original paper

Pregnancy in Irish renal transplant recipients in the cyclosporine era

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Abstract

Background The effect of renal transplantation on pregnancy in Irish women not receiving CyA has been reported previously.

Aim To examine all pregnancies occurring in Irish female renal transplant recipients since the introduction of CyA.

Methods Using a community based approach, we identified 29 pregnancies in 19 women, aged between 16 and 45, mean age 30.3 years.

Results These pregnancies ended in four miscarriages (13%), two intra-uterine deaths (6.9%) and 23 live births (79.3%). Of these live births, 73.9% were premature (≤36 weeks) and 65.2% were of low birth weight (<2500g). Admission to the neonatal intensive care was necessary in 61%, and two babies (8.7%) died in the neonatal period. Mean gestational age was 34 weeks, and mean birth weight was 2190g. There was no change in graft function during pregnancy, with a small rise in serum creatinine post-partum (+9.64μmol/L). The renal graft failed in three women (15.8%) by the end of the follow-up period. Compared with the pre-cyclosporine era, the live birth rate was higher (79.3% versus 58%) with a trend towards lower birth weight and shorter gestation.

Conclusion Renal transplantation with CyA use is not a contraindication to pregnancy, but it is associated with increased risk, especially when the serum creatinine is >175μmol/L. (Ir J Med Sci 2000; 169: 19-21)

Introduction

In 1986, Mulcahy et al reported on a series of 19 pregnancies in Irish female recipients of renal allografts.[1] All of the patients were maintained on immunosuppressive regimens consisting of azathioprine and prednisolone. There were 12 live births, with adverse foetal and maternal outcomes occurring in some women with hypertension and/or poor graft function.

These findings have been mirrored in other studies[2-6], and some general guidelines for kidney recipients wishing to become pregnant have thus evolved. These include the absence of serious co-morbid disease, a duration post-transplant of at least 12 to 24 months, adequately controlled blood pressure, and a serum creatinine level under 175μmol/L.

With the introduction of the immunosuppressive agent Cyclosporine A (CyA) in the 1980s, there was a major improvement in graft survival. However, this drug added an unknown variable to pregnancy outcome in women with renal transplants.

Consequently, we undertook a follow-up study to that performed by our colleagues, with a view to documenting the Irish experience with pregnancy in renal transplant recipients over the ten years since the introduction of CyA at the National Kidney Centre.

Methods

All Irish female renal transplant recipients who received their graft between 1985 and 1998 inclusive, and who were receiving Cyclosporine A (CyA) as prophylaxis against graft rejection, were identified. Those aged between 16 and 45 years were included. In order to identify those who had been pregnant, a questionnaire was mailed to all of the women. Those who had not responded within four weeks were contacted by telephone.

All women who were found to have conceived while on CyA underwent detailed telephone interview to obtain data on the following variables: pregnancy gestation, outcome, foetal weight, complications, changes in graft function CyA dosage, levels during the pregnancy, graft loss, presence of hypertension, diabetes or recurrent urinary tract infection.

Additional information was obtained where required from obstetric and medical records. Each woman was followed up until death or the development of end-stage graft failure.

Results

During the time period under study, 476 women received a renal allograft. Of these, 218 were aged between 16 and 45. Information was obtained on 163 women (74.8%), 103 (47.2%) having returned the questionnaire and 60 (27.5%) having been contacted by telephone.

Twenty nine pregnancies (including one twin pregnancy) were identified in 19 women (11.6%). Conception occurred at a mean age of 30.3 years (range 19.9-42.8) and at an average of 4.0 years post transplant (range 0.2-8.5). Three of the women (10.7%) conceived less than one year post-transplant.

All women were receiving as standard immunosuppression CyA, prednisolone and azathioprine. Mean CyA dose was 311mg/day (range 140-500). The women were followed up for an average of 33.2 months (range one-115) post-partum.

Among the group as a whole, serum creatinine remained unchanged during the first trimester, with a small rise post-partum (Table 1). The mean increment in the serum creatinine compared to that pre-conception was 9.64umol/L (95% CI = -8.63 to +27.9).

Table 1: Effect of pregnancy on graft function, n=29

Mean serum creatinine	Preconception (range):	140.8 umol/L (82-243)
	Mid-trimester (range):	127.8 umol/L (68-218)
	Post-partum (range):	152.6 umol/L (78-375)
	at last follow-up (range)[a]:	151.5 umol/L (74-316)
Graft function post-partum[b]	Improved:	5 (20.8%)
	Disimproved:	9 (37.5%)
(n=24)	Unchanged:	10 (41.7%)

a: Excluding women developing end-stage graft loss
b: Unchanged = change in serum creatinine < 10umol/L

Table 2: Maternal co-morbid factors and mode of delivery

Drug-treated hypertension pre-conception:	74.1%
Diabetes pre-conception:	7.7%
Pre-eclampsia:	32.0%
Spontaneous labour[a]:	43.5% (n=23)
Elective Caesarean section[a]:	30.4% (n=23)
Emergency Caesarean section[a]:	26.1% (n=23)

a: Excluding intra-uterine death and miscarriage

Table 3: Neonatal outcome, n=23

Mean	Gestational age (range):	34.0 wks (26-40)
	Birth-weight (range):	2190g (681-3760)
Premature (<36 wks):	73.9%	(n=17)
Low birth-weight (<2500g):	65.2%	(n=15)
Very low birth-weight (<1500g):	26.1%	(n=6)
Admitted to Neonatal ICU:	61%	(n=14)
Neonatal death:	8.7%	(n=2)

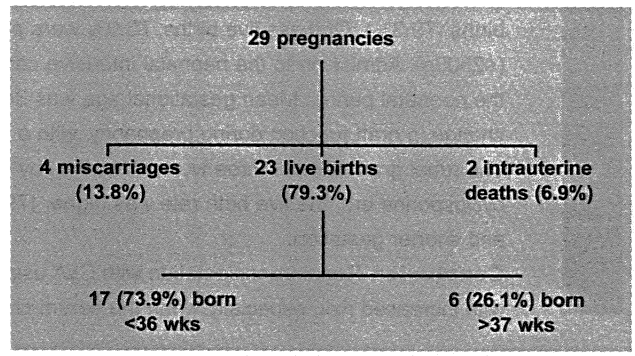
There was only one episode of rejection recorded during pregnancy (3.4%), with the subsequent loss of the graft ten months later, while two further women had developed end-stage graft failure at the time of last follow-up.

In nine pregnancies (32.0%), a clinical picture consistent with pre-eclampsia was noted, although this can be particularly difficult to diagnose accurately in transplant recipients because of underlying proteinuria and hypertension.[7] Twelve pregnancies (56.5%) ended in Caesarean section (Table 2), six of them were emergencies (26.1%). One Caesarean section had rapidly worsening graft function at the time of delivery. Changes in graft function, maternal co-morbid factors and neonatal outcomes are summarised in Tables 1-3.

At the time of conception, five women (17.9%) had a serum creatinine above 175umol/L. One of these had a miscarriage, while the remaining babies were born prematurely and required admission to a neonatal ICU. There was an associated decline in graft function in three of the five (mean increment in creatinine=38umol/L, 95% CI=-42 to 118), with loss of the graft eight months post-partum in one.

Pregnancy outcomes are summarised in Figure 1. There were 23 (79.3%) live births, two of whom (8.7%) died in the neonatal period. The majority of the infants were premature (73.9%) and/or of low birth-weight (65.2%), and there was a high neonatal complication rate (Table 3), with 14 babies being admitted to the neonatal intensive care unit.

Figure 1: Pregnancy outcomes



Discussion

CyA has revolutionised transplantation medicine. Since its introduction, one-year renal transplant survival has increased from approximately 55% to over 85%[8], thereby allowing more women with end-stage renal disease to become pregnant.

Compared to renal transplants not maintained on CyA, however, there is an increased incidence of hypertension and chronic graft dysfunction in patients taking this drug[9], both of which are potentially detrimental in pregnancy.

In the present study, we found that pregnancy in Irish renal transplant recipients was associated with a live birth in over three-quarters of pregnancies, and two-thirds of these were of low birth weight and/or premature.

This compares with the last Irish study of pregnancy and renal transplantation, prior to the introduction of CyA[1], in which 11 of the 19 pregnancies (58%) were successful and resulted in 12 live births, with a mean gestational age of 36.6 weeks and a mean birth weight of 2271g.

Three of these women had suffered a decline in graft function, with a return to dialysis post-partum in two. We used a similar study design to highlight the Irish experience with pregnancy since CyA has been introduced.

In addition, we used a community-based approach in an effort to identify all women becoming pregnant on CyA, thereby allowing us to identify miscarriages and intra-uterine deaths. We found a trend among live births towards lower birth weight

(2190g versus 2271g) and shorter gestation (34 weeks versus 36.6 weeks) when compared to Mulcahy's study.

This might be explained by the higher incidence of drug-treated hypertension in our study (67% versus 25%). This observation was also made by Armenti et al.[10] There was a higher live birth rate (79% versus 58%), which may in part be explained by an enhanced awareness of the risks of pregnancy following transplantation.

The results arising from pregnancy in women on maintenance immunosuppression for renal transplantation have been described in 1,944 cases, of whom 336 were receiving CyA. It has been estimated that between 2% and 6% of transplanted women become pregnant.[3]

In our study, 11.6% of those aged between 16 and 45 at the time of transplant became pregnant. It has become apparent that the presence of a renal allograft is not an absolute contraindication to pregnancy. In most studies, comparing transplanted women on CyA with those who were not, there is a trend towards babies with a shorter gestation and lower birth weight in women on CyA.[10-12]

While worrying, these findings were not statistically significant, and have been attributed to the higher serum creatinine at conception, and higher incidence of hypertension in CyA treated patients.

The largest series have been reported by Armenti et al with data derived from the National Transplant and Pregnancy Registry. [10,12,13] Seventy per cent of pregnancies ended in a live birth, of whom 54% were premature and 46% were of low birth weight, figures that are somewhat lower than ours. After two years of follow-up, 7.6% of women had lost their grafts.

In our study, the 8.7% neonatal death rate and 65.2% neonatal ICU admission rate underscore the fact that these are high risk pregnancies and mandate early joint care by an obstetrician, a nephrologist and a neonatologist.

The relatively high rate of poor graft function at conception (serum creatinine>175μmol/L in 17.9%), and pregnancies in the early post-transplant period (10.7%<12 months), emphasise the need for targeted counselling of these women.

We suggest that advice should be given at the time of discharge after transplantation about contraception, and the avoidance of pregnancy, until graft function and drug dosages have stabilised (after 12 months). These women should also be informed that pregnancy outcomes are more likely to be adverse in the presence of hypertension and/or graft dysfunction. All planned pregnancies should be discussed in advance with the nephrology and obstetric services.

Thus, with improved awareness of the pitfalls of pregnancy in the transplant recipient, risk to both mother and child can be minimised.

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