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Organ Transplantation and Pregnancy

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As the number of patients receiving an organ transplant has increased over the past decade, so has the number of organ transplant recipients of reproductive age. This circumstance has therefore demanded an increased awareness of the factors relevant to organ transplantation and pregnancy. This Risk Newsletter is intended to serve as a review of the major issues and medications associated with organ transplantation and pregnancy.

Transplantation and Pregnancy

In general, pregnancy is well tolerated in women with good pre-pregnancy graft function following all types of organ transplants. Throughout pregnancy, it is important that immunosuppressive therapy be maintained, as a small percentage of transplant recipients will have rejection episodes during pregnancy. No specific pattern of malformation has been identified in babies born to mothers who have had organ transplants. Each year new and more powerful immunosuppressive agents enter the market, and on the whole the data regarding potential teratogenicity is limited. However, medical experience has demonstrated that despite the medications and changes in maternal physiology in women post-transplantation, successful pregnancy can be maintained (Armenti et al, 2000).

Since even large individual centers have limited experience with pregnancies in transplant recipients, registry data and surveys provide the primary outcome data from various recipient groups (Armenti et al. 2000).

Obstetric Management Issues

Current recommendations suggest that women who have undergone any type of transplant wait 18 months to 2 years after the surgery to conceive a pregnancy. This allows the graft time to stabilize function, and immunosuppression to achieve appropriate maintenance levels. Post-transplantation pregnancies should be monitored as high-risk. Vigilant monitoring of transplant function, hematology, blood pressure control, diagnosis and treatment of rejection, treatment of any infections, and serial fetal surveillance is critical in the prenatal care of the transplant patient. Women who have had transplantations are very likely to experience premature delivery (prior to 37 weeks gestation), regardless of type of transplant or drug therapy. Vaginal delivery is always the aim, and is not contradicted even in the case of renal transplant (does not cause mechanical injury to a renal transplant; graft does not obstruct birth canal). It may be necessary to increase the levels of prophylactic steroids at delivery, and all surgical procedures should be covered by prophylactic antibiotics (Armenti et al. 2000). Pain relief is possible using the same medications commonly used in healthy women.

Transplant Medications in Pregnancy

Corticosteroids (Prednisone)

Prednisone (Deltasone) is a glucocorticoid that becomes active biologically after its conversion to prednisolone in the liver. There are reports that have indicated that prednisone, like the naturally occurring glucocorticoid, cortisone, causes cleft palate in mice and rats. Although an increase in cleft palate or other major malformations was not uncovered in a prospective study of 184 women who used prednisone prenatally (Carmichael et al, 1999), three retrospective epidemiology studies have associated oral clefting with human pregnancy exposure to corticosteroids based on small numbers of affected children with exposures (Rodriguez-Panilla, 1998). Odds ratios in

these reports were in the 3 to 5 range. In a study of 1,184 live born children with non-syndromic oral clefts, a relationship between exposure to corticosteroids during the first trimester and in increased risk for cleft lip was demonstrated (OR = 6.55; $p = 0.015$) after controlling for confounders such as smoking, hyperthermia, and affected first-degree relatives (Rodriguez-Pinella and Frias, 1998). Thus, corticosteroid use should be avoided in the first trimester if at all possible.

Data available from both animal experiments and clinical observations suggest that prenatal exposure to prednisone may retard fetal growth and be associated with an increased incidence of low birth weight among offspring. In some cases, this outcome has been attributed to the underlying disease for which the corticosteroids were given (often asthma, collagen-vascular disease or transplantation) (Fitzsimmons, 1986). Other investigators, however, have observed a high incidence of fetal growth retardation in the offspring of renal transplant patients treated with glucocorticoids, despite good graft function and normal or only slightly elevated blood pressure (Pirson et al, 1985). Maternal effects of prednisone, other than immunosuppression, include peptic ulcer disease, osteoporosis, increased bruisability, pancreatitis, increased risk for hypertension, aseptic necrosis of the bone, weight gain, fluid retention, glucose intolerance. These maternal effects seem to be related to the dose and duration of therapy (Sims, 1991).

A population based case control study was also performed in Hungary over the period 1980-1994 to examine the teratogenic potential of oral and topical corticosteroid treatment in pregnancy. In this study, corticosteroid exposure in pregnancy was 1.55% among 20,830 cases of babies with congenital malformations and 1.41% among 35,727 healthy control births. Therefore, the adjusted odds ratio in this analysis of case control pairs did not identify an association between the rate of congenital abnormalities and corticosteroid treatment in the second and third month of gestation (Czeizel and Rockenbauer, 1997). In addition, the American Academy of Pediatrics classified prednisone and prednisolone as compatible with breastfeeding.

Cyclosporine A (Neoral®)

Cyclosporine A (Neoral®) is a systemic immunosuppressant. Cyclosporine is a potent immunosuppressive agent used to prolong the survival of allogenic transplants involving the skin, kidney, liver, heart, pancreas, bone marrow, small intestine, and lung. Cyclosporine has been demonstrated to suppress humoral immunity and cell-mediated immune reactions such as allograft rejection, delayed hypersensitivity, and graft versus host disease. Cyclosporine crosses the placenta and the fetal levels of this drug may range between 30 and 64% of the maternal plasma concentration; substantial amounts can be located in amniotic fluid and placental tissue (Ostensen, 1992). Elimination of cyclosporine is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in urine. The disposition of cyclosporine from blood is generally biphasic, with a terminal half-life of approximately 8.4 hours (range 5-18 hours). The bioavailability of cyclosporine is dependent upon the patient population. The bioavailability is estimated to be less than 10% in liver transplant patients and as great as 89% in some renal transplant patients (Novartis, 2000). Cyclosporine is extensively metabolized by the P-450 3A enzyme system in the liver, and to a lesser degree in the GI tract, and the

kidney. In the manufacturer studies on pregnancy, cyclosporine was not teratogenic in appropriate test systems.

In a manufacturer's study of 116 pregnancies in women receiving cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period, the only consistent patterns of abnormality were premature birth (gestational period 28 to 36 weeks) and low birth weight for gestational age. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) had complications including pre-eclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility, and/ or fetoplacental dysfunction. Pre-term delivery occurred in 47%. Neonatal complications occurred in 27%. Growth retardation has also been observed in human pregnancies involving cyclosporine, but several of these cases also included gestational exposure to corticosteroids, which may have played a role in stunting fetal growth. Comparison of the risk of abortion and preterm delivery in small numbers of transplant patients receiving either cyclosporine or prednisolone and azathioprine suggest that the incidence of these outcomes may be increased by exposure to cyclosporine.

In an earlier study of 75 pregnancies in 70 mothers taking cyclosporine A prenatally, growth retardation and prematurity occurred in about 40% of neonates. It is important to note that these mothers were almost all taking prednisone concomitantly. The average birth weight was 2,093 gm (Ostensen, 1992).

In a 1999 meta-analysis performed on Medline, EMBASE, IPA, Cochrane, and Toxline databases, studies were selected for freedom from selection bias and the inclusion of more than 10 cyclosporine A exposed neonates. In this analysis, thirteen studies met the inclusion criteria for congenital malformations (6 with control groups), nine for prematurity (4 with a control group) and 4 for low birth weight (2 with a control group). The overall odds ratio for congenital malformations of 3.47 (CI 0.86-14.4) was not statistically significant. The odds ratio for prematurity of 1.47 (CI 1.00-2.15) was statistically significant; overall prematurity rate was 58.9% in the cyclosporine A exposed group. The prevalence of low birth weight was also statistically significant with an odds ratio of 1.59 (CI 1.05-2.40), thus indicating a statistically significant risk of low birth weight for infants with fetal exposure to cyclosporine A (Bar-Oz et al, 1999).

Since cyclosporine is excreted in human milk, breast-feeding should be avoided. However, estimates of neonatal exposure to cyclosporine in breast milk indicate that it is likely to be far less than the levels to which the fetus had been exposed prenatally.

Azathioprine (Imuran®)

Azathioprine is metabolized to 6-mercaptoprine, a substance which can cross the placenta. Early in pregnancy, the fetal liver is unable to metabolize this substance as it does not make the necessary enzyme. There are reports of infants born to renal transplant recipients exposed to azathioprine with an increased risk for congenital malformations ranging from 6.4%-9%. However, there are no specific patterns of malformation noted. The more comprehensive European Dialysis and Transplant Association (EDTA) report on 490 pregnancies (500 babies) concluded that azathioprine and prednisone immunosuppression was not associated with more congenital malformations in post-transplant mothers than seen in the general population (Rizzoni et al, 1992).

Congenital anomalies were observed in four (4%) of 103 infants born to women who had received renal transplants prior to becoming pregnant (Cararach et al, 1993). Approximately 90% of these women were treated with azathioprine during pregnancy. All of the reported anomalies were different. In another series of cases, an analysis of 40 pregnancies in systemic lupus erythematosus patients, no increased risk for congenital malformations was identified (Ostensen, 1992). Although there is a lack of evidence that azathioprine exposure is associated with a marked increase in birth defects or miscarriage, growth retardation has been reported in fetuses exposed to this and other cytotoxic agents,

especially when used in combination with prednisone and at higher doses (Pirson et al, 1985). Maternal use of azathioprine has also been associated with neonatal immunosuppression, leukopenia, and/or pancytopenia (Davison et al, 1985). It is not known how often immunologic or hematologic complications in the newborn should be expected following maternal azathioprine therapy; however, one study found an association between maternal leukopenia and hematologic abnormalities in the offspring (Davison et al, 1985). It should be noted that many of the reports concerning azathioprine involve coadministration of other medications (especially prednisone) and involve women with serious medical illnesses such as renal failure. As this drug is excreted in small amounts in breast milk, breastfeeding while receiving azathioprine is not recommended.

Mycophenolate mofetil (Cell Cept®)

Mycophenolate mofetil is an immunosuppressant used in organ transplantation and rheumatoid arthritis. The manufacturer reports that doses roughly equivalent to those used clinically in transplant patients caused fetal resorptions and malformations in pregnant rats and rabbits. The malformations consisted largely of defects of the head and eyes, and were found in the absence of signs of maternal toxicity. This raises a greater level of concern for the potential for adverse effects on fetal development.

There are reports on 6 pregnancies (all transplant patients) that have included fetal exposure to CellCept®, none of these reports found major malformations in the offspring, but all were born prematurely. These cases, which have included first trimester exposures, may provide some reassurance that this agent can be used in pregnancies without frequent adverse developmental effects, but they are not sufficient to conclude that the use of this agent during pregnancy is safe (Pergola et al, 2001).

Additionally, there is a case report in the literature of a kidney transplantation in the first trimester of pregnancy with subsequent exposure to mycophenolate mofetil, tacrolimus, and prednisone throughout the entire pregnancy. The baby girl was born prematurely at week 37 ½ with the only detectable abnormalities being hypoplastic nails and shortened 5th fingers (Pergola et al, 2001).

Polydrug Transplant Therapy

It may be more difficult to identify specific cause and effect relationships with certain immunosuppressants and adverse pregnancy outcomes as more women are on treatment regimens consisting of combinations of the newer agents. However, with lowered doses of multiple agents, there is less exposure to each drug individually, and therefore, the potential for teratogenicity is theoretically less. However, there is the risk for potentiating effects among several drugs as well as unknown interactions, with the potential for adverse fetal outcomes (Armenti et al. 2000). Further investigation is required to accurately assess risk.

Pregnancy Outcomes in Various Transplant Recipients

LIVER

In a University of Washington Medical Center study between 1991-1999, six pregnancies were followed in women with prior orthotopic liver transplantation. Four of the six pregnancies were complicated by chronic hypertension, fetal growth restriction, and preterm delivery; all pregnancies were complicated by renal insufficiency. Pregnancies complicated by second- trimester renal insufficiency are at risk for preeclampsia, fetal growth restriction and fetal demise. It is believed that better obstetric outcome can occur in women with mild renal insufficiency and well-controlled chronic hypertension. In planned pregnancies, preconceptional hypertensive control may decrease the risk for preeclampsia and poor obstetric outcome (Carr et al, 2000). Generally, female liver recipients can have successful pregnancies while on cyclosporine A drug therapies (Scantlebury et al, 1990). In a registry report of 58 female liver recipients in 89 pregnancies (the majority on cyclosporine A therapy), there was no specific pattern of malformation reported in the newborn (Armenti et al, 2000).

KIDNEY

Kidney transplantation restores ovulatory menstrual cycles and fertility, which is often impaired while in dialysis. Maternal and fetal complications have been observed in pregnancy following renal transplantation. The most serious maternal complication is the rejection of the transplanted kidney; however, overall, the rejection rate has not been seen to increase during pregnancy compared to the general rate. Women who are post-kidney transplant are at increased risk for hypertension during pregnancy and must be carefully monitored by both obstetrician and nephrologist (Muirhead et al, 1992). There is also a high risk for infection and prophylactic antibiotic therapy should be administered for any invasive procedure, including amniocentesis (Framarino et al, 1993). Fetal problems that have been observed in this population include premature birth (19-45%) and IUGR (ranging from 13-25%) (Penn et al, 1980). In a retrospective case series of 44 consecutive pregnancies compared to maternal age matched controls, significantly more stillbirths (12/44; $p = 0.037$), preterm deliveries ($p < 0.001$), and increased incidence of low birth weight ($p < 0.001$) were noted in the renal transplant group. The offspring followed in this study ($n = 32$) had normal postnatal growth and development, with the exception of three offspring with developmental delay. Further studies will be needed to determine if this is a coincidence or an association (Sgro et al, 2002). The rate of miscarriage does not appear to be increased in the renal transplant population. Congenital malformations resulting from drug therapy exposure also do not seem to be increased in this population (Framarino et al, 1993). Some studies have indicated difference in perinatal outcome specific to the type of medication administered for immunosuppressive therapy following kidney transplantation. Specifically, in a comparison of 57 babies born to mothers on azathioprine and 94 babies born to mothers on cyclosporine A, the babies with prenatal exposure to azathioprine had a significantly higher mean birthweight (2567 +/- 491.1 gm) compared to those exposed prenatally to cyclosporine A (2252 +/- 629.2 gm), with no incidence of congenital anomalies observed in either group (Toma et al, 1999).

BONE MARROW TRANSPLANTATION

Before transplantation, high dose cyclophosphamide (and/or cyclophosphamide plus irradiation) is used to prepare most patients for the transplant. These treatments, in combination with patient age at transplant seem to be significant factors with respect to the development of ovarian failure. In general, women over 25 who were treated with cyclophosphamide plus irradiation experienced primary ovarian failure. Therefore, this may need to be addressed with respect to future reproductive planning when choosing a treatment method for women in need of bone marrow transplantation. There are reports of successful pregnancies found in the literature. There are numerous reports which suggest that there is no increased risk of congenital anomalies in the offspring of transplant recipients. The prenatal course may be at increased risk for complications such as preeclampsia and prematurity (Sims, 1991).

HEART AND HEART LUNG

There are successful reports of pregnancies following heart and heart-lung transplants. An international study by Wagoner et al (1993) did not find a significant difference in neonatal complications or maternal graft survival in an analysis of 35 recipients with 47 pregnancies. There were 7 deaths in this group over 5.6 years of post-partum follow-up: three deaths were due to non-compliance and one due to allograft vasculopathy. No structural malformations were identified. There is still only a limited amount of data regarding lung recipients; however, concern has been raised about the significant rejection and mortality rates. There are however, a few successful case reports (Armenti et al, 2000).

MALE TRANSPLANT RECIPIENTS

There are many reports of male transplant recipients fathering successful pregnancies.

In a study of 204 male transplant recipients, 288 pregnancies were successfully completed and there were 2 neonatal deaths (total = 290). Analysis of outcomes in relation to the immunosuppressive regimens including Neoral and MMF (Cell Cept) revealed one child with ureteral obstruction, correctable by surgery, and one child with hydrocele (Armenti et al, 2000). The National

Transplantation Pregnancy Registry has data on 19 male transplant patients who fathered children while taking mycophenolate mofetil; none of these men had children with congenital malformations (Pergola et al, 2001). In a smaller study, specifically following the outcomes for 11 fathers treated with cyclosporine A, all newborns were healthy and had a mean birth weight of 2,730 gm (Ostensen, 1992).

CONCLUSIONS

In general, as the number of successful organ transplants increases, the desire for transplant recipients to become pregnant will also increase. In planning a pregnancy in an organ recipient, there are numerous additional concerns for both the health of the mother and the fetus. First and foremost, it is important and necessary to attempt to design an immunosuppressive regimen which will keep the mother healthy and minimize risk of a rejection episode. At the same time, special considerations must be taken for the potential teratogenic effects of any agent on a fetus. For example, alternating a poly drug therapy regimen to exclude corticosteroids in the first trimester may be a way to minimize any potential risk for oral clefting. It may be more prudent to choose drugs which have been on the market longer and therefore are better studied in pregnant women. This becomes more of a concern as new anti-rejection drugs enter the market each year. By working closely with patient, obstetrician, and the specialist (dependent upon type of transplant), a poly drug regimen can be designed to optimize, although not guarantee, safety for both mother and fetus.

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