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Pregnancy in kidney recipients under cyclosporine

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About 1 of every 50 women of child-bearing age who have a functioning kidney transplant become pregnant. Successful pregnancies following kidney allotransplantation with conventional immunosuppressive treatment are well described [8], and there is no evidence of abnormalities in the infants born. The use of cyclosporine (CSA) means new problems for the pregnant women and the fetus: the risk of congenital abnormalities, fetal growth retardation, hepato- and nephrotoxicity.

We report the experience of 16 pregnancies in 16 of our kidney transplant patients, of which 7 were treated with CSA.

Key words: Immunosuppression – Cyclosporine – Pregnancy

Materials and methods

From May 1969 to August 1991, 1438 kidney transplants were performed on 1355 patients; 471 of the 514 women were of child-bearing age. The kidney is usually located retroperitoneally, in the iliac fossa, using the recipient iliac vessels; an antireflux ureteroneocystostomy will have been preferably performed.

Nine patients were treated with conventional therapy at the mean dosage of 16 mg of prednisone every other day and 1.5 mg/kg daily of azathioprine.

From 1983, 7 patients have been treated with CSA at the mean dosage of 3 mg/kg daily.

Before their transplant, 13 patients presented with important alterations of their menses, and 5 of them had severe amenorrhea.

Menstrual patterns returned to normal within 6 months of the transplant in all patients.

The women become pregnant from 4 months to 11 years after transplantation. Eight women of this group were pregnant before the transplant but 5 aborted because of their uremic status. The clinical data of the 16 pregnant women on the basis of immunosuppressive therapy are reported in Table 1.

Six pregnancies started after an extensive evaluation of the patients' clinical situation by the physician. Good conditions for pregnancy included sufficient renal function (serum creatinine level less than 2 mg% in patients treated with conventional therapy and 2.5 mg% in those treated with CSA), no sign of rejection, normal blood pressure values, no urinary tract dilatation, normal psychological status.

We checked the women monthly with ultrasonography examinations, serum determination of viral antibodies (cytomegalovirus (CMV), hepatitis B surface antigen, HbSAg, German measles) and other more routine examinations.

In case of fetal sufference we did amniocentesis.

Results

The immunosuppressive dosage was not modified throughout the pregnancy. The mean systolic pressure value was 140 mm Hg for the conventional therapy group and 125 mm Hg for the CSA group. Six women had a high blood pressure value during pregnancy. In 4 of them, there was preexisting hypertension.

Clinical signs of rejection were present in 2 women at the beginning of pregnancy that culminated in kidney failure 2 and 3 years after delivery. Other patients showed transient renal dysfunction between the 12th and 16th weeks. Generally mild variations in the creatinine levels were observed during pregnancy (Table 2).

Table 1. Clinical data of 16 women who became pregnant after transplantation on the basis of immunosuppressive therapy

	CsA therapy	Conventional therapy
No. of pregnant women	7	9
Kidney from living donor	–	4
Second transplant	–	1
Recipient's age at transplantation (years)[a]	27.5 ± 7.5	26.2 ± 5.4
Months of dialysis before transplantation[a]	52 ± 49.9	42.6 ± 34.5
Kidney placed in RIF (N^)	7	4
HBsAg positivity	3	2
Months between transplantation and pregnancy	36.2 ± 23.2	53.3 ± 40.3

[a] Mean ± SD
CsA, cyclosporine; HBsAg, hepatitis B surface antigen

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Table 2. Creatinine levels in 14 pregnant women before, during, and after pregnancy on the basis of immunosuppressive therapy

	CsA therapy	Conventional therapy
Creatinine level before pregnancy	1.1 ± 0.3	1.3 ± 0.6
Creatinine level during pregnancy	1.08 ± 0.2	1.4 ± 0.6
Creatinine level after pregnancy	1.08 ± 0.19	1.5 ± 0.8

Mean values ± SD

Four women (3 from the CSA group) developed hepatopathy or their condition worsened but returned to normal after delivery.

Five patients showed a HbSAg positivity during pregnancy without any clinical signs. Hepatitis B immunoglobulin was given to their babies within 12 h of birth, followed by hepatitis B vaccine. One women treated with conventional therapy developed gestational diabetes that required insulin therapy from the 25th week. Another patient treated with CSA had hyperglycemia which was well controlled by dieting.

Four cases of urinary tract infection had been observed, but only 1 was symptomatic. This patient had a vesicoureteral reflux that worsened during pregnancy, but no surgical treatment was necessary.

The hematocrit value went down in our group, but only 1 patient became severely anemia.

In all, 16 children were born, 8 of them preterm; 10 were boys and 6 girls. The mean gestational period was 35.7 ± 2.2 weeks for CSA-treated mothers and 34.7 ± 5.1 for the conventional groups, a course almost uneventful for the 16 mothers. All children are healthy except 1, from a patient affected by chronic rejection, who was born preterm at the 23rd week because of placenta rupture and died 3 days after delivery due to respiratory distress syndrome.

An elective cesarian section was decided for all patients. Eight children had a normal birth weight, in relation to the gestational period. Three weighed less than 2500 g, and 4 children had a weight over the 90th percentile. The baby born in the 23rd week weighed 600 g. Excluding this last baby, the mean birth weight was 2.703 kg ± 0.591. The Apgar scores are shown in Table 3.

There were no major congenital abnormalities in the babies; one baby presented with small hemangiomas on the face and neck that regressed spontaneously. No bone abnormalities have been noted. The children are growing normally, remaining over the 20th percentile.

Bottle feeding was preferred for almost all of the babies.

Discussion

The risks of pregnancy undertaken by a kidney transplant patient are not increased either for the mother or for the baby by use of CSA for the immunosuppressive regimen, in according with other studies [3].

The abortion rate is related to the renal function [6].

An increase of acute reversible rejection after delivery has been noted [4, 5, 8].

We consider it unnecessary to increase the immunosuppressive regimen during pregnancy as other authors suggest [1].

Table 3. Clinical data of 15 children in relation to immunosuppressive therapy of the transplanted mothers[a]

	CsA therapy	Conventional therapy
Gestational period (weeks)	35.7 ± 2.2	35.0 ± 3.5
Birth weight (kg)	2.517 ± 0.444	2.797 ± 0.692
Apgar score	7 ± 0.8	7.8 ± 0.6

[a] We did not consider in this table the baby born preterm at the 23rd week

Ultrasonography study is of primary importance to evaluate the course of fetal growth.

We agree with Cockburn's conclusions from a study of 51 pregnancies in 48 patients treated with CSA, in which he did not note any congenital anomalies in the babies nor damage to the mothers. CSA is often related to hypertension. The incidence of eclampsia could theoretically be higher than with conventional therapy, but in our group this was not noticed. However, the incidence of eclampsia is related to preexisting hypertension and/or renal impairment [6].

Our decision to perform cesarian sections on all the mothers was made in order to avoid trauma to the kidney during delivery.

Our incidence of 6.2 % perinatal mortality is related to prematurity and is comparable with the incidence of 8 % reported by Fine [6].

In 10 of our infants the birth weight appeared less than 2500 g, in according with other authors for either the CSA-treated [6] or the conventional group [7].

It is possible that the association of CSA and AZA could be dangerous for the synergic mutagenic effect of the two drugs [11].

Many problems are still to be cleared up about the use of CSA in pregnancy. The measurement of the whole blood CSA level may be an inappropriate measure of the free drug concentration during pregnancy because of the change in red cell volume [10].

Another problem is the higher concentration of CSA in the placenta related to the maternal or fetal blood [2].

It is better not to breast feed because of the high presence of drugs in the breast milk.

References

1. Biesenbach G, et al. (1989) Successful pregnancy in a rhesus incompatible cyclosporine-treated renal transplant recipient. Nephrol Dial Transpl 4: 511
2. Bourget P, et al. (1990) Transplacental passage of cyclosporine. Transplantation 49: 663
3. Cockburn I, et al. (1989) Present experience of cyclosporine in pregnancy. Transplant Proc 21: 3730
4. Davison J, Lindheimer (1982) Pregnancy in renal transplant recipients. J Reprod Med 27: 613
5. Davison J, Lind T, Lind P (1976) Planned pregnancy in a renal transplant recipients. Br J Obstet Gynecol 83: 518
6. Fine R (1982) Pregnancy in renal allograft recipients. Am J Nephrol 2: 117
7. Lau J, Scott J (1985) Pregnancy following renal transplantation. Clin Obstet Gynecol 28(2): 339
8. Penn I, Makowski E, Harris R (1980) Parenthood following renal and hepatic transplantation. Kidney Int 30: 397
9. Pujals JM, et al. (1989) Osseus malformation in baby born to a woman receiving cyclosporine. Lancet I: 667
10. Ross WB, et al. (1988) Transplantation 45: 1142
11. Zankl H, et al. (1987) Nephrol Dial Transpl 2: 467