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PREGNANCY AFTER LIVER TRANSPLANTATION WITH TACROLIMUS IMMUNOSUPPRESSION: A SINGLE CENTER'S EXPERIENCE UPDATE AT 13 YEARS[1]

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Background. **Chronic liver disease often leads to amenorrhea in women of childbearing age. There are several reports of successful pregnancy after liver transplantation (LTx) with cyclosporine A immunosuppression. Tacrolimus has been increasingly used in solid-organ transplantation, and the effect of the drug on pregnancy is still of interest to clinicians. This study updates our single-center experience.**

Methods. **All pregnancies after LTx with tacrolimus immunosuppression were followed prospectively. Patients' clinical courses during pregnancy and labor along with gestational period and birth weight were catalogued. Changes in liver function, renal function, and immunosuppression also were recorded. The birth weight percentile was calculated on the basis of the gestational period using a standard chart.**

Results. **Thirty-seven mothers delivered 49 babies. Three mothers delivered three times, and six mothers delivered two times. Thirty-six mothers (97%) survived the pregnancy, and 36 allografts (97%) survived. The one death and graft loss was in a patient who demonstrated infra-aortic arterial graft, which clotted by the gravid uterus during labor. The patient developed a gangrenous liver and died before she could undergo retransplantation. The mean gestational period was 36.4±3.2 weeks, excluding two premature deliveries at 23 and 24 weeks gestation. Twenty-two babies (46.9%) were delivered by cesarean section, and the other babies were delivered vaginally. In addition to the two premature babies, one baby, who was born to a mother with Alagille syndrome, died from congenital birth defects. The rest of the newborns survived. The mean birth weight was 2,797±775 g, with 38 babies (78%) weighing more than 2,000 g. The mean birth weight percentile to gestational period was 54±23. Four babies (8.5%) had a birth weight percentile of less than 25, and 28 babies (59.6%) had a birth weight percentile greater than 50. Twelve patients demonstrated an increase in hepatic enzymes without jaundice during the pregnancy. All of them responded to augmentation of immunosuppression.**

Conclusion. **The present report reconfirms the safety of tacrolimus during pregnancy after LTx. Preterm delivery and low birth weight seem to be a persistent problem in all solid-organ transplantation under any form of immunosuppression. However, toxemia of pregnancy and new onset of hypertension seem to be have a low occurrence with the use of tacrolimus.**

Chronic liver disease can lead to amenorrhea in women, and pregnancy is often not possible in women of childbearing age. There are reports after liver transplantation (LTx) indicating that the normal menstrual cycle is restored, and that childbearing is possible. There are also reports of pregnancy during which azathioprine (Aza) and cyclosporine A (CsA)-based (*1–3*) immunosuppression is administered. Tacrolimus was introduced in clinical trials at our center 13 years ago and has been used by many other centers during the last 10 years. During the last 5 to 10 years, we have published our initial reports on successful pregnancies after LTx with tacrolimus-based immunosuppression (*4*, *5*).

This report updates our center's experience and examines the outcome of pregnancies after LTx with tacrolimus-based immunosuppression during the last 13 years from a single center.

PATIENTS AND METHODS

All pregnancies with tacrolimus-based immunosuppression after LTx were examined prospectively. The course of the pregnancy in the mother, changes in allograft function, complication in the mother, and immunosuppression were examined. Gestational period, type of delivery, birth weight, intrauterine development of the fetus, and congenital defect in the fetus were recorded. Intrauterine growth of the fetus was determined by calculating birth weight percentile using the scatter gram from Lubchenco, Hansman, and Boyd (*6*).

RESULTS

Overall, 37 mothers delivered 49 babies. Three mothers delivered three times (cases 2, 11, and 35), and six mothers delivered two times (cases 1, 5, 9, 10, 14, and 16). The primary diagnosis of end-stage liver failure is given in Table 1. Eight mothers underwent two transplants and three mothers underwent three transplants before pregnancy. Seven mothers (18.9%) had undergone LTx at the age of 12 years or less; the youngest patients were 6 (case 32) and 8 years (case 31) at the time of LTx. The mean age of the mother at the time of delivery was 29.1±6.3 years (median 27.5; range 18.3–43.4 years). The mean interval from LTx to delivery was 70.2±51.8 months (median 48; range 8–163 months). All mothers received tacrolimus for the entire gestational period. A total of 20 mothers received tacrolimus from the outset after LTx, and 17 mothers originally received CsA and were converted to tacrolimus for ongoing rejection. They were con-

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TABLE 1. Demographics

Mother No.	Baby No.	Diagnosis	Age at delivery (yr)	Months to delivery after LTx	Gestational period (wk)	Type of delivery (vaginal or C/S)	Reason for C/S	Birthweight (g)	Boy/girl	Birthweight (percentile)	Obstetric history
1a	1	Caroli's disease	25.8	17.9	36	C/S	Previous classic C/S	2,236	Boy	40	G1P0
1b	2		27.5	38.6	34	C/S	Previous classic C/S	2,438	Boy	80	G2P1
2a	3	Cryptogenic cirrhosis	25.5	97	35	Vaginal		2,180	Girl	40	G1P0
2b	4		27.4	120.6	40	Vaginal		2,410	Boy	10	G2P1
2c	5		33.5	194.8	36	Vaginal		2,869	Boy	60	G3P2
3	6	Ethanol-induced cirrhosis	32.6	34.4	34	C/S	Previous classic C/S	1,850	Girl	30	G3P3
4	7	Primary biliary cirrhosis	35.4	70.4	33	C/S	Placenta abruptio	1,712	Girl	40	G1P1
5a	8	Non-A and non-B hepatitis	31.2	22.3	40	Vaginal		3,912	Girl	>90	G2P2
5b	9		36.8	90.7	34	Vaginal		3,011	Girl	>90	G3P3
6	10	Autoimmune hepatitis	18.3	20	37.5	Vaginal		2,580	Boy	25	G1P0
7	11	Cryptogenic cirrhosis	20.2	6.1	23[a]	Vaginal		587[a]	—		G1P1
8	12	Acute fulminant hepatic failure	33.5	43.7	35	Vaginal		2,594	Girl	75	G1P2
9a	13	Ethanol-induced cirrhosis	31.5	18.4	37	Vaginal		2,438	Boy	25	G2P2
9b	14		35.6	67.6	37	Vaginal		2,585	Girl	30	G3P3
10a	15	Cryptogenic cirrhosis+hepatitis B	34.6	17.7	24[a]	C/S	Preeclampsia	510[a]	—		G0P0
10b	16		36.5	39.7	32	C/S	Previous classic C/S	1,565	Girl	50	G1P0
11a	17	Autoimmune hepatitis	23.5	32.8	39	Vaginal		3,374	Boy	70	G0P0
11b	18		25.8	65.4	28	Vaginal		1,632	Girl	>90	G1P1
11c	19		33.1	154.5	36	Vaginal		3,011	Girl	75	G2P2
12	20	Hepatitis B viral-induced cirrhosis	24.6	45.3	31	C/S	Premature/fetal distress	1,215	Boy	15	G7P4
13	21	Ethanol-induced cirrhosis+hepatitis B	30.5	29.1	40	C/S	Fetal distress	3,310	Boy	60	G0P0
14a	22	Wilson's disease	32.6	49.2	40	Vaginal		4,346	Boy	>90	G2P2
14b	23		34.1	67.9	40	Vaginal		3,693	Girl	80	G3P3
15	24	Primary biliary cirrhosis	24.3	33.5	36	C/S	Delayed labor	2,980	Boy	70	G0P0
16a	25	Primary schlerosing cholangitis	28.9	43.2	40	Vaginal		2,897	Girl	25	G1P1
16b	26		32.1	82.4	40	Vaginal		3,272	Girl	55	G2P2
17	27	Hepatitis B viral-induced cirrhosis	23.9	66.2	36	Vaginal		2,159	Boy	20	G0P0
18	28	Fulminant hepatic failure, acetaminophen overdose	19.8	38.5	37.5	C/S	Failure to progress/arrest of dilation	2,711	Girl	35	G0P0
19	29	Wilson's disease	26.7	94.6	40	Vaginal		3,324	Boy	65	G0P0
20	30	Autoimmune hepatitis	26.9	37.2	36	C/S	Placenta previa	2,280	Girl	25	G0P0
21	31	Autoimmune hepatitis	22.3	31.7	40	C/S	Prophylactic	3,522	Boy	75	G0P0
22	32	Cryptogenic cirrhosis	33.7	51.8	38	Vaginal		2,430	Boy	25	G1P1
23	33	Byler's disease+hepatitis C viral infection	25.5	103	39	C/S	Failure to progress	3,570	Girl	90	G0P0
24	34	Primary biliary cirrhosis	33.2	20.3	40	C/S	Prolonged labor	3,690	Boy	75	G1P0
25	35	Ethanol-induced cirrhosis	43.4	18.6	40	Vaginal		2,954	Girl	30	G1P0
26	36	Caroli's disease	41.8	75.3	32	C/S	Ruptured membrane	2,040	Girl	>90	G2P1
27	37	Autoimmune hepatitis	33.2	26.2	37.5	C/S	Failure to progress	2,890	Boy	50	G1P0
28	38	Autoimmune hepatitis	26.2	77.9	37	C/S	Failure to progress	2,580	Girl	25	G0P0
29	39	Wilson's disease	22.2	93	35.5	Vaginal		2,855	Boy	80	G0P0
30	40	Cryptogenic cirrhosis	36.1	97.8	38	C/S	Fetal distress	2,585	Boy	25	G0P1
31	41	Familial intrahepatic cholestasis	22.3	174.6	28	Vaginal		924	Boy	<10	G0P2
32	42	Secondary biliary cirrhosis	18.3	148.5	38	C/S	Elective/spina bifida/small pelvis	3,242	Boy	70	G0P3
33	43	Autoimmune hepatitis	40	48.1	36	Vaginal		3,362	Boy	85	G0P4
34	44	Hemangioma	20.3	111.5	34	Vaginal		1,983	Boy	50	G0P5
35a	45	Alagille's syndrome	21.9	117.9	33	C/S	Breech presentation	1,439	Girl	20	G0P6
35b	46		23.1	132.4	40	Vaginal		3,182	Boy	50	G1P1
35c	47		25.4	160.7	32	C/S	Breech presentation	1,449	Girl	25	G2P2
36	48	Congenital hepatic fibrosis	25.8	163	37.5	Vaginal		3,750	Girl	>90	G0P0
37	49	Primary Schlerosing cholangitis	38.3	46.3	37	C/S	Breech presentation	3,721	Boy	>90	G0P0
		Mean	29.1	70.2	36.4			2,697		53.51	
		Median	27.5	51.8	37			2,711		50	
		SD	6.3	48	3.2			775		26.88	

[a] Premature baby died soon after birth.

C/S, cesarean section; g, gravida; p, para; SD, standard deviation.

verted to tacrolimus before pregnancy. The mean time they received tacrolimus before delivery was 49.9±40.8 months (median 31.2; range 5.8–114.8 months).

Survival

Mothers. Thirty-six mothers (92.3%) survived the pregnancy. One mother (case 32) underwent two LTxs; primipara at age 40 years, her infra-renal aortic graft clotted during labor. She developed liver failure 2 days later and died of fulminant gangrene of the allograft on transfer to our center before retransplantation could be accomplished. However, the newborn baby survived. Of the remaining 36 mothers, three died during the subsequent follow-up period. One mother (case 3) had a documented history of noncompliance with substance abuse and died as a result of liver failure from chronic rejection 67 months postdelivery and 101 months post-LTx. Another mother (case 12) was also noncompliant and died of liver failure from recurrent hepatitis B virus infection and chronic rejection 40 months after delivery and 84 months post-LTx. A third mother (case 7) underwent retransplantation 30 months postdelivery for de novo hepatitis C virus infection. Postoperatively, she sustained ischemic brain injury from respiratory failure and died 34 months postdelivery.

Liver Allograft. All mothers maintained liver allograft function during the pregnancy except case 32 (described previously), who experienced ischemic graft injury during labor. After delivery, one mother (case 11) lost the liver allograft from recurrent autoimmune hepatitis and chronic rejection. After two successful pregnancies, she underwent combined liver and kidney transplantation 46 and 19 months after delivery after the first and second babies, respectively. She subsequently delivered for the third time 69 months after kidney and liver retransplantation. The rest of the surviving mothers have kept their original graft from the time of pregnancy.

Newborn Babies. Twenty-seven babies (55%) were delivered vaginally, and 22 babies (46.9%) were delivered by caesarean section. The reasons for caesarean section are given in Table 1.

Of 49 live babies, two were premature and died soon after delivery (cases 5 and 10a); both mothers conceived soon after transplantation and are described in our previous report. Of the remaining 47 live babies, one baby (case 35) was born to a mother who underwent transplantation for Alagille syndrome and died 4 months later from multiple congenital birth defects of cardiopulmonary and esophageal origin. The mother subsequently remarried and has two viable babies (cases 35b and 35c) from the second marriage. The remaining 46 babies (25 boys and 21 girls) were alive and well at the last follow-up.

Gestational Period. The mean gestational period for the viable babies was 36.4±3.2 weeks (excluding the two premature babies; range 28–40, median 37 weeks).

Thirty-two babies (68%) had gestational periods of 36 weeks or more, 12 babies (26%) had gestational periods ranging from 32 to 36 weeks, and the remaining three babies (6%) had gestational periods of less than 32 weeks.

Birth Weight

The mean birth weight was 2,697±775 g (median 2,652; range 924–2,346 g). Thirty-eight babies (78%) weighed more than 2,000 g, excluding two premature babies.

Birth Weight Percentile for Gestational Period. The mean birth weight percentile was 54±27 (range <10–>90; median=50). Four babies (8.5%) had a birth weight percentile of less than 25, 15 babies (31.9%) had a birth weight percentile of 25 to 50, and the remaining 28 babies (59.6%) had a birth weight percentile of 50 or greater.

Congenital Anomaly

There was a multiple congenital defect in case 35a consisting of a tracheoesophageal fistula and valvular heart disease. There was a nonfunctional unilateral cystic kidney in case 14a. The baby also had an accessory nipple on the right side. The mother had a history of a similar abnormality in two sons with one extra nipple and one son with two extra nipples before LTx. She did not inform us initially, because she felt it was a familial condition. No other congenital anomaly was detected.

Renal Function

Overall, renal function before conception, during the first, second, and third trimesters, and after delivery remained stable. There was a slight improvement in mean serum creatinine during the pregnancy, but this returned to baseline after delivery. The details of mean blood urea nitrogen and serum creatinine are given in Table 2. During the follow-up period, one patient (case 11) underwent kidney transplantation (with retransplantation of liver described earlier in the present report) 19 months after the second delivery. Also, one patient (case 30) developed end-stage renal failure 28 months postdelivery and is currently on hemodialysis. She had a longstanding history of diabetes and hypertension. One patient (case 36) passed kidney stones during the pregnancy.

Liver Function

Twelve pregnancies (24.5%) were associated with an increase in liver enzymes without jaundice (six during pregnancy and six in the postpartum period). These were usually treated with an augmentation of baseline immunosuppression or a steroid bolus or both. None of the grafts were lost for immunologic reasons.

Hypertension and Toxemia of Pregnancy

Four mothers (cases 8, 10, 22, and 30) were hypertensive before pregnancy, which required treatment. Calcium channel blocker has been the antihypertensive agent of choice at our center, and usually single agent was adequate. They remained stable during the pregnancy, except in case 10a in which emergency cesarean section was required. Their gestation periods were 35, 32, 38, and 38 weeks with birth weights of 2,594, 1,565, 2,430, and 2,585 g and birth weight percentiles for gestational periods of 75, 50, 25, and 25, respectively.

Insulin-Dependent Diabetes Mellitus

Three mothers (cases 4, 29, and 30) were receiving insulin before and during the viable pregnancy. The mean gestational periods in these three mothers were 33, 35.5, and 38 weeks with birth weight percentiles of 40, 80, and 20, respectively.

TABLE 2. Liver and renal function with tacrolimus dose and concentration

Before pregnancy			First trimester			Second trimester			Third trimester			After delivery		
Liver function (mean values)														
Bilirubin	AST	ALT	Bilirubin	AST	ALT	Bilirubin	AST	ALT	Bilirubin	AST	ALT	Bilirubin	AST	ALT
0.6	35.3	38.0	0.6	31.5	32.0	0.6	37.0	38.7	0.5	36.7	31.2	0.7	48.7	41.6
0.4	21.1	25.1	0.4	19.6	23.5	0.4	40.3	33.6	0.4	47.0	25.7	0.5	70.6	53.3
0.6	27.5	32.0	0.5	26.5	28.0	0.5	27.0	24.0	0.4	27.0	23.5	0.7	28.0	25.0
Renal function (mean value)														
Creatinine		BUN	Creatinine		BUN	Creatinine		BUN	Creatinine		BUN	Creatinine		BUN
1.2		20.3	1.0		17.0	1.0		15.0	1.1		14.2	1.2		18.8
0.5		7.5	0.4		6.6	0.4		6.4	0.4		8.1	0.5		10.2
1.1		18.5	0.9		17.0	0.9		14.0	0.9		13.0	1.1		15.0
Mean tacrolimus—dose mg/day and whole-blood trough concentration ng/mL														
Dose		Level	Dose		Level	Dose		Level	Dose		Level	Dose		Level
9.8		7.0	9.5		7.0	9.6		4.5	9.5		4.5	10.9		5.7

Bilirubin mg/dL (1 mg/dL=17 μmol/L, SI units), creatinine mg/dL (1 mg/dL=88.4 μmol/L-SI units).

BUN, blood urea nitrogen-mg/dL (1 mg/dL=0.357 μmol/L SI units); AST, aspartate amino transferase U/L; ALT, alanine amino transferase U/L.

Immunosuppression

All patients received tacrolimus during the entire pregnancy period. Seventeen of the 37 mothers initially received CsA but were converted to tacrolimus before pregnancy. The mean tacrolimus dose and tacrolimus trough concentration before, during, and after pregnancy are given in Table 2. Three patients received Aza (cases 6, 11, 11c, and 36). In one mother (case 6), Aza was discontinued during the first trimester; the other two mothers continued to take Aza during the pregnancy (75 and 50 mg/day), respectively.

Prednisone

Twelve mothers (27%) received prednisone (5–10 mg/day) before and at the time of conception. In two of them, the prednisone was discontinued during the pregnancy without any ill effects.

Fludrocortisone

Nine of the 37 mothers (25%) received fludrocortisone (0.1 mg/day) to control hyperkalemia.

DISCUSSION

Tacrolimus has proven to be a potent immunosuppressive agent (*7–11*). It was first used in clinical trials 13 years ago at our center, and many other centers have confirmed our initial findings of safety and efficacy of the drug in clinical LTx (*12*). Its safety in pregnancy has been similarly described by us (*5*) and others (*13–16*). It is important to note that this is a case series with only 39 mothers and 49 babies, and that it is premature to draw a firm conclusion.

In our previous report, we showed that the drug is transmitted transplacentally and also is excreted in the breast milk (*5*); we therefore advise mothers not to breast-feed their babies. We also reported transient hyperkalemia and slight impaired renal function in the babies; this is still not a major problem. In addition, congenital anomalies are rare. One patient (case 9) with a unilateral renal cyst with an accessory nipple was probably familial. In patients with Alagille syndrome, congenital multiple defects are well documented. Although LTx offers the phenotypic correction of liver function in Alagille syndrome, the genetic defect continues to persist with the risk of transmission of the defective genome to the offspring. One mother, who had lost her first baby as the result of multiple esophageal and cardiovascular pulmonary abnormalities, delivered two viable and healthy babies with a different male partner after her second marriage. Both babies were tested by genetic counseling and were healthy, indicating that the previous anomalies, in all probability, were not related to tacrolimus. Two premature babies conceived soon after LTx died. The general recommendation for women wanting to conceive post-LTx is to wait 1 to 2 years until overall immunosuppression is lower and graft function is stable.

The cesarean section rate has remained high for a variety of reasons. As is the case with CsA, preterm delivery remains a common occurrence without any long-term consequences.(*1–3*, *14*, *17–19*). No risk factors in particular were identified in the present series. The rate of preeclampsia, deterioration in renal function, development of hypertension, and rate of rejection are also reported in kidney transplantation with CsA (*20*, *21*). Preterm births continue to be a factor reported in all of organ transplantation without any long-term consequences. The median birth weight percentile is 50, although 10% of babies still have a birth weight percentile less than 25, and 32% of babies are born before 36 weeks of the gestational period. Graft loss and mothers' deaths are consistent with the rest of the LTx population with a 3% to 4% loss beyond 2-year survival (*12*). One death as the result of clotting of the infra-renal aortic graft by external compression from the gravid uterus has not been reported and should be kept in mind by both transplant surgeons and obstetricians. Fortunately, renal function and liver function is generally well preserved in this series, compared with other reports of solid-organ transplantation with CsA (*22–24*). All pregnancies in mothers post-LTx should be considered high-risk and followed carefully by transplant clinicians and obstetricians.

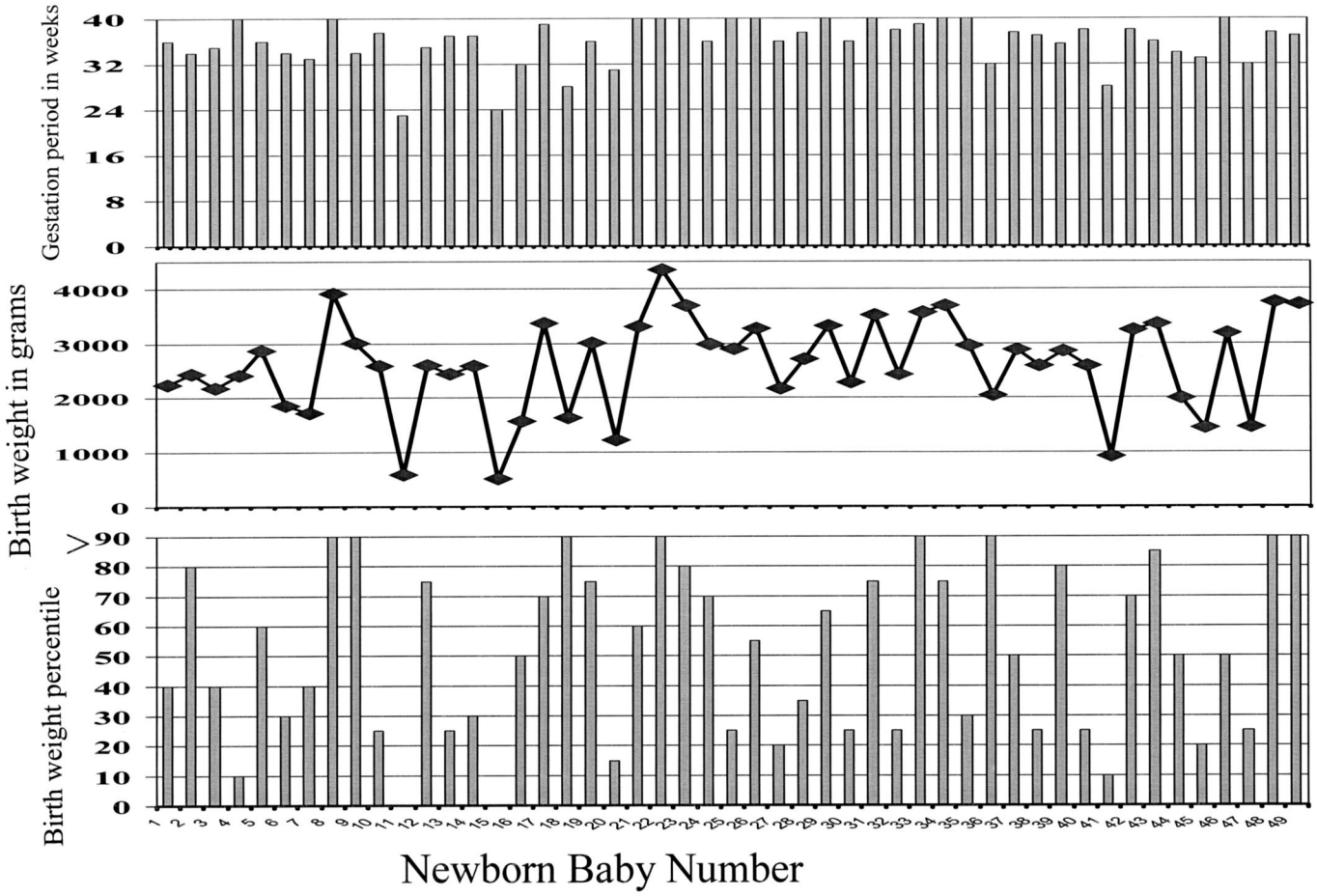

FIGURE 1. Gestation period in weeks for each pregnancy (*top*); birth weight for each newborn baby (*middle*); birth weight percentile based on gestation period for each newborn baby (*bottom*).

CONCLUSION

Preterm delivery, low birth weight, and the high rate of cesarean section with relatively lower rates of toxemia of pregnancy reconfirm our initial observation of the safety of tacrolimus use during pregnancy post-LTx. Late incidence of graft loss and death are comparable to that in other transplant patients. Patients with infra-aortic grafts for hepatic arterial flow may need to be monitored with color Doppler ultrasonography during labor.

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EFFECTS OF MIDDLE HEPATIC VEIN RECONSTRUCTION ON RIGHT LIVER GRAFT REGENERATION

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Background. **A right liver graft without the middle hepatic vein (MHV) trunk is now commonly used in living-donor liver transplantation for adult patients. The significance of MHV reconstruction on regeneration or functional recovery of right liver grafts after living-donor liver transplantation, however, remains unclear.**

Methods. **From 2000 to 2002 at the University of Tokyo Hospital in Tokyo, Japan, 56 adult patients received a right liver graft. The patients were divided into three groups by graft type: right liver graft without MHV trunk or MHV reconstruction (n=17); right liver graft without MHV trunk, but with MHV reconstruction (n=27); and extended right liver graft (n=12). Regeneration rate and postoperative liver function were compared among groups. Predictive factors associated with the graft regeneration were identified among clinical variables, including the graft type.**

Results. **The regeneration rate of the right paramedian sector and the whole graft was lowest in the right liver grafts without the MHV trunk or MHV reconstruction. The regeneration rate of the lateral sector was highest in this type of graft, but the difference was not statistically significant. The factors that significantly correlated with the regeneration rate were preoperative graft volume and graft type. There was no significant difference among groups in any of the liver function parameters.**

Conclusions. **In the present series, satisfactory outcome was independent of the type of graft used, which indicates that MHV reconstruction should not be omitted routinely but should be performed in selected patients.**

Living-donor liver transplantation (LDLT) is now widely performed to compensate for the critical cadaveric organ shortage for adult patients (*1*). An extended right liver graft (*2*), which includes the trunk of the middle hepatic vein (MHV), was devised to alleviate the problem of graft size disparity. This type of graft, however, increases the extent of the donor operation and is therefore an important ethical issue in LDLT (*3*).

A right liver graft without the MHV trunk is now commonly used. The graft includes the MHV and only its distal parts. Hepatic venous outflow of the right paramedian sector drains mainly into the MHV (*4*). The tributaries of the MHV consist of V8 and V5, which drains segments VIII and V, respectively, according to Couinaud's nomenclature for liver segmentation. Without caval anastomosis for drainage of V5 or V8, this type of graft can cause severe congestion of the right paramedian sector. Such congestion can lead to severe graft dysfunction and atrophy of the right paramedian sector (*5*).

MHV drainage into the recipient's venous system can be reconstructed using vein grafts (*6*), providing a functioning liver mass comparable to an extended right liver graft (*7*). Lee and colleagues (*5*) emphasized the necessity of aggressive reconstruction of the MHV under any circumstances. In contrast, most of the initial cases (*8–10*) seemed to achieve successful results without MHV reconstruction. Therefore it remains unknown whether all right liver grafts without the MHV trunk require MHV drainage.

Right liver graft for the patients was selected from the following three types: right liver graft without MHV trunk or

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