Pregnancy in heart transplant recipients

Case report and review

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CASE REPORT

Miss A. A. was a 19 year old caucasian primigravida who was admitted as an emergency with heavy vaginal bleeding and abdominal pain. She was 14 weeks advanced in her first pregnancy.

Three years previously she had had an orthotopic heart transplantation after an attack of acute viral myocarditis that resulted in heart failure. Post-transplant she has had good ventricular function, no arrhythmia, normal coronary angiography and heart biopsies have demonstrated normal myocardial histology.

Clinical examination followed by an ultrasound scan led to the diagnosis of an incomplete miscarriage and it was decided to proceed with uterine evacuation under a general anaesthetic.

Her case was discussed with the transplant surgeon at Harefield Hospital.

On examination her haemoglobin was 15.1 gm/dl, blood pressure 160/95 mm Hg, pulse 92 bpm and respiratory rate 26 cpm. She was on cyclosporin 45 mg/day, prednisolone 10 mg/day and prophylactic antibiotics. The uterus was evacuated under a general anaesthetic and the patient, after making an uneventful recovery, was allowed home the next day.

REVIEW

Young women constitute an important minority of the heart transplant population. With the return of libido and sexual function and the resumption of normal menstruation, childbearing becomes a consideration and issues regarding the safety of pregnancy become important. Evidence shown from renal transplant recipients leads to the concluion that pregnancy in heart transplant recipients carries a risk to both mother and fetus. Whether such risk is worth taking, is an individual decision to be made by the patient.

Cardiac transplant recipients who get pregnant, are different from other allograft recipients, as the denervated allograft has to respond to the haemodynamic alterations associated with pregnancy, and rejection surveillance requires serial right ventricular biopsies and other invasive cardiac function tests.

SURVEY

Over 2500 heart transplants are performed each year with the expected 5

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year survival of over 70%. Scott *et al.* 1993 identified 30 pregnancies in heart (27) or heart and lung (3) allograft recipients, in women ranging in age from 20-36 years at the time of conception.

Twenty five pregnancies resulted in live births. The caesarean section rate was 32%, and these were performed successfully either under regional or general anaesthesia. Three patients underwent therapeutic and two spontaneous abortions. Preterm delivery occurred in 9 cases, 6 because of premature spontaneous labour and 3 from complications requiring early delivery.

Because of this high incidence the average birth weight of transplant recipient neonates was low. Fortyeight of the patients had hypertension before or during pregnancy and 24% had preeclampsia.

There were no maternal deaths during pregnancy but 3 patients died within 30 months after delivery. * There were 25 singleton deliveries and 2 sets of twins. There were no fetal deaths nor anomalies but the incidence of fetal growth retardation was 20%.

CARDIAC CHANGES

Maternal cardiovascular changes were well tolerated and rejection episodes unusual. The denervated cardiac graft is known to respond to increased demand through the use of several atypical physiological adaptive mechanisms. Transplant patients do not suffer chest pain which is a sign of myocardial ischemia. As circulating catecholamine levels rise increased heart rate and contractility permit a further increase in cardiac output.

RENAL CHANGES

In the presence of reasonable normal renal function, pregnancy should not be expected to cause deterioration of renal function. It is important to monitor cyclosporin levels and adjusting the doses meticulously to avoid nephrotoxicity during pregnancy and the post-partum period. This nephrotoxicity is progressive and women who are determined to have children should be encouraged to complete their families while renal functions remain well preserved. The use of cyclosporin is associated with a high incidence of uncontrollable hypertension.

ANTE-NATAL SURVEILLANCE

A multidisciplinary approach to the management of these women is important, where a neonatalogist, psychologist, cardiologist and an obstetrician take part in the management.

Obstetric follow-up includes monthly ultrasonography to monitor the fetal growth. Fluoroscopically guided monthly myocardial biopsies are performed in some centres for rejection surveillance, but it raises the point of fetal radiation exposure. Other centres use non-invasive parameters like echo, doppler and cytoimmunologic monitoring.

REJECTION

The incidence of rejection in pregnancy in renal transplant recipients is not greater than that expected from nonpregnant allograft recipients. Acute rejection does not occur more often although chronic rejection continues, hence immunosuppressive drugs must continue.

(*) One woman died 2 years post-partum from cryptococcal meningitis following a cholecystectomy. Another became depressed post-partum and discontinued her immuno-suppressive drugs and rejected the transplanted heart 5 months after delivery. The third patient also stopped her immuno-suppressives 30 months after delivery resulting in rejection and death.

INFECTION

Infection including rare organisms are common in the immunosuppressed and of particular concern in pregnancy. The need for strict aseptic techniques and early resort to antibiotics cannot be over emphasised. Prophylaxis for all operative deliveries is also advocated. Surveillance for the development of maternal CMV and Toxoplasma infection is important in the sero-negative.

IMMUNO-SUPPRESSION

Most centres use three agents: cyclosporin A, azathioprine and prednisolone. Considerable information on these drugs can be derived from pregnancy in renal transplant recipients. Concern usually refers to prematurity, low birth weight, stillbirth, spontaneous abortion, congenital anomalies and carcinogenicity.

Among the pregnancies that progressed past the first trimester and for which immuno-suppressive therapy has been reported the following drug combinations were used: cyclosporin A, prednisolone and azathioprine (14), cyclosporin and prednisolone (3) and cyclosporin and azathioprine (3). The mean doses were cyclosporin) 391.7 mg/day (range 200-650) prednisolone 12.1 mg/day (range 5-30) and azathioprine 105.0 mg/day (range 25-250).

RISK TO THE FETUS

There have been no adequate or well controlled studies in pregnant women who use cyclosporin, although there have been reports on successful pregnancies in women treated with it. It has been used during 34 pregnancies. There have been 6 abortions (one after early detection of anencephaly, 3 elective terminations, 1 missed abortion 1 spontaneous miscarriage at 20 weeks gestation). All 27 of the completed pregnancies resulted in live births. Clearly a period of observation with a larger group of offspring is required before any firm conclusions are reached.

AZATHIOPRINE

More than 1200 pregnancies have been reported in women with renal transplants in whom azathioprine was used. Experience to date suggests that its use in pregnancy is relatively safe. Abnormalities noted at birth in 7 of 100 babies, supported by the Registry of the European Dialysis and Transplant Association included mild mental retardation, bilateral equinovarus, cerebral palsy and cerebral haemorrhage in a set of twins, hypospadias and congenital CMV infection. Theoretically the fetus should be protected from the teratogenic effects of azatrioprine because it lacks the enzyme inosinate pyrophysphorylase that converts azathioprine to its active metabolite.

PREDNISOLONE

The long term administration of corticosteroids has not been associated with an increase in teratogenicity in humans. However, a detailed anomaly scan should be offered to all these patients at 18-20 weeks.

BREAST FEEDING

Women taking immuno-suppressive drugs have the same milk concentration of IgA as do women taking no medication

Breast fed infants born to renal transplant recipients receiving treatment with azathioprine and prednisolone have had normal blood cell counts, no increase in infection and an above average growth rate. Azathioprine and its metabolites are found in breast milk although in low concentrations. Cyclosporin, however, has been detected in breast milk at levels

approximating maternal concentrations, and the general practice has been to advise mothers who are taking immunosuppressive drugs not to breast feed, to avoid any potential risk to neonates.

CONTRACEPTION

Heart transplant recipients who have no desire to have children or those who have completed their families should be offered sterilisation. The effectiveness of intra-uterine contraceptive devices decreases in association with immuno-suppressive therapy and the risk of infection should be considered. Barrier methods are a safe choice when reproductive capacity is to be preserved. Oral contraceptives remain controversial. More data is required to study the beneficial effects, if any, of modern low dose or tri-phasic formulations or progesterone-only pill, on heart transplant patients.

RUBELLA IMMUNITY

Patients awaiting heart transplantation who are not immune to rubella and who might wish to become pregnant can only be vaccinated providing they will not enter the transplant waiting list in the following three months, because the immuno-suppressive therapy will be started once they receive the allograft.

CONCLUSION

The length and quality of life of patients with heart transplants has become impressive. Fertility is not affected by immunosuppressive medication, female transplant patients tolerate pregnancy well. A stable immuno-suppressive regimen appears to be safe for the fetus as documented by the large number of successful deliveries after renal transplant.

The fact that life expectancy is relatively short, prevents advocating childbearing in all these women. They may not live long enough to rear their own children. Couples should be presented with an honest prognosis of heart transplant.

The establishment of a registry of pregnancy outcome would be a worthwhile endeavour.

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