Prednisone dosage and pregnancy outcome in renal allograft recipients

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Abstract

Background. The literature contains reports of 2309 pregnancies in some 1600 women who have undergone renal transplantation. Certain pre-pregnancy factors, especially hypertension, renal graft dysfunction, short interval between transplant and pregnancy, and high immunosuppressive drug dosage, appear to increase the neonatal risks.

Method. We describe the outcome of 42 pregnancies in 27 allograft recipients at Rabin Medical Center (Beilinson Campus) in Israel during the last 8 years. All were treated with combination immunosuppression regimens.

Results. The average interval from transplantation to conception was $3.7 \pm 0.4$ years (2 months to 9 years). Rejection episodes occurred in 37% prior to pregnancy but in none during or immediately after pregnancy. Twenty-eight percent of the pregnancies ended in therapeutic or spontaneous abortions, and 29 of the 30 deliveries ended in a live birth. The prematurity rate (63%) was similar to that described in the literature for this patient group. Renal deterioration was evident in seven women (26%) within 2 years after delivery. Use of 7.5 mg/d prednisone (vs. 10 mg/d) before pregnancy was observed as the most significant preconception parameter related to better pregnancy outcome. A long interval from transplantation to conception and lack of pre-existing hypertension were also significant.

Conclusion. The better pregnancy outcome associated with lower prednisone dosage is probably related to the fact that the patients selected to receive the low-dose regimen have had a longer and less complicated post-transplantation course.

Key words: immunosuppression; pregnancy; renal transplantation

Introduction

Organ transplantation has achieved tremendous success and more patients have been able to return to a normal life, including bearing children.

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In 23 pregnancies, the patient had received the graft from a living donor, and in 19, from a cadaver donor. Immunosuppression was maintained during all pregnancies. Azathioprine (AZA) 2–3 mg/kg/d was used in 33 out of the 42 pregnancies (79%), prednisone 7.5–10 mg/d (0.11–0.15 mg/kg/d) in all the pregnancies, and cyclosporin A (CyA) 4 mg/kg/d in 32 pregnancies (76%). Thus, triple therapy was used in 23 pregnancies, a combination of prednisone and AZA in eight, and a combination of prednisone and CyA in seven. Hypertension in pregnancy was generally treated with nifedipine. Patients treated with ACE inhibitors were advised to stop treatment at diagnosis of pregnancy.

We analysed several pre-pregnancy factors, including health status, age, parity, type of renal allograft (live donor or cadaveric), time interval from transplantation to conception, episodes of acute rejection, evidence of hypertension, evidence of proteinuria (micro- or macroalbuminuria), and renal function (serum creatinine). The dose of the immunosuppressive drugs prior to pregnancy was also taken into consideration.

Pregnancy outcome was rated on the basis of occurrence of spontaneous or therapeutic abortion, days of hospitalization before delivery, occurrence of pre-eclampsia (defined as initial diastolic blood pressure [DBP] ≤90 mmHg with an increase of at least 25 mmHg, to a DBP >90 mmHg, or initial DBP >90 mmHg with an increase of at least 15 mmHg and evidence of more than 300 mg protein on 24-h urine collection [8,9]. Perinatal characteristics, including gestational age at delivery, birth weight, occurrence of preterm delivery (<37 weeks of gestation), mode of delivery, and neonatal parameters, including incidence of intrauterine growth retardation (IUGR), and days of hospitalization in the neonatal intensive care unit, were also analysed. Factors evaluated on long-term follow-up (2 years after pregnancy) were maternal renal function and infant status (incidence of severe handicap).

Microalbuminuria was determined using a radioimmunoassay technique [10,11] after 8-h overnight urine collection.

A successful pregnancy outcome was defined as a live, healthy infant without severe handicap 2 years after delivery. To predict the pregnancy outcome on the basis of the pre-pregnancy health status and immunosuppressive therapy regimen stepwise logistic regression models were fitted. The probability of successful pregnancy outcome could be calculated using the formula:

\[ P = \frac{e^{10.68 + 1.78(t1 - 1.45(t2) - 11.41(t2))}}{1 + e^{10.68 + 1.78(t1 - 1.45(t2) - 11.41(t2))}} \]

where \( P = \) probability for successful pregnancy outcome; t1 = long interval from transplantation to conception (more than 2 years); t2 = pre-existing hypertension; OP2 = 10 mg/d prednisone.

Probability values ≤0.05 were considered statistically significant.

**Results**

Mean maternal age at the time of conception was 29 ± 0.7 years (range, 20–40 years); in 26 of the 42 pregnancies (62%) the mothers were primiparas. One woman delivered three times and six patients delivered twice.

The average interval from time of transplantation to conception was 3.8 ± 0.4 years (range, 2 months to 9 years). Ten of the 27 patients (31%) had episodes of acute rejection prior to pregnancy. In 17 of the 42 pregnancies (40%), the mother began pregnancy on anti-hypertensive medication. Mean serum creatinine values were 1.27 ± 0.05 mg/dl (range, 0.7–4.1 mg/dl).

In 26 pregnancies (62%), there was no proteinuria at conception; in nine, microalbuminuria was demonstrated and in seven, macroalbuminuria (values exceeding 300 mg/24 h).

Using a logistic regression model, use of 7.5 mg/d prednisone was found to be the most significant preconception parameter related to successful pregnancy outcome (odds ratio 0.00001 for worse pregnancy outcome, \( P = 0.0003 \)). In the group treated with 7.5 mg/d prednisone, 17 out of 17 pregnancies had a successful outcome, whereas in the 10 mg/d prednisone group, this was true for only 15 out of 25 pregnancies (60%).

Successful outcome was significantly related to an interval of more than 2 years from the time of transplantation to conception (odds ratio = 5.9, \( P = 0.03 \)). Lack of pre-existing hypertension was also significant in predicting successful outcome (odds ratio = 0.23, \( P = 0.05 \)). None of the other pre-pregnancy factors studied, such as type of renal allograft (\( P = 0.385 \)), number of episodes of acute rejection (\( P = 0.19 \)), evidence of proteinuria (\( P = 0.928 \)) and serum creatinine (\( P = 0.31 \)), or the immunosuppression therapy parameters (use of CyA, \( P = 0.52 \), and AZA, \( P = 0.69 \)) significantly affected pregnancy outcome.

The interactions between prednisone dose (10 mg/d or 7.5 mg/d), interval from transplantation to conception (long: >2 years, or short: <2 years), and pre-existing hypertension in predicting pregnancy outcome are shown in Table 1. We found that a renal transplant patient who received a pre-pregnancy prednisone dose of 10 mg/d and had a short interval from transplantation to conception and pre-existing hypertension had only a 10% chance of successful pregnancy outcome. A 7.5 mg/d prednisone dose was associated with a 100% chance of successful outcome, regardless of time to conception or presence of hypertension.

**Table 1. Calculated predicted probability for successful pregnancy outcome by prednisone use, interval from transplantation, and pre-existing hypertension**

<table>
<thead>
<tr>
<th>P value* (%)</th>
<th>Prednisone dose*</th>
<th>Interval†</th>
<th>Pre-existing hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>OP2</td>
<td>Short</td>
<td>Y</td>
</tr>
<tr>
<td>32</td>
<td>OP2</td>
<td>Short</td>
<td>N</td>
</tr>
<tr>
<td>40</td>
<td>OP2</td>
<td>Long</td>
<td>Y</td>
</tr>
<tr>
<td>74</td>
<td>OP2</td>
<td>Long</td>
<td>N</td>
</tr>
<tr>
<td>100</td>
<td>OP1</td>
<td>Short</td>
<td>Y</td>
</tr>
<tr>
<td>100</td>
<td>OP1</td>
<td>Short</td>
<td>N</td>
</tr>
<tr>
<td>100</td>
<td>OP1</td>
<td>Long</td>
<td>Y</td>
</tr>
<tr>
<td>100</td>
<td>OP1</td>
<td>Long</td>
<td>N</td>
</tr>
</tbody>
</table>

*P: predicted probability of having successful pregnancy outcome (%) calculated by stepwise logistic regression model. *OP2: 10 mg/d prednisone; OP1: 7.5 mg/d prednisone. †Short interval from transplantation to conception <2 years, long interval, >2 years.
Pregnancy outcome is summarized in Table 2. Six pregnancies (14%) ended in therapeutic abortion and six in early spontaneous abortion. Thirty progressed beyond the second trimester and 29 of them ended in a live birth. There was one case of intrauterine death in a twin pregnancy at 32 weeks of gestation; the cause was unknown.

In those cases that went beyond the first trimester, there were five instances of superimposed pre-eclampsia (17%) and three of severe disease (10%). In 38% of the pregnancies, the mother was hospitalized at least once; the average number of hospitalization days prior to delivery was 13.5 ± 4.2. Mean gestational age at delivery was 34.8 ± 0.58 weeks; 63% of all deliveries were pre-term (< 37 weeks gestation).

The IUGR rate was 33% and the caesarean section rate, 37%. The average hospitalization time in the neonatal intensive care unit was 35.2 ± 16.2 days. On follow-up, two of the 29 infants delivered (7%) were severely handicapped, mainly as a result of prematurity.

Three women (14%) progressed to end-stage renal disease within 2 years of delivery. Two underwent repeated renal transplantation and one is receiving haemodialysis. Four demonstrated a significant increase in serum creatinine (> 1 mg/d) within 2 years of delivery.

Discussion

Over the last 20 years most renal transplantations in Israel (total number, 1300) have been performed at Rabin Medical Center (Beilinson Campus). Therefore, most of the renal transplant recipients who have since become pregnant have been treated at our center.

The incidence of pregnancy in renal transplant recipients in Israel (1/17 women of all ages) is almost equal to that in the Spanish [5] and Norwegian [12] populations, and lower than that reported in a South African hospital (21/122 recipients, 15–35 years of age) [13].

The incidence of prematurity in the general population varies from 5–15% [4], whereas in transplant recipients it is much higher: 63% in our study, and 45–60% in the literature [1,2,14–18]. This may be attributable to the higher incidence of urinary tract infections and chronic prednisone use in renal transplant recipients. It may also be a result of obstetric interventions for uncontrolled hypertension, IUGR and foetal distress. Our incidence of IUGR (33%) matched the findings in the literature (38%) [14,16–20].

None of the patients in the present study had a rejection episode during pregnancy or in the early post-delivery period, as expected from the literature [14,15,19]. Although it is quite difficult to distinguish hypertension from pre-eclampsia in women with transplants [15,19,20], superimposed pre-eclampsia developed in five of 30 deliveries in the present study. Pre-eclampsia was diagnosed on the basis of significant clinical deterioration expressed as significantly high blood pressure, massive proteinuria, and liver and coagulation disturbances.

Once the first trimester was successfully completed, the perinatal and maternal outcome in the majority of the pregnancies was satisfactory (89%, successful pregnancy outcome). Nevertheless, such pregnancies must be considered high risk and should, if possible, be carefully planned. Regarding the long-term follow-up results, four women progressed to end-stage disease (9.5% of all pregnancies) and five (12%) demonstrated a significant increase in serum creatinine. In the literature of the last ten years, the overall five-year survival rate for recipients of a living or cadaveric donor transplant has been 88% and 71%, respectively [17].

Guidelines for pre-pregnancy counselling of women with renal allografts were published as early as 1976 [21]. With minor corrections, those guidelines are still cited in the literature, but the criteria are relative and some are controversial [1]. The results of the present study confirm the importance of pre-pregnancy counselling of renal allograft recipients.

In our patients use of a lower dose of prednisone (7.5 mg/d) as compared with 10 mg/d before pregnancy was observed as the most significant preconception parameter related to successful pregnancy outcome. Prednisone has been used during pregnancy to treat many conditions. Experimental data have suggested that steroids may cause congenital anomalies, such as cleft lip and palate, but this has not been documented in humans. Some complications in neonates exposed to prednisone during gestation, such as adrenal insufficiency and thymic hypoplasia, have been only rarely reported [22]. This may be attributable to the low ability of the drug to cross the placenta at the 1:10 ratio of foetal-to-maternal blood concentrations of the active metabolite, prednisolone [17]. It has also been suggested that premature rupture of the membranes may be related to prednisone use owing to its possible effect on connective tissue [20,23]. With these potential problems in mind, the prednisone maintenance dose for immunosuppression in pregnancy should be tapered to the lowest level possible. Most sources agree with Davison’s recommendation that prednisone should be maintained at or below 15 mg/d [1]. We observed a significantly better pregnancy outcome at a lower dose (7.5 mg/d), perhaps because patients selected for a low-dose regimen are those with a long interval between transplantation and conception and no episodes of rejection. Moreover, some believe that prednisone dosage can be reduced or even discontinued in a patient with no episodes of rejection for more

Table 2. Outcome of 42 pregnancies in 27 renal allograft recipients

<table>
<thead>
<tr>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deliveries at term</td>
<td>11</td>
</tr>
<tr>
<td>Pre-term deliveries</td>
<td>19</td>
</tr>
<tr>
<td>Therapeutic abortion</td>
<td>6</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>6</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>11</td>
</tr>
<tr>
<td>IUGR</td>
<td>10</td>
</tr>
</tbody>
</table>
than a year after transplantation [24]. The use of 7.5 mg/d prednisone was a more significant factor in predicting successful pregnancy outcome than the time interval from transplantation to conception or pre-existing hypertension (Table 1). A long interval and higher prednisone dose (10 mg/d) decreased the probability of successful pregnancy outcome to only 74%, whereas a short time interval and 7.5 mg/d prednisone dose were together related to 100% probability of successful outcome.

Prepregnancy use of AZA and CyA was not found to interfere with pregnancy outcome in our renal transplant patients, although others had contrasting results with CyA [5]. In any case, it is difficult to determine whether cyclosporin dosage is influential in affecting kidney function, and hence obstetric outcome, because of rejection or cyclosporin nephrotoxicity or both.

Regarding maternal pre-pregnancy health status, the interval from transplantation to conception and the presence of hypertension significantly affected pregnancy outcome. Our results confirm the generally accepted opinion that an interval of two years or more from transplantation to pregnancy is advisable so that the patient has been able to recover from surgery, graft function has stabilized, and immunosuppressive drugs are at the lowest maintenance level [1,2,25]. Our results agree with the report of Sturgiss and Davison [26] of a higher mean arterial pressure before pregnancy or in early pregnancy in women with an adverse pregnancy outcome as compared to those with a normal pregnancy. The progression to renal failure observed in seven of our patients was not related to any event of pregnancy or to rejection associated with a change in therapeutic regimen.

In conclusion, to reduce the frequency of induced and spontaneous abortion, we recommend that women wait at least two years from transplantation before becoming pregnant. We believe that the better pregnancy outcome associated with the lowest possible dose of prednisone is related mostly to the selection of patients with less complicated renal transplants. Both prospective parents should be informed of the chances of a successful pregnancy and the possible adverse effects of pregnancy on graft function. The patients must be made aware of the increased morbidity and mortality in renal transplant recipients after pregnancy.

References


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