Fertility and contraception

A major concern of patients is whether or not they can reproduce after receiving a transplanted organ. Several studies document the rapid return of fertility after transplantation (3). The hyperalimentation-paternal axis is suppressed in patients with ESRD, but gonadal suppression appears to be reversible, with reports of pregnancy occurring within months of successful transplantation (4). It is not known whether fertility is restored to age-appropriate “normal” levels after transplantation, because only scattered reports are available (as assisted reproduction) in transplant recipients. Men with ESRD have several defects in spermatogenesis that may be reversible (5, 6), but isolated deficits in ovarian function have not been documented to our knowledge. Another concern is whether immunosuppressive medications impair fertility. At this time it does not appear that immunosuppressive drugs impair fertility directly, but they may indirectly impair female fertility, although sirolimus (rapamycin) (7) is clearly associated with male infertility, and men wishing to father a child should therefore not take sirolimus.

Given that fertility is rapidly restored after transplantation, the patient and her partner need to be counseled about pregnancy prevention early in the process of pretransplant workup. Optimal contraception is a decision to be made between the patient and her gynecologist, inasmuch as there are no contraindications to the use of any contraceptive method. The options to consider include sterilization of either the transplant recipient or her male partner, and whether the patient

With pregnancy is not different from that in the nonpregnant transplant recipient (15, 16). Likewise, the risk of rejection is probably low as well, as long as there has not been evidence of poorly suppressed immunoreactivity (e.g., recent graft rejection) (14).

Immunosuppressive medications and pregnancy

Adequate immunosuppression must be maintained during pregnancy because drug levels vary widely throughout gestation. The mother is not immunosuppressed in her pregnancy, contrary to some folk beliefs, and therefore requires maintenance of adequate immunosuppression (17). Blood levels of the most potent drugs should be monitored frequently during the pregnancy (14). At our transplant centers we see the patient biweekly, checking calcineurin inhibitor and creatinine blood levels at each visit, and we continue this frequency for at least 2 months after delivery. The frequency of monitoring requires that the patient be willing to comply with close follow-up, and this requirement should be discussed with the patient before she becomes pregnant.

Maternal risks associated with pregnancy

Other risks to consider for the maternal transplant recipient are women’s hypertension and pre-eclampsia. Hypertension is common in transplant recipients and often worsens during the pregnancy (18, 19). Generally, the recommendations are to keep the transplant recipient normotensive if possible, which differs from the advice given to pregnant patients with chronic kidney disease (20). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated because of their fetotoxic potential (21), and therefore maternal transplant recipients are generally prescribed methyldopa or labetalol for the treatment of hypertension (20). Other acceptable agents include nifedipine, hydralazine, and thiazide diuretics (20).

Pre-eclampsia is also commonly diagnosed in pregnant transplant recipients. In the registries, pre-eclampsia was diagnosed in over 30 percent of pregnancies, in contrast to 7 percent in the general population (14). Pre-eclampsia occurs more frequently in patients with chronic kidney disease than in the general population as well (20). It is not known whether there is an independent effect of immunosuppression on the risk of pre-eclampsia that contributes to the high risk of pre-eclampsia, but data now show that pre-eclampsia is also common in recipients of heart, lung, and liver transplants, who presumably do not have significantly impaired renal function (22).

The accurate diagnosis of pre-eclampsia is difficult in transplant recipients because surrogates markers occur frequently in patients with impaired renal function. Transplant patients often are hypertensive, have proteinuria, and have increased uric acid levels (because of calcineurin inhibitors). Pregnancy may be associated with worsening proteinuria, hypertension, and hyper tension, thereby mimicking pre-eclampsia. Furthermore, small changes in serum creatinine levels may hide more serious changes in GFR because of the natural hyperfiltration of pregnancy. Newer markers of pre-eclampsia, such as s-flt and soluble endoglin, have not been validated in the renal transplant population (23, 24).

There are many other medical considerations in the maternal transplant recipient, including gestational diabetes, anemia, and infections such as urinary tract infections (23–27). It is recommended that maternal kidney transplant recipients be screened every trimester for gestational diabetes (28). Other comorbidities, such as urinary tract infections, are quite common in renal transplant patients, and therefore frequent screening is mandatory (25, 28). Several other infections need to be considered in the maternal transplant recipient; the reader is referred to an earlier review for details (14). Many infants are delivered by cesarean section (29). However, the presence of the transplanted kidney in the false pelvis does not interfere with vaginal delivery (28, 30). Thus, unless there is an obstetric reason to indicate caesarean delivery, vaginal delivery is preferred (10).

Fetal risks of pregnancy in transplant recipients

There are potential risks to the developing fetuses that should be discussed with the maternal transplant recipient and her partner. We believe that a frank discussion of these concerns should be conducted long before pregnancy occurs so that the future parents are prepared for the possibility of adverse outcomes, including prematurity, intrauterine growth retardation (IUGR), and long-term developmental problems.

Data from all three registries have demonstrated an extremely high risk for premature delivery (2). Premature delivery is defined as any delivery occurring earlier than 37 weeks. Premature delivery has been documented in recipients of all solid organs but occurs in about 50 percent of renal transplant pregnancies (2). Among the consequences of premature delivery are increased risk of learning disabilities and neurocognitive deficits (31). There is also a very high risk for IUGR, suggesting a primary pathologic process involving the placenta. IUGR occurs in approximately 20 percent of deliveries and is associated with comorbidities including hypertension, diabetes mellitus, neurologic abnormalities, and developmental delay (14).

Pregnancy and the Kidney

By Dianne B. McKay and Michelle A. Josephson

The Nobel Laureate Joseph Murray provided the first report of pregnancy in a transplant recipient (1). Since that time, over 16,000 pregnancies have been documented in the world literature (2). Many more pregnancies have clearly occurred, now that pregnancy after transplantation is commonplace and is rarely reported. The data about pregnancy in transplant recipients come from case reports and registry reports, but these sources underrepresent the population of transplant recipients who have become pregnant (2).

This review relies on data from registry reports in the United States, the United Kingdom, and Europe, but we caution that the derivation of guidelines from these reports must be considered in light of their relatively small numbers. Furthermore, it is important to realize that registry reports are generally based on voluntary patient reporting and that they do not do prospective or retrospective reviews of hospital records or laboratory testing. Many investigators suggest that large well-designed prospective analyses are needed to address many of the questions regarding the risks of pregnancy after transplantation for both mother and child.
Interestingly, gross congenital abnormalities are not common in infants exposed in utero to immunosuppressive medications, with the exception of mycophenolate mofetil (2, 32–34). Recent data have shown a pattern of congenital abnormalities in infants exposed in utero to mycophenolate mofetil, and the Food and Drug Administration has classified it as a category D. It is therefore recommended that women considering pregnancy cease taking any mycophenolate drug (CellCept or Myfortic) at least 6 weeks before attempting pregnancy (14). Whether to add azathioprine to the patient's drug regimen is something to consider doing this at our institution. It is believed that severe immunosuppression is maintained. At this time there are insufﬁcient data about the safety of sirolimus or everolimus, and therefore we have also recommended a change in these medications 6 weeks before pregnancy is attempted.

Although obvious congenital abnormalities are rare, there are several other less obvious abnormalities that are induced by in utero exposure to immunosuppressive medications is not known. All immunosuppressive medications cross the maternal–fetal barrier, although there are important differences in the delivery of active metabolites to the developing fetus (14). For instance, prednisone easily crosses the placental circulation, while prednisolone excretion in breast milk is minimal, with no active neonatal metabolism. Whether the same is true for mycophenolate mofetil is unknown. Calcineurin inhibitors easily pass through the maternal–fetal interface, and active metabolites have been reported in the fetal circulation (14). In fact, serum levels of cyclosporine have been reported in newborns at levels below equivalent to that of the mother. Whether phenomena occur in human infants is not known. Serum levels of tacrolimus in the developing fetus (14). For instance, prednisone easily crosses the placental circulation, while prednisolone excretion in breast milk is minimal, with no active neonatal metabolism. Whether the same is true for mycophenolate mofetil is unknown. Calcineurin inhibitors easily pass through the maternal–fetal interface, and active metabolites have been reported in the fetal circulation (14). In fact, serum levels of cyclosporine have been reported in newborns at levels below equivalent to that of the mother. Whether phenomena occur in human infants is not known. Serum levels of tacrolimus in the developing fetus is unlikely to be affected by calcineurin inhibitors throughout gestation. There is substantial evidence from animal models that in utero exposure to cyclosporine and tacrolimus induces autoimmune disease in newborns through the maternal–fetal interface. Whether the same phenomena occur in human infants is not known.

There is limited information on the neurocognitive or immunologic development of these fetuses exposed to immunosuppressive medications, and well-designed studies are needed. The National Transplantation Pregnancy Registry has tried to follow up children after delivery to determine whether more subtle defects are associated with fetal exposure to immunosuppressive medications. In the data from the National Transplantation Pregnancy Registry there was a 27% incidence of learning disabilities in school-age children exposed to immunosuppressive medications. Recently another report has suggested that this was associated with premature birth (35).

Breastfeeding

Many patients inquire about the possibility of breastfeeding their infants. Unfortunately, there are few data from which to derive recommendations for or against breastfeeding. The immunosuppressive levels in breast milk vary widely, and the pharmacokinetics and pharmacodynamics of immunosuppressive secretion in breast milk have not been defined (36–58). Large controlled studies that evaluate breast milk concentrations of immunosuppressants or solid organs after breast feeding have not been performed, to our knowledge. The mother should be informed that it is unknown whether the risks of further exposure of her infant to immunosuppression outweigh the benefits of breastfeeding.

Conclusion

The first woman to become pregnant after a kidney transplant died this year at the age of 76. Fifty-three years since the report of her first pregnancy and many thousands of pregnancies later, it is clear that pregnancies in transplant patients can occur successfully with close follow-up, for the prevention and management of medical and obstetric complications.

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References