the National Transplantation Pregnancy Registry: outcomes of pregnancy after transplantation. Clin Transpl 2006: 57-70.

6. Sibanda N, Briggs JD, Davison JM et al. Pregnancy after organ transplantation: a report from the UK Transplant pregnancy registry. Transplantation 2007; 83: 1301-7.

7. Watnick S, Rueda J. Reproduction and contraception after kidney transplantation. Curr Opin Obstet Gynecol 2008; 20: 308-12.

8. Palmer BF. Sexual dysfunction in uremia. J Am Soc Nephrol 1999 Jun; 10 (6): 1381-8.

9. Ghazizadeh S, Lessan-Pezeshki M, Mahdavi M, Razeghi E, Seifi S. Menstrual problems among kidney transplant recipients. Transplant Proc 2003 Nov; 35 (7): 2720-1.

10. Armenti VT, Radomski JS, Moritz MJ et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2004 : 103-14. Available U. S. F. a. D. A. D and at http://www.fda.gov/drugs/drugsafety

11. Gill JS, Zalunardo N, Rose C, Tonelli M. The pregnancy rate and live birth rate in kidney transplant recipients. American Journal of Transplantation 2009; 9: 1541-9.

12. Lessan-Pezeshki M. Pregnancy after renal transplantation: points to consider. Nephrol Dial Transplant 2002 May; 17 (5): 703-7.

13. Centers for Disease Control and Prevention (CDC). U. S. Medical Eligibility Criteria for Contraceptive Use, 2010. MMWR Recomm Rep. 2010 Jun 18; 59 (RR-4): 1-86.

14. Vidaeff AC, Yeomans ER, Ramin SM. Pregnancy in women with renal disease. Part I: general principles. Am J Perinatol 2008; 25: 385-97.

15. Cunningham FG, Cox SM, Harstad TW, Mason RA, Pritchard JA. Chronic renal disease and pregnancy outcome. Am J Obstet Gynecol 1990; 163: 453-9.

16. Jones DC, Hayslett JP. Outcome of pregnancy in women with moderate or severe renal insufficiency. N Engl J Med 1996; 335: 226-32.

17. Davison JM. The effect of pregnancy on kidney function in renal allograft recipients. Kidney Int 1985; 27: 74-9.

18. Davison JM, Mine JE. Pregnancy and renal transplantation. Br J Urol 1997; 80 (Suppl 1): 29-32.

19. Stagno S, Whitlet RJ. Herpes virus infections of pregnancy. Part I: cytomegalovirus and Epstein-Barr virus infection. N Engl J Med 1985; 313: 1270-4.

20. Hou S. Pregnancy in chronic renal insufficiency and end-stage renal disease. Am J Kidney Dis 1999; 33: 235-52.

21. Meyer MM, Norman DJ, Danovitch GM. Long-term post-transplant management and complications. In: Danovitch GM ed. Handbook of Kidney Transplantation. Boston: Little Brown and Co., 1996.

22. Josephson MA, McKay DB. Considerations in the medical management of pregnancy in transplant recipients. Adv Chronic Kidney Dis 2007; 14: 156-67.

23. Deshpande N, James NT, Kucirka L et al. Pregnancy outcomes in kidney transplant recipients: A systematic review and meta-analysis. Am J Transplant 2011; 11: 2388-404.

24. Armenti VT, Coscia L.A, Moritz MJ, Davison JM. National Transplantation Pregnancy Registry (NTPR): three risk factors predictive of pre-eclampsia in cyclosporine-treated female kidney recipients? Hypertens Pregnancy 2000; 19: S24.

25. European best practice guideline for renal transplantation. Section IV: long-term management of the transplant recipient: IV.10. Pregnancy in renal transplant recipients. Nephrol Dial Transplant (2002); 17 (Suppl 4): 50-5

26. McKay DB, Josephson MA, Amenti VT et al. Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. Am J Transplant 2005; 5: 1592-9.

27. McKay DB, Josephson MA. Pregnancy in recipients of solid organs – effects on mother and child. N Engl J Med 2006; 354: 1281-93.

28. Umans JG. Medications during pregnancy: antihypertensives and immunosuppressives. Adv Chronic Kidney Dis 2007; 14 (2): 191-8.

29. Concepcion BP, Schaefer HM. Caring for the pregnant kidney transplant recipient. Clin Transplant 2011; 25: 821-9.

30. Magee LA, von Dadelszen P, Darley J, Beguin Y. Erythropoiesis in renal transplant pregnancy. Clin Transplant 2000; 14: 127-35.

31. Coscia L, Constantinescu S, Moritz MJ et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2009; 7: 103-22.

32. Coscia LA, Constantinescu S, Moritz MJ et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2007; 29-42.

33. Sgro MD, Barozzino T, Mirghani HM et al. Pregnancy outcome post renal transplantation. Teratology 2002; 65: 5-9.

34. Armenti VT, Ahlswede KM, Ahlswede BA et al. Variables affecting birthweight and graft survival in 197 pregnancies in cyclosporine-treated female kidney transplant recipients. Transplantation 1995; 59: 476-9.

35. Armenti VT, Constantinescu S, Moritz MJ, Davison JM. Pregnancy after transplantation. Transplant Rev (Orlando) 2008; 22: 223-40.

36. del MarColon M, Hibbard JU. Obstetric considerations in the management of pregnancy in kidney transplant recipients. Adv Chronic Kidney Dis 2007; 14: 168-77.

37. Galdo T, Gonzalez F, Espinoza M et al. Impact of pregnancy on the function of transplanted kidneys. Transplant Proc 2005; 37: 1577-9.

38. Gutiérrez MJ, Acebedo-Ribó M, Garcia-Donaire JA et al. Pregnancy in renal transplant recipients. Transplant Proc 2005; 37: 3721-2.

39. Gutiérrez MJ, González P, Delgado I et al. Renal allograft function and cardiovascular risk in recipients of kidney transplantation after successful pregnancy. Transplant Proc 2009; 41: 2399-402.

40. Rahamimov R, Ben-Haroush A, Wittenberg C et al. Pregnancy in renal transplant recipients: long-term effect on patient and graft survival: a single-center experience. Transplantation 2006; 81: 660-4.

41. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. J Am Soc Nephrol 2009; 20: 2433-40.

42. Stratta P, Canavese C, Giacchino F et al. Pregnancy in kidney transplantation: satisfactory outcomes and harsh realities. Pediatr Nephrol 2003; 16 (6): 792-806.

43. Constantinescu S, Silva P, Sifontis NM et al. Early postpartum allograft dysfunction in female kidney recipients. Am J Transplant 2008; (Suppl 2): 555A.

44. Armenti VT, Radomski JS, Moritz MJ, Philips LZ, McGrory CH, Coscia LA. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes

of pregnancy after transplantation. Clin Transpl 2000; 123-34.

45. Rudolph JE, Schweitzer RT, Bartus SA. Pregnancy in renal transplant recipients. Transplantation 1979; 27: 26-9.

46. Board JA, Lee HM, Draper DA et al. Pregnancy following kidney homotransplantation from a non-twin. Report of a case with concurrent administration of azathioprine and prednisone. Obstet Gynecol 1967; 29: 318-23.

47. Østensen M. Disease specific problems related to drug therapy in pregnancy. Lupus 2004; 13: 746-50.

48. Green TP, O'Dea RF, Mirkin BL. Determinants of drug disposition and effect in the fetus. Annu Rev Pharmacol Toxicol 1979; 19: 285-322.

49. Fuchs KM, Coustan DR. Immunosuppressant therapy in pregnant organ transplant recipients. Semin Perinatol 2007; 31: 363-71.

50. Coscia LA, Constantinescu S, Moritz MJ et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2010: 65-85.

51. Tendron A, Gouyon JB, Decramer S. In utero exposure to immunosuppressive drugs: experimental and clinical studies. Pediatr Nephrol 2002 Feb; 17 (2): 121-30.

52. Joint Formulary Committee (2011). British National Formulary. British Medical Association and the Royal Pharmaceutical Society. London. (http://www.rpharms.com)

53. Rosenkrantz JG, Githens JH, Cox SM, Kellum DL. Azathioprine (Imuran) and pregnancy. Am J Obstet Gynecol 1967; 97 (3): 387-94.

54. Githens JH, Rosenkrantz JG, Tunnock SM. Teratogenic effects of azathioprine (Imuran). J Pediatr Nephrol 1965; 66: 959-61.

55. Davison JM, Dellagrammatikas H, Parkin JM. Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients. Br J Obstet Gynaecol 1985; 92: 233-9.

56. Armenti VT1, Ahlswede KM, Ahlswede BA, Jarrell BE, Moritz MJ, Burke JF. National Transplantation Pregnancy Registry: outcomes of 154 pregnancies in cyclosporine-treated female kidney transplant recipients. Transplantation 1994; 57: 502-6.

57. Davison JM. Dialysis, transplantation, and pregnancy. Am J Kidney Dis 1991; 17: 127-32.

58. Farley DE, Shelby J, Alexander D, Scott JR. The effect of two new immunosuppressive agents, FK506 and didemnin B, in murine pregnancy. Transplantation 1991; 52: 106-10.

59. Sifontis NM, Coscia LA, Constantinescu S, Lavelanet AF, Moritz MJ, Armenti VT.. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation 2006; 82 (12): 1698-702.

60. Pergola PE, Kancharla. A, Riley DJ. Kidney transplantation during the first trimester of pregnancy: immunosuppression with mycophenolate mofetil, tacrolimus, and prednisone. Transplantation 2001; 71: 994-7.

61. Le Ray C, Coulomb A, Elefant E, Frydman R, Audibert F. Mycophenolate mofetil in pregnancy after renal transplantation: a case of major fetal malformations. Obstet Gynecol 2004; 103: 1091-4.

62. Petri M. Immunosuppressive drug use in pregnancy. Autoimmunity 2003; 36: 51-6.

63. Fischer MJ, Lehnerz SD, Hebert JR, Parikh CR. Kidney disease is an independent risk factor for adverse fetal and maternal outcomes in pregnancy. Am J Kidney Dis 2004; 43: 415-23.

64. Ibrahim HN, Akkina SK, Leister E et al. Pregnancy outcomes after kidney donation. Am J Transplant 2009; 9: 825-34.

65. Reisaeter AV, Røislien J, Henriksen T, Irgens LM, Hartmann A. Pregnancy and birth after kidney donation: the Norwegian experience. Am J Transplant 2009; 9: 820-4.