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ORIGINAL ARTICLE

Outcome of pregnancy after organ transplantation: a retrospective survey in Italy

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Abstract The number of women who decide to have a child after organ transplantation has increased. We determined the outcomes of 67 pregnancies of women who had undergone kidney, liver or heart transplantation. All recipients had been maintained on immunosuppressive therapy before and during pregnancy. Pregnancy complications at term were observed in 17 out of 67 women (25%), hypertension being the most frequent complication (16.17%). Two transplant rejections were reported. Sixty-eight infants were delivered (including one pair of twins); five women had two pregnancies at term. Twenty-eight miscarriages (29.2%) were recorded. Of these 68 babies (including the pair of twins), 40 (58.8%) were born at term and 28 (41.2%) before term. The babies were followed-up for 2 months to 13 years. According to our previous experience, our study shows that patients who have undergone organ transplantation can give birth to healthy infants as long as they are monitored accurately during pregnancy.

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Introduction

In recent years advances in surgical techniques and immunosuppression have improved not only survival rates but also the quality of life for patients with transplanted organs [1]. Hence, the number of women of childbearing age who decide to have a child—which indicates the resumption of a normal life—has increased [2, 3]. Most studies have focused on pregnancy outcomes of women who have kidney transplants, but only small cohorts, from individual centres, of women who have liver, heart and pancreas transplants have been studied [4, 5]. The most pressing questions that have been raised concern the administration of immunosuppressive drugs and the effects that they might have on the developing foetus, the course of pregnancy, childbirth and transplant-related complications [6, 7]. Pre-term births and intrauterine growth retardation (IUGR) are frequently encountered. According to some studies, the miscarriage rate is higher than in the general population. Foetal malformations, ranging from labiopalatoschisis to heart defects, have been reported [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30]. Furthermore, the effects of immunosuppressive therapy on the immune system of the developing foetus are still not clear [20, 31, 32, 33, 34]. This retrospective study focuses on pregnancy outcomes of women after they had undergone organ transplantation observed by a multicentre transplant group in Italy. It is the first survey of this kind ever carried out in Italy.

Materials and methods

Questionnaires were sent to all participating investigators, with an aim both to determine the prevalence and outcomes of pregnancy (complications, miscarriages, stillbirths, therapeutic abortions and live births) and to collect data on pregnancies at term and on spontaneous/therapeutic abortions that occurred before transplant surgery. Furthermore, to determine the risk of transplant rejection we requested information regarding the mothers' follow-up, the interval from transplantation to pregnancy and the therapy the mothers had received during pregnancy. The infants' general health and their follow-up were examined closely. After the patients' doctors had been called or visited, the patients were interviewed in person, whenever possible, or by telephone.

Data regarding delivery (natural childbirth or by caesarean section), the babies' weight, length, head circumference, Apgar score and labour values were assessed. The infants were classified according to two criteria: (1) gestational age, (defined as pre-term, at term, or post-term); (2) weight, [qualified as appropriate, small for date or large for date (or macrosomal)]. According to their gestational age, pre-term babies were further divided into three groups: low birth weight (LBW), very low birth weight (VLBW) and extremely low birth weight (ELBW) [35]. The first group includes moderately premature babies delivered between 32 and 37 weeks of gestation and weighing between 1,500 g and 2,500 g; VLBW babies are very premature, born before 29 to 32 weeks of gestation and weighing 1,000 g to 1,500 g at birth; ELBW babies are delivered between week 22 and 28 and weigh between 500 g and 1,000 g. We also asked the women questions regarding growth, vaccinations and allergic reactions, if any; the diseases the babies had had; the laboratory tests they had undergone and the last measured height and weight.

Results

Our survey includes 96 pregnancies observed between 1987 and 2002. Of these pregnancies, 67 were at term

(including one pair of twins), of which 52 were after the women had undergone kidney transplantation, seven after liver transplantation and eight after heart transplantation. We registered 29 miscarriages, equal to a frequency rate of 30.2% (Tables 1 and 2). Eight women had an abortion. The therapeutic abortions were performed because of hypertension and/or altered kidney function.

The average time from transplantation surgery to childbirth was 66 months (range 12–180 months). All patients received immunosuppressive therapy during pregnancy, which consisted of cyclosporine (CsA), azathioprine (AZA), steroids or tacrolimus (FK506) (Table 3). At the time the transplantation had been carried out, the patients' average age was 25.6 years (range 16–36 years). The average age at delivery was 30.6 years (range 23–37 years).

Pregnancy complications

Complications during pregnancy were observed in 17 of 67 pregnancies at term (25.4%); hypertension was the most frequent, since it was observed in 11 women (16.4%). With regard to other complications that were experienced, four women had threatened abortions, three had abnormal liver function, three had anaemia, two had altered kidney function, one a reduced platelet count, one hyperparathyroidism, hypercalcaemia, and hypercalcinuria, one gravidic cholestasis, one increased CsA blood levels leading to a temporary interruption of the treatment, one suffered CsA-induced kidney toxicity and one had corticosteroid-induced bilateral necrosis of the femur head (Fig. 1). Hypertension was observed in all kidney transplant recipients, and two women had hypertension before pregnancy; eight babies from mothers with hypertension were born before term (three LBW, VLBW, EVLBW) and one baby was born at term with IUGR.

Table 1 Pregnancies outcome

Parameter	Spontaneous abortion	Therapeutic abortion	Total abortion	Pregnancies at term
Number of cases	11	18	29	67
Percentage	11.4%	18.8%	30.2%	69.8%

Table 2 Immunosuppressive therapy/abortions (therapy was reported in 19 cases of abortions)

Type of transplant	Number of abortions	Drugs received	Number of cases
		AZA, steroids	6
Kidney	24	CsA, AZA, steroids	4
Heart	1	CsA, steroids	4
Liver	4	CsA	3
Total abortions (*n*)	29	FK506	1
		FK506, steroids	1

Table 3 Immunosuppressive therapy during pregnancy

Drugs received	Number of cases	Percentage
CsA, AZA	1	1.7%
CsA, steroids	14	24.6%
CsA, steroids, AZA	16	28.1%
AZA, steroids	8	14.1%
CsA	15	26.3%
FK506, steroids	2	3.5%
AZA, FK506, steroids	1	1.7%

Maternal follow-up

Two kidney transplant rejections were reported (5.4%), one of which was irreversible. This patient is still under dialysis and is waiting for a new transplant. These rejections were not related to modification of the immunosuppressive treatment. The other patient with a transplanted kidney had post-partum hypertension and was still on anti-hypertensive therapy when she was interviewed. Epstein–Barr virus encephalitis was observed in early post-partum of one patient with a transplanted kidney. One patient with a transplanted liver died from heart failure 4 days after delivery.

Infants

A flow chart of the outcome of the 96 pregnancies is shown in Fig. 2.

A total of 68 infants was delivered. Of five women who had two pregnancies at term, three had a transplanted kidney, one had a transplanted liver and one had a transplanted heart. Out of the 68 babies, 40 (58.2%) were born at term and 28 (41.8%) before term (mean gestational age 33.8 weeks; mean birth weight 2045 g). The overall mean gestational age was 36.1

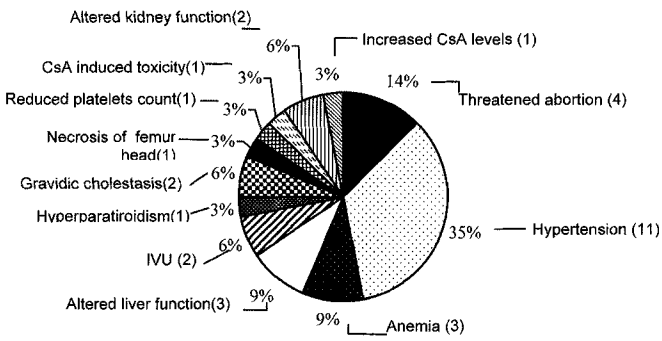

Fig. 1 Type and percentage of complications during the pregnancies

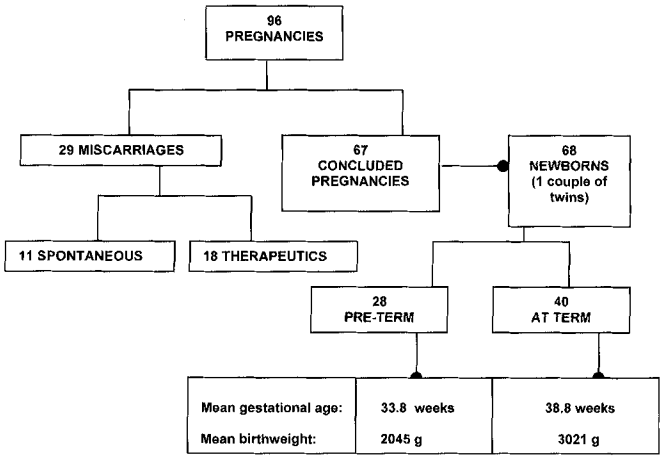

Fig. 2 Flow chart of the outcome of the 96 pregnancies

weeks with a range from 22 to 40 weeks. We performed 61 caesarean sections (91.1%), and only six (8.9%) vaginal deliveries were recorded (Tables 4 and 5). The mean birth weight was 2,485 g, (range: 1,150 g–4,000 g). The mean length was 47.1 cm, with a range from 36 cm to 52 cm. The mean head circumference was 34 cm, with a range from 31 cm to 37 cm. The Apgar score ranged from 6/10 to 10/10.

Complications were observed in 12 cases, namely six cases of IUGR, one case of neonatal hypotonia, one of hypoglycaemia, hypothermia and bradycardia (the mother was also taking ß-blockers), two of anaemia, and one of reduced platelet count; one child that had been delivered after only 6 months of gestation died from ARDS. One of the babies presented a congenital valgum talipes. Among the 28 babies born before term, seven could be classified as LBW (25% born pre-term, 10.5% of the total number of infants), four as VLBW (14.3% of the pre-term group, 5.9% of the total group) and two as EVLBW (7.1% of the pre-term babies, 2.9% of the total group). As for the 39 babies delivered at term, two were "small for date" (5.1% of the babies born at term, 2.9% of the total group). After IUGR diagnosis, one baby had to be delivered by caesarean section at the 39th week of gestation. His weight was 2,650 g; hence, he could not be included in the "small-for-date" group (weight $\leq$ 2,500 g), but his case was reported separately since his weight was below the 10th percentile. The weights of the remaining infants were regarded as appropriate for gestational age.

Table 4 Gestational age

Range	Number of cases	Average gestational age Weeks	Median gestational age Weeks
Delivery at term 38–40 weeks	39	38.8	39
Pre-term delivery 22–37 weeks	28	33.8	35
Total 22–40 weeks	67	36.2	37

Table 5 Delivery

Childbirth	Pre-term	Term	Total
Caesarean section	27	34	61 (91.1%)
Natural	1	5	6 (8.9%)
Total	28	39	67

The infants' follow-up

None of the babies had been breastfed, since the immunosuppressive drugs taken by the mothers are secreted in the milk [36]. The children were followed-up for a period ranging from 2 months to 13 years. Vaccinations were given to all of them, and none of them had any side effects.

Their development has been uneventful, the conditions they presented at birth have been completely resolved and their growth has been regular.

Discussion

The first pregnancy after organ transplantation was described in 1963 in a kidney allograft recipient [5]. Now, pregnancy represents a realistic opportunity after solid-organ transplantation, and it is estimated that one in every 50 women of childbearing age will become pregnant after undergoing organ transplantation [1]. The main topics of the debate on pregnancy after organ transplantation are: the course of pregnancy, the function and survival of the transplanted organ and the effects of the immunosuppressive agents on the developing foetus, including the long-term outcome of the infant [37, 38].

Studies performed on kidney, liver or heart transplant recipients showed a percentage between 69% and 74% of infants born alive. In our survey the percentage of pregnancy at term was comparable (72%). The most frequent complications reported include hypertension and maternal infections, pre-term delivery and low-birth weight of the newborn infant [23, 24, 39, 40]. Our survey agrees with these data showing that pre-maturity is common (51% of pregnancies) and much more frequent than in the general population, in which the overall prematurity incidence is approximately 11% according to estimates [28, 40, 41, 42, 43, 44]. In the general population small-for-date newborn babies are 5.1%; in our study group they represent 10% of the babies born at term. In the general population 5% of the premature infants are LBW, 1% VLBW and 0.25% EVLBW.

In our study 41.8% of the babies we reviewed were born pre-term, of which 25% were classified as LBW, 14.3% as VLBW and 7.1% EVLBW [45, 46].

According to the official guidelines, women who have undergone transplant surgery must be tested for stable graft function and must be maintained on immunosuppression before planning to have a baby in order to minimize risks [5, 25]. Most pregnancies in patients with normal and stable organ function had no effect on the graft function or survival; in contrast, a deterioration in graft function represents a significant risk of graft loss within 2 years of delivery [25, 28, 47]. In some reports acute rejection during, or within 3 months after, pregnancy ranges between 9% and 14.5%. In our series, rejection occurred in two kidney transplant recipients, one of which was definitive (2.1%). This was reported by previous studies showing that the incidence of clinically diagnosed rejection of renal allografts during pregnancy was unchanged and not higher than expected for non-pregnant allograft recipients [26, 38, 48]. This probably means that the centres involved in this survey carried out a careful and thorough assessment of the clinical and biological parameters before the patients decided to have a baby.

Our results show that miscarriage (11.5%) is more frequent than expected (10%) in the Italian population [49]. An increased abortion rate was also observed by other authors [2, 3, 26, 27, 45]. The percentage of caesarean sections in our study is 91.1%, as opposed to 23% in the general population [47]. This is partly because of the need to plan the baby's birth, partly due to the occurrence of maternal (i.e. hypertension and bilateral necrosis of the femur head) or foetal (IUGR) complications. It should not be overlooked, however, that after kidney transplantation natural childbirth may be unadvisable because of the location of the transplanted organ. In other series the rate of post-transplantation caesarean sections was lower that observed in our study, but still higher than in the general population. Albeit difficult to explain, this difference may be the result of the guidelines issued by the obstetrics centres. Four patients had two pregnancies at term, without complications or transplant rejection. This agrees with other reports in the literature concerning women with transplants who had more than one pregnancy [40].

Foetal malformations as a result of immunosuppressive therapy are reported [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30]. In our survey perinatal complications were mild, but one perinatal death from ARDS occurred. No foetal malformations were observed. The incidence of autoimmune diseases may be higher in the offspring of patients treated with CsA [13, 31]. In our survey no congenital malformations or autoimmune diseases were observed; however, in most cases the observation period may be regarded as being too short for the real risk to be fully assessed and for final conclusions to be drawn. Long-term immunological monitoring of children born from allograft recipients is then necessary.

In organ recipients an interval of 1 to 2 years between transplant surgery and conception is recommended, even though some successful cases have been reported after a shorter period. In our cohort the average interval between transplantation and pregnancy was longer (64 months, but in one case only 1 year had elapsed). In line with our previous experience, the study shows that patients with transplanted organs can give birth to healthy infants so long as they are monitored accurately during pregnancy [23, 24, 25, 28, 37, 38, 39, 40, 41, 42, 44, 47]. However, these pregnancies are to be regarded as a high risk and require a multi-disciplinary approach. It is crucial for patients to consult the doctor before deciding to have a baby; this is the best time to understand the pregnancy-related risks for the infant and the mother, even with regard to her life expectancy. Even the possibility that the same disease that made the transplant necessary for the mother might be transmitted to the foetus has to be taken into account.

The findings of this survey may be considered as the starting point for future monitoring protocols for pregnant patients or for specific studies on their babies. This survey might have a major social, educational and emotional impact on the patients who have already undergone or are going to undergo transplant surgery.

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