Transpl Int (1998) 11 [Suppl 1]: S90–S93

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Cyclosporine A blood concentration during pregnancy in renal allograft recipients

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Abstract Pregnancy-induced changes increase hazards associated with cyclosporine (CsA) treatment. Blood CsA trough levels (C_0) were estimated in 15 pregnant renal allograft recipients treated with prednisolone + CsA + azathioprine using the TDx Abbott fluorescent polarization immunoassay. Despite therapeutical dose levels of CsA administered during pregnancy (3.52–3.67 and 3.59 mg/kg body weight in the first, second, and third trimesters, respectively), C_0 significantly decreased (first trimester 130.8 ± 36.9, second 92.0 ± 32.7, and third 99.0 ± 36.9 ng/ml). The mean increase of patient's body weight in mid-pregnancy was 3.0 ± 2.19 kg and was associated with a significant ($P < 0.05$) fall in a hematocrit value (from 42 ± 4.9% prior to pregnancy to 34 ± 6% at the 20th week). We postulate that C_0 concentration does not reflect the true exposure to CsA as no episodes of acute graft rejection were observed during pregnancy.

Key words Kidney transplantation · Pregnancy · Cyclosporine monitoring

Introduction

Kidney transplantation improves the hormonal status of women with terminal renal insufficiency, thus the chances for conceiving and bearing a child dramatically increase. However, pregnancy in a renal transplant recipient can be considered as an important risk factor for graft survival. Kidney graft failure following delivery is reported within the range 10–20% [1–3]. One of the potential pathomechanisms leading to the deterioration of graft function may be suboptimal immunosuppression due to pregnancy-induced changes in cyclosporine (CSA) absorption, metabolism, and excretion. Increasing microsomal placental activity, CsA concentration in fetal tissues (mostly in the liver), as well as increased plasma volume would contribute to the observed decreased CsA levels during gestation [4, 5].

Thus, establishing the best monitoring strategy for CsA dosing in pregnant renal allograft recipients seems to be an important goal.

Patients and methods

The characteristics of 15 pregnant cadaver kidney graft recipients are presented in Table 1. Consent for the study was obtained from all patients. Studies were performed in the first, second, and third trimester of pregnancy. CSA was given orally, twice daily at 7:00 a.m. and 7:00 p.m precisely. Venous blood samples were drawn just before the morning oral dose, i.e., 12 h after administration of the evening dose [CSA trough level (C_0)]. To evaluate transplacental passage of CsA, cord venous blood samples were withdrawn. Whole blood was tested immediately using a TDx multiparametric analyzer (Abbott) with fluorescent polarization immunoassay. Selective monoclonal antibodies were used.

Hematocrit values were estimated with an autoanalyzer (Celldyn 3500).

Statistical analysis was performed with Student's *t*-test (Statistica software).

Results

Whole blood C_0 in 15 women, who conceived following kidney transplantation, have been studied. The mean

Table 1 Characteristics of 15 patients after kidney transplantation

Immunosuppressive regimen	Prednisolone 5–10 mg/day Cyclosporine 3–6 mg/kg body weight per day Azathioprin 1 mg/kg body weight per day
Age at transplantation	27.3 ± 5.4 years
Time from transplantation to gestation	$2^{7}/_{12} \pm 1^{7}/_{12}$ years
Serum creatinine concentration prior to pregnancy	1.3 ± 0.05 mg/dl
Mean time of gestation	35 ± 3.02 weeks

time from transplantation was 2 years and 7 months. Gravidas were treated with a daily dose of 5–10 mg prednisolone, 3–6 mg/kg CsA, and 1 mg/kg azathioprine. Graft function during the 6 months prior to gestation was stable with serum creatinine concentrations of 1.3 ± 0.05 mg/dl. No signs of acute graft rejection or CsA-induced nephrotoxicity prior to, during, and following pregnancy were found.

The mean C_0 measured in the first trimester (before the 14th week of pregnancy was complete) was 130.8 ± 36.9 ng/ml, in the second (between 16 and 20 weeks of pregnancy) C_0 was 92.0 ± 32.7 ng/ml, and in the third trimester C_0 was 99.07 ± 36.9 ng/ml (Fig. 1). The decrease of C_0 found in the second trimester was statistically significant ($P < 0.0002$).

We found a significant increase in body weight associated with pregnancy, from 56.0 ± 7.14 kg prior to pregnancy to 59.2 ± 8.13 kg in midpregancy ($P < 0.0006$) (i.e., in about the 20th week of gestation). This increase was then followed by a corresponding increase in CsA dose (in the first trimester 3.52 ± 0.6; in the second 3.67 ± 0.7, and 3.59 ± 0.6 mg/kg in the third trimester).

CsA concentration found in cord venous blood was 78.4 ng/ml.

Discussion

There are some data reporting a decrease in CsA blood levels during pregnancy [6–8]. However, no consensus has been reached as to the period of pregnancy when its decrease is most pronounced and as to the impact of this phenomenon on graft function. We found a significant decrease in C_0 in the second trimester of pregnancy (92.0 ± 32.7 ng/ml), which may be insufficient to maintain effective immunosuppression as there are data that the incidence of acute rejection is higher at low CsA blood concentrations [9].

Despite the significant increase of body weight in midpregnancy of 3.0 ± 2.19 kg, the adjusted dose of CsA per kilogram of body weight did not change significantly (3.52 versus 3.67 mg/kg), thus the observed fall of C_0 was not caused by a reduced CsA dose. An inverse correlation of CsA blood concentrations and hematocrit values has been reported in the literature [10]. In our study we did not find such a correlation.

The gestational fall of hematocrit values is mostly caused by hemodilution and the compensatory mechanisms lead to an increase of red cell mass of about 18% [11]. As CsA is highly lipophilic and 50% is bound to

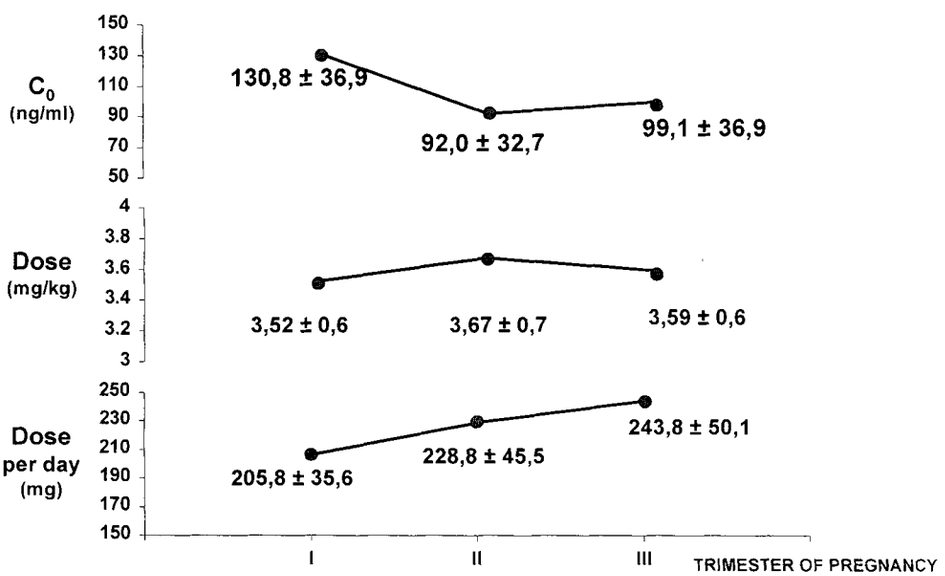

Fig. 1 Cyclosporine measurements during pregnancy (C_0 cyclosporine trough level)

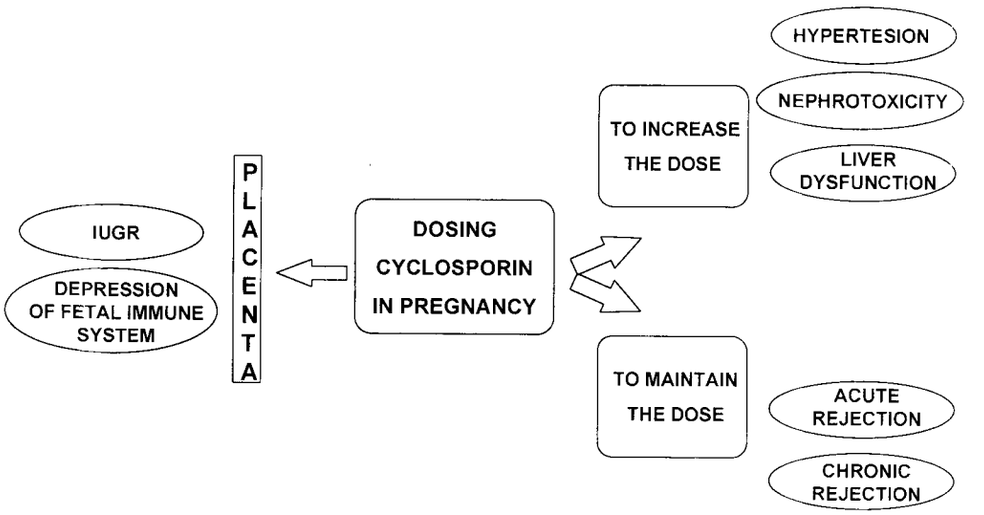

Fig. 2 Cyclosporine treatment during pregnancy (*IUGR* intrauterine growth retardation)

red blood cells, both mechanisms may lead to the decrease of CsA blood concentration [12].

It is difficult to establish whether the observed fall of C_0 reflects true, "insufficient" immunosuppression. Pregnancy modulates the immunological humoral response and some authors postulate that it is an "immunoprivileged state" [13, 14]. Decreased CsA levels may therefore be sufficient for stable graft function. We did not find signs of graft deterioration during pregnancy and in the 6 months following delivery, although this is not a long enough time to evaluate the risk connected with chronic rejection.

CsA crosses the placenta and our data suggest that it may affect the fetal immune system [15]. We found CsA in cord venous blood at a concentration of 78.4 ng/ml. The decision to increase the CsA dose should, therefore, be considered very carefully (Fig. 2). Data based on a large number of patients indicate that there is a higher rate of preterm deliveries in patients treated with CsA than with patients treated with azathioprine and prednisolone [16]. The babies born to mothers receiving CsA demonstrate smaller birth weight, lower Apgar score, and higher rate of intrauterine growth retardation.

Elevated CsA concentrations increase the risk of hypertension and nephrotoxicity, both factors worsening the maternal and fetal prognosis. On the other hand, the data of First et al. [17] showed that CsA dosages in pregnant patients who maintained good graft function were consistently higher than in those who experienced graft dysfunction following delivery [17]. Finally, it is not currently known which CsA concentration measurements (C_0, maximal level, area under the curve) best correlate with clinical outcome.

To answer whether the low C_0 found in the second trimester of gestation justifies the increase of CsA dose, we have started a new program to compare the area under the curve measurements with other CsA monitoring parameters (C_{max}, C_{6h}). Our preliminary data (not yet published) suggest that, despite the significant fall of C_0, values of the areas under the curve did not change significantly (first trimester 3423 ± 412, 3367 ± 449 in the second, and 3189 ± 97 ngh/ml in the third trimester). Whole blood C_0 levels, despite commonly accepted as a routine method for CsA treatment monitoring in renal allograft recipients, may have important limitations in pregnant subjects. To improve the outcome of such pregnancies for baby, mother, and graft, further studies are needed.

Acknowledgements. The work was supported by grant NO 4 PO 5 E 112 08 from the State Scientific Research Committee.

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