Acute and Chronic Lung Allograft Rejection During Pregnancy*

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Young women who undergo lung transplantation may regain normal fertility and become pregnant. Currently, little is known about the outcome of pregnancy after lung transplantation. We present a case of pregnancy after bilateral lung transplantation complicated by acute and chronic allograft rejection, resulting in irreversible loss of lung function.

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Key words: lung transplantation; obstructive bronchiolitis; pregnancy; rejection

Abbreviations: CMV=cytomegalovirus; LFT=liver function test; OB=obstructive bronchiolitis

Over the last decade, lung transplantation has become a viable option for patients with end-stage lung disease. Due to the relatively small number of lung transplants done nationally, little experience has been gained in the outcome and management of pregnancies in the post-lung transplant patient, and little published data exist to assist the patient’s physician regarding issues related to pregnancy after lung transplantation. The vast majority of information on pregnancy after transplantation comes from renal allograft recipients,1-4 including one review of more than 2,000 cases.5 Analysis of these pregnancies reveals a higher incidence of prematurity and low-birth-weight infants. Maternal effects include a substantial risk for the development of new hypertension, preeclampsia, or a permanent deterioration in renal graft function. There has been little evidence, however, for an increased incidence of acute rejection in these patients. Despite these complications, 92% of pregnancies that proceed beyond the first trimester end successfully. Much less experience has accumulated in pregnancies after liver or heart transplantation, although similar outcomes have been observed in these patients.

Although these aforementioned results suggest that pregnancy after solid organ transplantation is associated with reasonably good maternal and fetal outcomes, we describe a patient who underwent double lung transplantation and subsequently became pregnant with a course notable for severe obstructive bronchiolitis (OB). Our patient suffered a 50% irreversible decrement in FEV1 immediately after her therapeutic abortion. This case illustrates a serious complication of pregnancy in the lung transplant recipient and underscores the potential for untoward immunologic changes for the allograft of a pregnant woman.

Case Report

A 25-year-old white woman was diagnosed as having bronchiectasis in 1984 after she presented with a chronic productive cough. A chest radiograph revealed bronchiectasis and mild interstitial infiltrates. Spirometry demonstrated an FEV1 of 1.86 L (58% predicted) and an FVC of 3.19 L (80% predicted). Transbronchial biopsy specimens showed acute and chronic inflammation, squamous cell metaplasia, and mild fibrosis. The etiology of her bronchiectasis was investigated with an evaluation that included three normal results of sweat chloride tests, a negative DNA study for cystic fibrosis mutations, a normal α1-antitrypsin level, normal immunoglobulins and immunoglobulin G subsets, and negative hypersensitivity tests for Aspergillus and Thraeoactinomyces species. She was treated with antibiotics and bronchodilators, but her condition slowly deteriorated despite therapy. By 1981, her spirometry and gas exchange were as follows: FEV1, 0.8 L; FVC, 1.5 L; PO2, 54; PCO2, 36; and pH, 7.47. Supplemental oxygen therapy was started and she was listed for double-lung transplantation.

On April 24, 1992, the patient underwent double-lung transplantation and made a rapid recovery. Although her spirometry improved quickly, she required IV corticosteroid therapy for 4 biopsies specimen-proved episodes of acute rejection in the first 2 postoperative months. Surveillance bronchoscopies thereafter revealed no evidence of rejection over the next 21 months. She was also treated with ganciclovir for biopsy specimen-proved cytomegalovirus (CMV) pneumonitis 7 weeks after her transplant. Additional courses of ganciclovir were given for a persistently elevated CMV IgM level during months 14 and 23 posttransplant. By 18 months posttransplant, her spirometry had reached 100% of predicted, and she had gained 20 kg. She obtained full-time employment and began a new relationship.

During the 23rd postoperative month, after 21 rejection-free months, the patient presented with new bilateral upper lobe infiltrates without a change in lung function. Transbronchial biopsy specimen revealed grade II/III acute rejection. Methylprednisolone sodium succinate (Solu-Medrol) therapy followed by an increase in prednisone and cyclosporine dosages resulted in resolution of her infiltrates. Two months later, her lung function was at her baseline (FEV1=2.75 L; FVC=3.2 L) and she felt well.

Three months after her bout of acute rejection, she reported fatigue, sore throat, cough with yellow sputum, and nausea with vomiting. An oral antibiotic was prescribed and her local physician obtained a serum beta human chorionic gonadotropin sample when she reported amenorrhea. The beta-human chorionic gonadotropin level was elevated and a sonogram revealed an intrauterine pregnancy with an estimated gestational age of 7 weeks. The patient suffered persistent nausea and vomiting. Cyclosporine levels, previously in the therapeutic range, fell to 94 mg/mL. Her cyclosporine dose was increased twice without benefit. A decision was made to terminate the pregnancy because of her persistent symptoms of nausea and vomiting and the inability to maintain adequate levels of immunosuppressants.

The patient presented to the Obstetric Clinic at University of North Carolina Hospitals in June 1994, 1 week after the sonogram, to have a therapeutic dilation and curettage. Preprocedure chest radiograph revealed recurrent bilateral upper lobe infiltrates, a pattern identical to the acute rejection episode 3 months previously. Methylprednisolone therapy was initiated and a dilation and curettage was performed promptly. Her nausea and vomiting abated quickly and her cyclosporine level rose to 470 mg/mL in 2 days.

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without dose change. A 3-day methylprednisolone course was completed and an oral prednisone boost was initiated. She felt well and denied respiratory symptoms several days later.

A fortnight later, dyspnea, productive cough, and fever developed. Her chest radiograph showed no infiltrates, but her FEV$_1$ had declined from 2.75 to 1.29 L, and her FVC from 3.2 to 2.17 L (Fig 1). She was treated empirically with methylprednisolone, ganciclovir, ceftazidime, tobramycin, and azithromycin and her condition stabilized. Bronchoscopy with transbronchial biopsy specimens revealed no acute rejection, no CMV, and airway submucosal fibrosis consistent with OB (Fig 2). The BAL fluid had 15% neutrophils, 33% lymphocytes, and 50% macrophages. Bacterial, viral, and fungal stains and cultures were negative. Cytologic study was negative for malignant cells, *(Pneumocystis carinii)*, and CMV. The cyclosporine level was in the therapeutic range. Methylprednisolone therapy was continued for 3 days and her prednisone dose was increased to 20 mg qd. Cyclic estrogen therapy was started for contraception. She was discharged from the hospital with the diagnosis of OB.

Two weeks later, her FEV$_1$ and FVC had fallen to 1.06 L (36%) and 2.06 L (61%), respectively, and she reported progressive dyspnea. Another 3-day course of methylprednisolone was administered without effect. Over the next 6 months, her spirometry and clinical status remained unchanged. A slow prednisone taper was initiated on the 29th postoperative month. A small recovery in FEV$_1$ and FVC was noted by the 32nd post-operative month. Except for dyspnea on exertion, the patient remained symptom free. To date, she has suffered 58% and 33% declines in her FEV$_1$ and FVC, respectively. After a long discussion of the impact of her pregnancy on her lung function, she elected to have a bilateral tubal ligation in the 35th postoperative month.

**DISCUSSION**

With the advent of solid organ transplantation for patients with end-stage organ failure, women with infertility from chronic illness may achieve normal reproductive function and become pregnant following transplantation. The effects of pregnancy on the transplanted organ, the potential for increased maternal morbidity during the pregnancy, and the likelihood of carrying a normal fetus to term become important issues in the pregnant woman following transplantation. The effects of immunosuppressives and other drugs commonly used after transplantation during pregnancy have not been studied extensively in humans and are another important concern for pregnant women. We present this case to demonstrate the potentially catastrophic consequences that pregnancy may have on a woman's health and the immunologic consequences of pregnancy on transplanted lungs.

A relatively large experience has been gained in women who have undergone renal transplantation and have subsequently become pregnant.$^{1-5}$ Davison$^5$ has reported on a series of 2,309 pregnancies in 1,594 women following renal transplantation. In this group, there was a 13% incidence of spontaneous abortion and a 27% incidence of therapeutic abortion. Forty percent of pregnancies, therefore, ended in the first trimester. Of the remaining pregnancies that progressed beyond the first trimester, 92% ended successfully. There was a high incidence of prematurity and intrauterine growth retardation, with rates of 50% and 25% of pregnancies, respectively. Initial follow-up on the children born to these women, however, is very promising. Further analysis of other maternal outcomes revealed a 30% incidence of developing hypertension, preeclampsia, or both during pregnancy. Acute allograft rejection occurred in 9% of cases, an incidence that is not different than in nonpregnant renal transplant recipients.

Although much less experience has been gained with pregnancy after liver or heart transplantation, similar outcomes have been observed in moderate-sized case series.$^{5-8}$ Twenty successful live births were reported by Scantlebury et al$^7$ in 17 patients who underwent liver transplantation. In

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**FIGURE 1.** Lung function (FVC and FEV$_1$) and clinical events following double lung transplantation.
this group of 17 women, 3 therapeutic abortions and 1 spontaneous abortion had occurred posttransplantation before the women ultimately had a successful pregnancy. Six cases of new hypertension requiring treatment, including 4 with toxemia, occurred in these 20 pregnancies. Ten infants (50%) were born prematurely, all by cesarean section. Four of 20 pregnancies were complicated by intrauterine growth retardation, including one set of twins. Liver function test (LFTs) results were stable or only mildly elevated during the antepartum period in 16 of 19 pregnancies, while 3 of 19 had moderate elevation in LFT results. One of these patients was found to have acute graft rejection on liver biopsy specimen. During the early postpartum period, however, 10 of 29 patients developed a moderate elevation in LFT results. Three of these patients underwent liver biopsy, with none showing acute rejection. Four others were treated empirically for rejection with steroid boluses, resulting in immediate improvement in only one patient. Slow improvement over 4 weeks occurred in the other 3 patients. Children born to these women developed normally, without evidence of congenital defects.

A series of 32 pregnancies in recipients of heart (n=29) and heart-lung (n=3) transplants has also been reported by Wagoner et al. Five fetal deaths resulted from abortions (2 spontaneous and 3 therapeutic), and the incidence of prematurity and low birth weight was 41% and 17%, respectively. Other maternal complications commonly seen included hypertension (44%), preeclampsia (22%), premature labor (30%), worsening chronic renal failure (15%), and maternal infections (15%). All 29 children were reported in good health, and no evidence of fetal anomalies was observed. Routine surveillance for rejection with endomyocardial biopsy specimens identified 6 patients (22%) with at least 1 episode of rejection during pregnancy. All of these episodes were successfully treated by altering dosages of standard immunosuppressants.

To our knowledge, no cases of pregnancy after isolated lung transplantation have been reported in the medical literature, and very limited experience exists in the United States. In the United Kingdom, however, several lung transplant recipients have become pregnant. In this small group of patients (n=6), maternal complications were common, including significant loss of lung function (n=2), death (n=1), and need for retransplantation (n=1) (personal communication, D. Parry, MD; December 1995). Since invasive procedures were considered to carry considerable risk in these patients, a histologically proved etiology for the decline in lung function was not determined. The information one can give to women who have become pregnant, or are contemplating this, is significantly limited by this information void.

In the case presented, our patient had good lung function for the first 2 years after transplantation, despite episodes of acute rejection and CMV infection in the early postoperative period. Twenty-four months after transplantation, the patient became pregnant, suffered from hyperemesis gravidarum, and was unable to maintain adequate cyclosporine levels. The patient then developed acute rejection, which responded quickly to appropriate treatment with high-dose corticosteroids. A therapeutic abortion was performed be-
cause the hyperemesis precluded adequate immunosuppressive therapy. Two weeks later, however, dyspnea and cough returned suddenly, and the diagnosis of OB was made clinically and confirmed histopathologically. A dramatic drop in pulmonary function ensued despite repeated courses of pulse methylprednisolone therapy.

This case demonstrates that while pregnancy is often considered a “privileged immunologic state,” patients who have received lung transplants can develop acute and chronic rejection during pregnancy. Whether rejection itself leads to a deleterious immunologic response to the allograft, appropriate immunosuppression may be difficult to maintain. It has been shown that cyclosporine requirements increase during pregnancy due both to an increased volume of distribution of the drug and increased cyclosporine metabolism. Other patients, as demonstrated by this case, may have significant problems with cyclosporine absorption due to nausea and vomiting during pregnancy.

Most interesting, in the case, is the sudden development of OB shortly after elective abortion. OB is thought to be a form of chronic rejection. The pathogenic mechanism leading to this immunologic injury is yet to be defined, although CMV pneumonitis, ischemic airway injury, and more severe acute rejection have all been associated with the subsequent development of OB. The presence of biopsy specimen-proved early CMV infection in this patient and serologic evidence of CMV infection later in her course (month 23 onward) raises this possibility that CMV could have played a role in the development of OB.

The presence of a heightened immune response after pregnancy resulting in “rebound rejection” has been postulated, but a clear association between chronic rejection and pregnancy has not been noted in other organ transplants. The temporal association in this biopsy specimen-proved case of OB 2 weeks after therapeutic abortion is certainly compelling, however. A hypothesis to explain this association may be through immunologic stimulation after the presentation of paternal antigens during either delivery or abortion. One may speculate that the incidence of rejection after kidney or liver transplantation is underestimated, because these patients do not have biopsies routinely to diagnose this entity, even when the renal or hepatic graft function has decreased in the peripartum period. Of note, a 22% incidence of acute rejection during pregnancy in heart transplant recipients, in whom routine surveillance biopsies are performed, was noted in the case series by Wagener et al.

In summary, this case demonstrates a woman whose pregnancy led to acute and chronic lung rejection and irreversible loss of lung function. One might predict, based on experience gained in other organ transplant recipients, that pregnancy after lung transplant would lead to an increased incidence of maternal and fetal complications. Pooling of results across all lung transplant centers would certainly be helpful in clarifying the risks and outcomes of pregnancy after lung transplantation. Until this is done, advice to potential mothers must reflect the risks reported in the literature, as well as a large degree of predictive uncertainty in treating lung transplant recipients who become pregnant.

REFERENCES

Extensive Pulmonary Metastases in Malignant Pleural Mesothelioma*

A Rare Clinical and Radiographic Presentation

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We report a case of malignant pleural mesothelioma in a patient who presented with pleural effusion and reticulonodular shadow on chest radiograph. Pulmonary metastases were diagnosed by transthoracic lung biopsy specimen and the patient died of extensive pulmonary metastases. This pattern of clinical and radiographic presentation is seldom reported for malignant pleural mesothelioma.

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Key words: computed tomography; lung metastasis; malignant pleural mesothelioma

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