

Pregnancy Outcomes of Liver Transplant Recipients: A Systematic Review and Meta-Analysis

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Approximately 14,000 women of reproductive age are currently living in the United States after liver transplantation (LT), and another 500 undergo LT each year. Although LT improves reproductive function in women with advanced liver disease, the associated pregnancy outcomes and maternal-fetal risks have not been quantified in a broad manner. To obtain more generalizable inferences, we performed a systematic review and meta-analysis of articles that were published between 2000 and 2011 and reported pregnancy-related outcomes for LT recipients. Eight of 578 unique studies met the inclusion criteria, and these studies represented 450 pregnancies in 306 LT recipients. The post-LT live birth rate [76.9%, 95% confidence interval (CI) = 72.7%-80.7%] was higher than the live birth rate for the US general population (66.7%) but was similar to the post-kidney transplantation (KT) live birth rate (73.5%). The post-LT miscarriage rate (15.6%, 95% CI = 12.3%-19.2%) was lower than the miscarriage rate for the general population (17.1%) but was similar to the post-KT miscarriage rate (14.0%). The rates of pre-eclampsia (21.9%, 95% CI = 17.7%-26.4%), cesarean section delivery (44.6%, 95% CI = 39.2%-50.1%), and preterm delivery (39.4%, 95% CI = 33.1%-46.0%) were higher than the rates for the US general population (3.8%, 31.9%, and 12.5%, respectively) but lower than the post-KT rates (27.0%, 56.9%, and 45.6%, respectively). Both the mean gestational age and the mean birth weight were significantly greater ($P < 0.001$) for LT recipients versus KT recipients (36.5 versus 35.6 weeks and 2866 versus 2420 g). Although pregnancy after LT is feasible, the complication rates are relatively high and should be considered during patient counseling and clinical decision making. More case and center reports are necessary so that information on post-LT pregnancy outcomes and complications can be gathered to improve the clinical management of pregnant LT recipients. Continued reporting to active registries is highly encouraged at the center level. *Liver Transpl* 18:621-629, 2012. © 2012 AASLD.

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See Editorial on Page 619

Women with advanced liver disease have compromised reproductive function, with menstrual irregularities, amenorrhea, and infertility affecting nearly half of patients.¹⁻⁴ Successful liver transplantation (LT), however, can restore menstrual function in 97% of female

patients and restore childbearing potential.^{1,5,6} Currently, women constitute one-third of all LT recipients, and approximately one-third of female LT recipients are of reproductive age (18-49 years).⁷ This translates into approximately 14,000 women of reproductive age currently living after LT in the United States and another 500 women who undergo LT annually.⁸ Another 15% of female LT recipients are pediatric patients who

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Abbreviations: CI, confidence interval; KT, kidney transplantation; LT, liver transplantation; NA, not available; NS, not significant.

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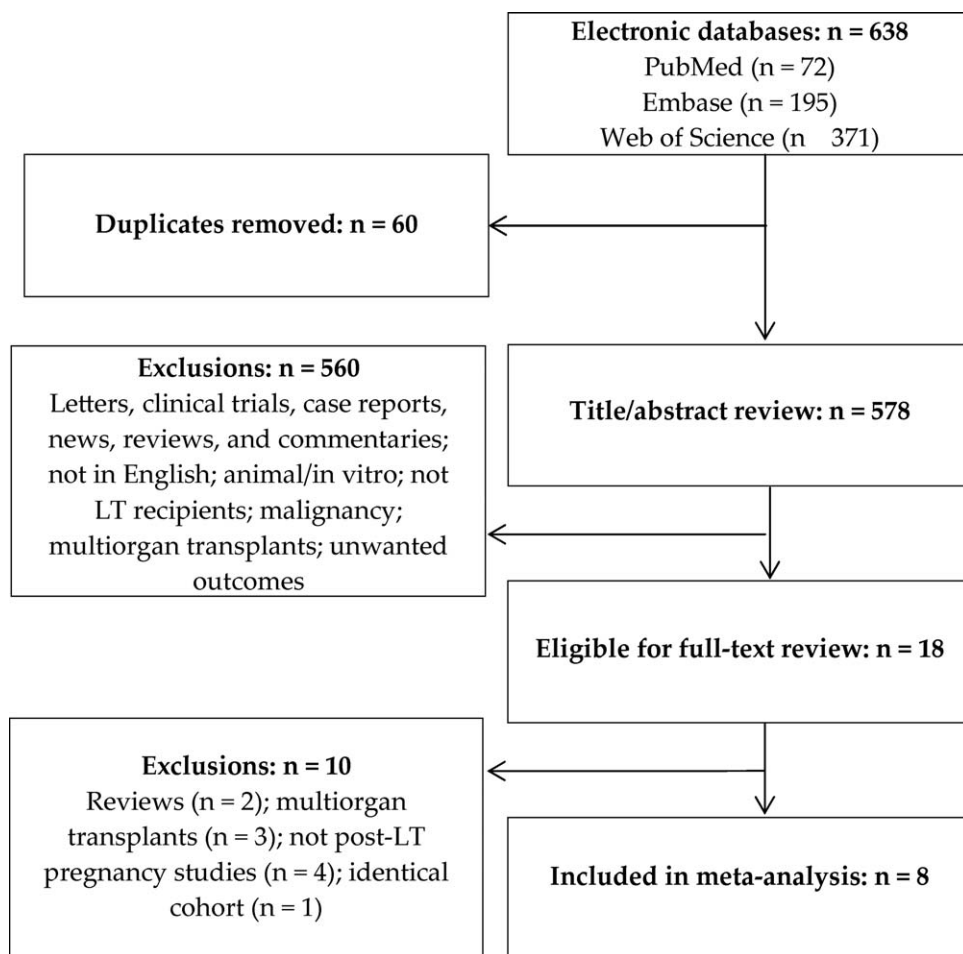


Figure 1. Study selection.

have a >70% chance of reaching reproductive age.^{9,10} Accordingly, preconception planning is a pertinent aspect of the LT counseling process for female candidates.

Immunosuppression, abdominal surgery, advanced maternal age, and comorbidities are all factors that may place abdominal transplant recipients at risk during pregnancy. In a recent systematic review and meta-analysis of pregnancy-related outcomes for recipients of kidney transplantation (KT),¹¹ we found pregnancies to be viable (live birth rate = 73.5%), but there were high rates of obstetric complications (hypertension, 54.2%; pre-eclampsia, 27.0%; and gestational diabetes, 8.0%) and high-risk delivery outcomes (cesarean section, 56.9%; preterm birth, 45.6%; and low birth weight, 2420 g) in comparison with the US general population. This motivated a similar investigation of post-LT pregnancies; in these pregnancies, the maternal-fetal risks are potentially higher and yet remain to be quantified in a generalizable manner.

Other than the National Transplantation Pregnancy Registry, worldwide efforts to collect data for post-LT pregnancy outcomes are limited. Although there are some published case and center reports, they have not been examined as a whole. Furthermore, there are still no robust, generalizable guidelines for managing and caring for post-LT pregnancies.³ Finally,

although it is likely that transplant recipients in general are prone to pregnancy complications, there has not been a systematic comparison of pregnancy-related outcomes by transplanted organs. As such, the goals of this study were (1) to systematically identify all studies of pregnancy-related outcomes for LT recipients and estimate the rates of pregnancy events, obstetric complications, and delivery outcomes and (2) to compare these rates to those of the general population and post-KT estimates.

PATIENTS AND METHODS

Search Strategy

A comprehensive literature search of PubMed/MEDLINE, Embase, and Web of Science entries between January 1, 2000 and January 1, 2011 was conducted (Fig. 1). The methodology was similar to that used in our recent study of post-KT pregnancies.¹¹ Studies in English that reported pregnancy outcomes, obstetric complications, and delivery outcomes for LT recipients were eligible. All letters, clinical trials, case reports, news, reviews, and commentaries were excluded, and so were studies not in English, animal/in vitro studies, and studies with non-LT or multiorgan transplant recipients. We consulted all citations

TABLE 1. Studies of Pregnancy-Related Outcomes for LT Recipients Included in the Meta-Analysis

Study	Years	Country	Recipients (n)	Pregnancies (n)	Mean Maternal Age (Years)	Mean Interval From Transplantation to Pregnancy (Years)
Coscia et al. ²⁶ (2009)	1991-2011	United States	151	239*	NS	4.3
Carr et al. ²⁷ (2000)	1991-1999	United States	5	6	25.8	1.38
Christopher et al. ³ (2006)	1988-2004	United Kingdom	45	71	29	3.33
Jabiry-Zieniewicz et al. ²⁸ (2007)	2001-2006	Poland	17	21	27.9	4.3
Jain et al. ²⁹ (2003)	NS	United States	37	49	29.1	5.85
Dei Malatesta et al. ³⁰ (2006)	NS	Italy	6	8	29	3.8
Nagy et al. ⁹ (2003)	1992-2002	United States	29	38	27.9	3.3
Sibanda et al. ³¹ (2007)	1994-2001	United Kingdom	16	18	NS	NS

*Coscia et al. report maternal factors for 240 recipients and birth outcomes for 238 recipients, so we have used the number 239 for the purposes of summary statistics.

of eligible articles and relevant review articles for supplementary references; however, none were found that were not already identified in the initial search. All abstracts of eligible studies were screened independently by 2 reviewers. If a study's eligibility was indeterminable from the abstract, it was included in the full-text screen. The same 2 reviewers then independently screened the articles at the full-text level. All disagreements were adjudicated by the principal investigator.

Data Extraction

Data were abstracted by one independent reviewer and then were checked for accuracy by a second reviewer. The following data were extracted from each article: the study design (country, years of data collection, and use or nonuse of a control group), maternal demographics (number of LT recipients, number of pregnancies, mean age at pregnancy, and mean interval between LT and pregnancy), pregnancy outcomes (number of live births, miscarriages, abortions, stillbirths, and ectopic pregnancies), obstetric complications (number of women with hypertension, pre-eclampsia, and gestational diabetes), and delivery outcomes (number of cesarean sections, number of preterm deliveries, mean gestational age, and mean birth weight). Other extracted data included the presence of birth defects, maternal comorbidities, the presence of maternal renal insufficiency, the type of immunosuppressive regimen, acute rejection episodes during pregnancy, and postpartum graft loss.

Pooled Estimates

Pooled estimates and 95% confidence intervals (CIs) were calculated with a weighted Graybill-Deal estimator¹² for all continuous outcomes (gestational age and birth weight). For binary outcomes, pooled incidence estimates and 95% exact binomial CIs were calcu-

lated. With a 2-sample test of proportions,¹³ the pooled incidence for each analysis was compared to the most recent and updated incidence for the US general population from the 2005 and 2006 National Vital Statistics Reports.¹⁴⁻¹⁶ All analyses were conducted with Stata 11.1/MP (Stata, College Station, TX). All hypothesis tests were 2-sided, and statistical significance was defined as a *P* value less than 0.05.

RESULTS

Systematic Review

Among the 638 citations that were initially retrieved from the 3 electronic database searches, 578 were found to be unique studies that qualified for abstract screening. After the screening, 18 full-text articles were reviewed, of which 10 were excluded: 1 article that specifically studied the teratogenic effects of mycophenolate mofetil in 3 LT recipients and the effects of sirolimus in 2 LT recipients,¹⁷ 2 review articles,^{18,19} 3 studies of multiorgan transplant recipients,²⁰⁻²² 4 studies that did not involve post-LT pregnancy outcomes,^{2,23-25} and 1 study of a duplicate/identical cohort.¹ Ultimately, 8 studies were selected for inclusion (Fig. 1): 4 from Europe and 4 from North America^{3,9,26-31} (Table 1).

Pregnancy Outcomes

Four hundred fifty pregnancies in 306 LT recipients resulted in 346 live births (76.9%), 70 miscarriages (15.6%), 28 abortions (6.2%), 4 stillbirths (0.9%), and 2 ectopic pregnancies (0.4%; Table 2). The live birth rate was higher for LT recipients versus the US general population (76.9% versus 66.7%), and the rates were similar for Europe and North America (Fig. 2). The live birth rate was slightly higher for LT recipients versus KT recipients (76.9% versus 73.5%), but the difference was not statistically significant (*P* = 0.08).

TABLE 2. Maternal Demographics, Pregnancy Outcomes, Obstetric Complications, and Delivery Outcomes Among LT and KT Recipients

Maternal Demographics	Mean for LT	United States, 2006*	KT Comparison	P Value
Age at pregnancy (years)	28.6	NA	29.0	NA
Transplant-pregnancy interval (years)	4.8	NA	3.2	NA
Pregnancy Outcomes	Pooled Incidence for LT	United States, 2005†	KT Comparison	P Value
Live birth (%)	76.9 (72.7-80.7)	66.7	73.5 (72.1-74.9)	0.08
Miscarriage (%)‡	15.6 (12.3-19.2)	17.1	14.0 (12.9-15.1)	0.31
Abortion (%)§	6.2 (4.2-8.9)	NA	9.5 (8.6-10.4)	0.02
Stillbirth (%)	0.9 (0.2-2.3)	NA	2.5 (2.0-3.0)	0.03
Ectopic pregnancy (%)	0.4 (0.1-1.6)	NA	0.6 (0.4-0.9)	0.60
Obstetric Complications	Pooled Incidence for LT	United States, 2006*	KT Comparison	P Value
Hypertension (%)	27.2 (22.9-31.9)	NA	54.2 (52.0-56.4)	<0.001
Pre-eclampsia (%)	21.9 (17.7-26.4)	3.8	27.0 (25.2-28.9)	0.04
Gestational diabetes (%)	5.1 (3.0-8.0)	3.9	8.0 (6.7-9.4)	0.07
Delivery Outcomes	Mean/Pooled Incidence for LT	United States, 2006*	KT Comparison	P Value
Cesarean section (%)	44.6 (39.2-50.1)	31.9	56.9 (54.9-58.9)	<0.001
Preterm birth (%)¶	39.4 (33.1-46.0)	12.5	45.6 (43.7-47.5)	0.07
Gestational age (weeks)	36.5 (36.1-37.0)	38.7	35.6 (35.5-35.7)	<0.001
Birth weight (g)	2866 (2733-2959)	3298	2420 (2395-2445)	<0.001

NOTE: For consistency across the extracted data, the number of pregnant LT recipients was used as the denominator for the analysis of maternal demographics. For the analysis of pregnancy outcomes, the number of pregnancies was used as the denominator. Finally, for the analyses of obstetric complications and delivery outcomes, the number of live births plus stillbirths was used as the denominator. The values within parentheses are 95% CIs.

*Comparison data were retrieved from the 2006 US National Vital Statistics Reports.¹⁶ All comparisons were statistically significant.

†Comparison data were retrieved from the 2005 US National Vital Statistics Reports.¹⁵ All comparisons were statistically significant.

‡Spontaneous abortions (including intrauterine fetal deaths and abnormal products of conception).

§Therapeutic abortions and abortions otherwise not specified.

||Chronic hypertension (before and during pregnancy).

¶Any delivery before 37 weeks of gestation.

The miscarriage rate was lower for LT recipients versus the US general population (15.6% versus 17.1%), and the rates were fairly identical for Europe (15.4%) and North America (15.6%; Fig. 3). The miscarriage rate was slightly higher for LT recipients versus KT recipients (15.6% versus 14.0%), but the difference was not statistically significant ($P = 0.31$). The abortion and stillbirth rates were significantly lower for LT recipients versus KT recipients (for abortions, 6.2% versus 9.5%, $P = 0.02$; for stillbirths, 0.9% versus 2.5%, $P = 0.03$). There was no significant difference between the rates of ectopic pregnancies (0.4% versus 0.6%, $P = 0.60$).

Obstetric Complications

Among nonterminated pregnancies (live births and stillbirths), the pre-eclampsia rate was higher for LT recipients versus the US general population (21.9% versus 3.8%), and the rate was slightly higher in North America versus Europe (25% versus 12%; Fig. 4); however, the rate was significantly lower for LT recipients versus KT recipients (21.9% versus 27.0%, $P = 0.04$). The rate of hypertension was significantly

lower for LT recipients versus KT recipients (27.2% versus 54.2%, $P < 0.001$); there was no significant difference in gestational diabetes between LT recipients and KT recipients (5.1% versus 8.0%, $P = 0.07$).

Delivery Outcomes

Among nonterminated pregnancies, the cesarean section rate was higher than the rate for the US general population (44.6% versus 31.9%), and the rate was slightly higher in Europe versus North America (50% versus 43%; Fig. 5); however, the rate was significantly lower for LT recipients versus KT recipients (44.6% versus 54.2%, $P < 0.001$). The preterm birth rate was also higher for LT recipients versus the US general population (39.4% versus 12.5%), and the rate was slightly higher in Europe versus North America (41% versus 36%). The difference in the preterm birth rates between LT recipients and KT recipients was not statistically significant ($P = 0.07$). However, the difference was possibly clinically significant, with LT recipients having a lower rate than KT recipients

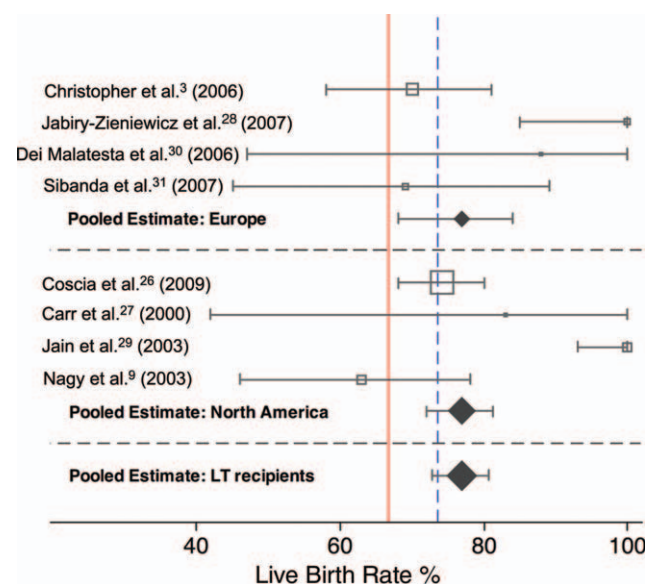


Figure 2. Live birth outcomes for LT recipients stratified by location: Europe (77%) and North America (77%). The solid red line represents the live birth rate for the US general population (66.7%). The dotted blue line represents the live birth rate for KT recipients (73.5%). The overall pooled incidence for LT recipients was 76.9%. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

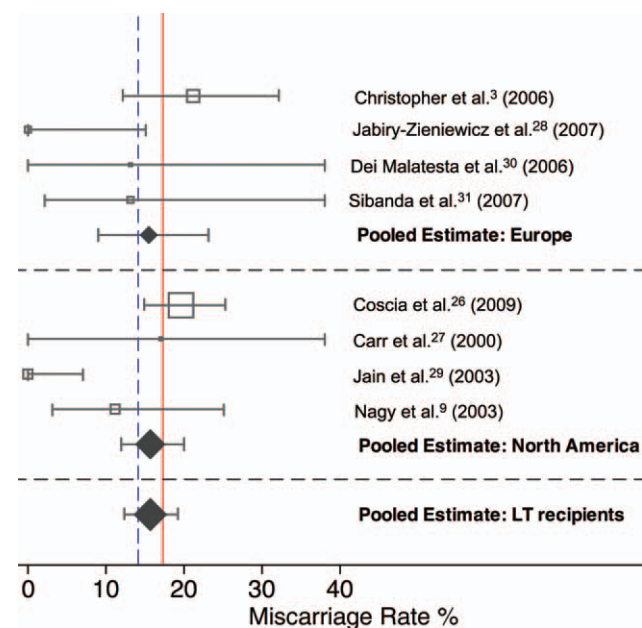


Figure 3. Miscarriage outcomes for LT recipients stratified by location: Europe (15.4%) and North America (15.6%). The solid red line represents the miscarriage rate for the US general population (17.1%). The dotted blue line represents the miscarriage rate for KT recipients (14.0%). The overall pooled incidence for LT recipients was 15.6%. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(39.4% versus 45.6%; Fig. 6). The mean gestational age for newborns of LT recipients was 36.5 weeks (US mean = 38.7 weeks), and the mean birth weight was 2866 g (US mean = 3298 g; Figs. 7 and 8). Both the

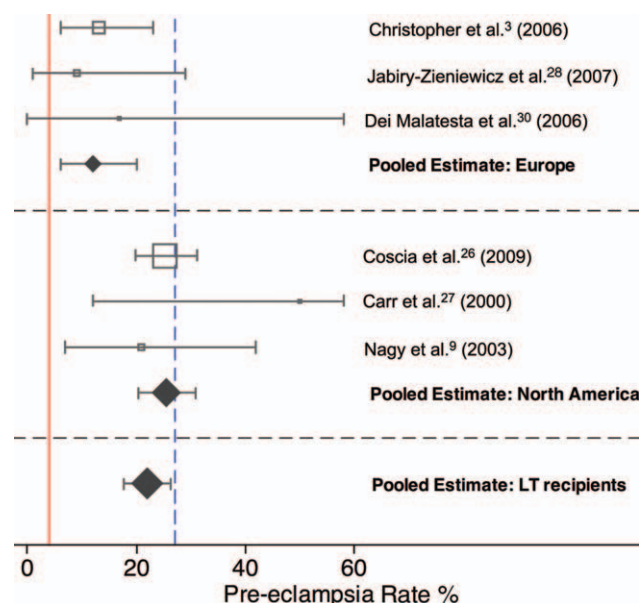


Figure 4. Pre-eclampsia outcomes for LT recipients stratified by location: Europe (12%) and North America (25%). The solid red line represents the pre-eclampsia rate for the US general population (3.8%). The dotted blue line represents the pre-eclampsia rate for KT recipients (27.0%). The overall pooled incidence for LT recipients was 21.9%. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

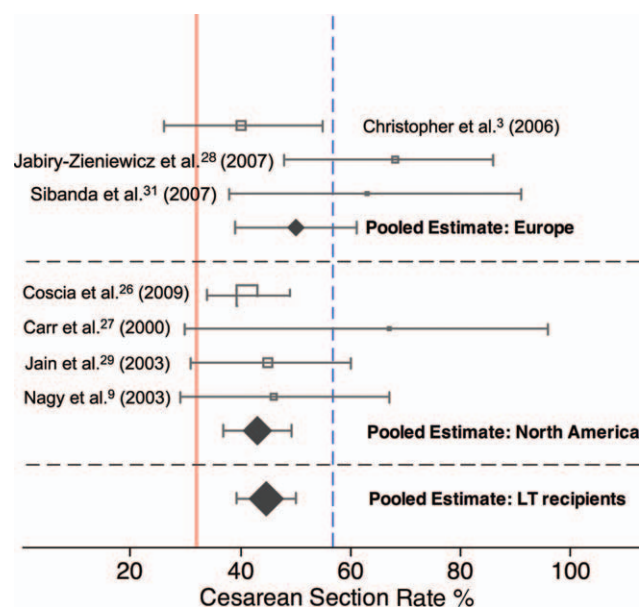


Figure 5. Cesarean section outcomes for LT recipients stratified by location: Europe (50%) and North America (43%). The solid red line represents the cesarean section rate for the US general population (31.9%). The dotted blue line represents the cesarean section rate for KT recipients (56.9%). The overall pooled incidence for LT recipients was 44.6%. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

mean gestational age and the mean birth weight were significantly higher for newborns of LT recipients versus newborns of KT recipients (36.5 versus 35.6 weeks and 2866 versus 2420 g, $P < 0.001$ for both).

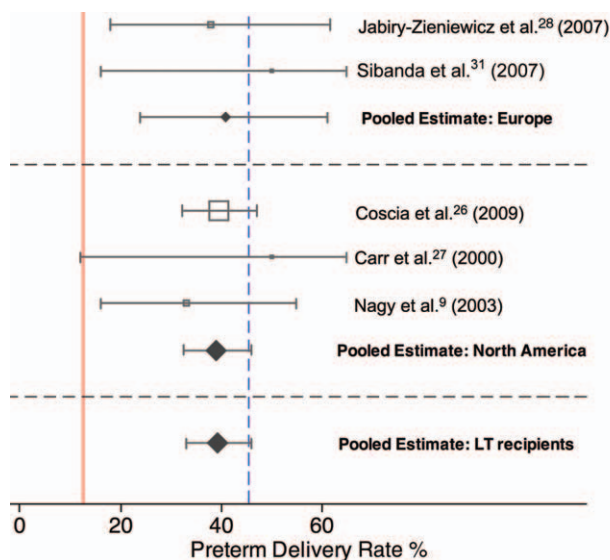


Figure 6. Preterm birth outcomes for LT recipients stratified by location: Europe (41%) and North America (36%). The solid red line represents the preterm birth rate for the US general population (12.5%). The dotted blue line represents the preterm birth rate for KT recipients (45.6%). The overall pooled incidence for LT recipients was 39.4%. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

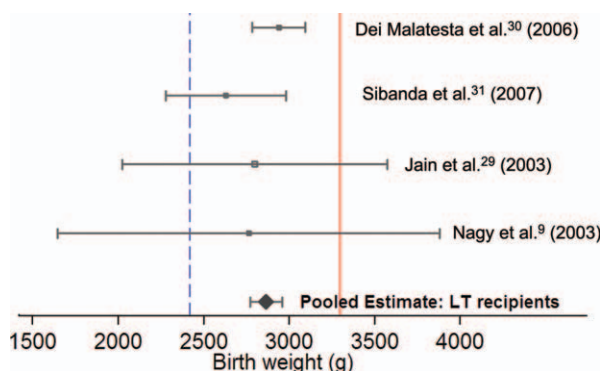


Figure 7. Mean birth weight for newborns of LT recipients. The solid red line represents the mean birth weight for the US general population (3298 g). The dotted blue line represents the mean birth weight for newborns of KT recipients (2420 g). The overall mean birth weight for newborns of LT recipients was 2866 g. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Birth Defects

Coscia et al.²⁶ reported 5 birth defects among 57 LT recipients who underwent transplantation before the age of 21 years (2 with multiple anomalies, 1 with a total anomalous pulmonary venous return, 1 with pyloric stenosis, and 1 with hypospadias). Jain et al.²⁹ reported 1 baby with a tracheoesophageal fistula and valvular heart disease and another baby with a non-functional unilateral cystic kidney and accessory nipple. Nagy et al.⁹ reported 3 mothers taking tacrolimus who had 2 infants with small membranous ventricular septal defects and 1 infant with bilateral hydroceles. One mother taking cyclosporine A had an infant with hypospadias.

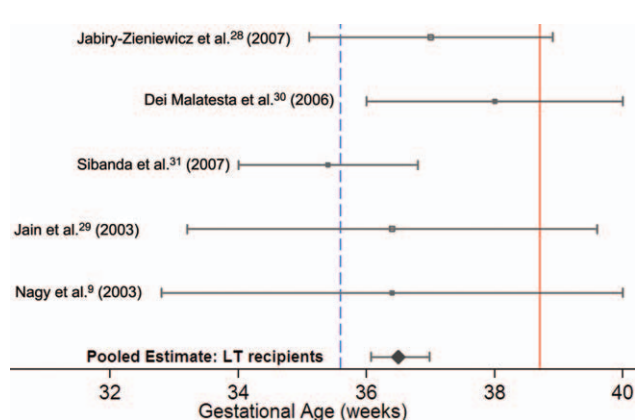


Figure 8. Mean gestational age for newborns of LT recipients. The solid red line represents the mean gestational age for the US general population (38.7 weeks). The dotted blue line represents the mean gestational age for newborns of KT recipients (35.6 weeks). The overall mean gestational age for newborns of LT recipients was 36.5 weeks. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Factors Associated With Adverse Pregnancy Outcomes: Interval from Transplantation to Pregnancy

Coscia et al.²⁶ reported better outcomes for mothers and newborns with a transplant-to-conception interval greater than 2 years. Christopher et al.³ reported increased rates of prematurity, low birth weight, and acute cellular rejection for pregnancies occurring within 1 year after LT. Dei Malatesta et al.³⁰ reported a statistically significant inverse relationship between the rate of complications (pre-eclampsia and/or hypertension) and the time interval between transplantation and conception ($P < 0.05$).

Factors Associated With Adverse Pregnancy Outcomes: Maternal Age

Little has been reported about associations between maternal age and adverse post-LT pregnancy outcomes. Coscia et al.²⁶ reported a pregnancy success rate of 75% for LT recipients who were less than 21 years old.

Factors Associated With Adverse Pregnancy Outcomes: Immunosuppression

Carr et al.²⁷ reported that 2 of 6 pregnancies were complicated by greater mean arterial pressures both before conception and during the first trimester; both subjects received cyclosporine for maintenance immunosuppression. These 2 patients experienced significant morbidity with renal failure after pregnancy and required maintenance dialysis. Christopher et al.³ stratified delivery outcomes and obstetric complications by the type of immunosuppression (cyclosporine A versus tacrolimus); however, there were no statistically significant differences. Data from the US National Transplantation Pregnancy Registry suggest

TABLE 3. Incidence of Pregnancy-Related Outcomes Stratified by the Study Mean Maternal Age and the Study Mean Interval Between Transplantation and Pregnancy

	Study Mean Maternal Age*	
	<29 Years (n = 3)	≥29 Years (n = 3)
Mean maternal age (years)	27.7 (27.5-27.9)	29.0 (29.0-29.1)
Pregnancy outcomes (%)		
Live birth	77.3 (73.1-81.5)	82.8 (80.3-85.3)
Miscarriage	7.6 (6.2-9.0)	12.5 (10.7-14.3)
Abortion	15.2 (11.9-18.4)	4.7 (4.0-5.4)
Stillbirth	0	0
Ectopic pregnancy	0	0
Obstetric complications (%)		
Hypertension	17.3 (11.6-23.0)	16.8 (16.0-17.7)
Pre-eclampsia	19.2 (15.7-22.7)	13.2 (12.9-13.4)
Gestational diabetes	NA	1.4 (1.4-1.4)
Delivery outcomes (%)		
Cesarean section	57.7 (54.6-60.8)	42.4 (41.9-42.9)
Preterm birth	37.3 (35.8-38.7)	NA

	Study Mean Interval Between Transplantation and Pregnancy*		
	<2 Years (n = 1)	3-4 Years (n = 3)	>4 Years (n = 3)
Mean maternal age (years)	25.8 (25.8-25.8)	28.6 (28.5-28.7)	28.7 (28.6-28.9)
Pregnancy outcomes (%)			
Live birth	83.3 (83.3-83.3)	69.2 (68.1-70.3)	80.4 (78.9-81.9)
Miscarriage	16.7 (16.7-16.7)	17.1 (16.2-18.0)	13.8 (12.8-14.9)
Abortion	0	13.7 (12.0-15.3)	4.2 (3.9-4.5)
Stillbirth	0	0	1.5 (1.4-1.7)
Ectopic pregnancy	0	0	0
Obstetric complications (%)			
Hypertension	66.7 (66.7-66.7)	20.2 (20.1-20.3)	28.2 (26.7-30.0)
Pre-eclampsia	50.0 (50.0-50.0)	15.0 (14.3-15.7)	21.8 (21.2-22.4)
Gestational diabetes	NA	1.4 (1.4-1.4)	4.7 (4.5-5.0)
Delivery outcomes (%)			
Cesarean section	66.7 (66.7-66.7)	41.9 (41.3-42.5)	40.7 (39.3-42.1)
Preterm birth	50.0 (50.0-50.0)	33.3 (33.3-33.3)	36.5 (36.4-36.6)

NOTE: The values within parentheses are 95% CIs.

*The n value is the number of studies within each category and refers to study-level data (not patient-level data).

NA = Parameter not reported in any studies in this category of mean maternal age or mean interval. If only some of the studies in this category reported this parameter, the number shown is based on only the studies that reported the parameter.

that in comparison with tacrolimus, cyclosporine A is associated with higher rates of pre-eclampsia and hypertension.²⁶ Jabiry-Zieniewicz et al.²⁸ reported that 12 of 17 patients were on tacrolimus, and Jain et al.²⁹ reported that all 37 patients were on tacrolimus, but neither performed any outcome comparisons stratified by the immunosuppressive regimen. Nagy et al.⁹ reported that renal dysfunction was more common in patients treated with cyclosporine A versus patients treated with tacrolimus.

Factors Associated With Adverse Pregnancy Outcomes: Renal Insufficiency

Carr et al.²⁷ reported that all 6 pregnancies in their study were complicated by renal insufficiency, and the worst obstetric outcomes took place specifically in the 2 subjects with a preconception serum creatinine

level > 1.5 mg/dL. Jain et al.²⁹ reported 1 patient who underwent KT 19 months after her second delivery and 1 patient who developed end-stage renal disease 28 months after delivery.

Acute Rejection and Graft Loss

Coscia et al.²⁶ reported rejection during pregnancy and graft loss within 2 years of delivery and stratified the results by the type of immunosuppression (data not available for all recipients): cyclosporine A or Sandimmune cyclosporine (8% and 10%, n = 96), Neoral cyclosporine (2% and 8%, n = 44), and tacrolimus (5% and 6%, n = 98). Among the 57 recipients who underwent transplantation before the age of 21 years, 5% had a rejection episode during pregnancy, and 10.5% lost their graft within 2 years of delivery. Christopher et al.³ reported 12 cases (17%, n = 71) of

biopsy-proven acute cellular rejection during pregnancy and 7 cases of retransplantation more than 1 year after birth, although the graft losses were not thought to be related to the pregnancies. Jain et al.²⁹ reported 1 patient who experienced ischemic graft injury during labor and 1 patient who lost her allograft because of recurrent autoimmune hepatitis and chronic rejection. In a literature review performed by Dei Malatesta et al.,³⁰ the authors report an acute rejection rate of 10%. Nagy et al.⁹ reported 4 cases of biopsy-proven graft rejection and a total rejection rate of 16.7% for 24 live births but no cases of graft loss. However, rates of rejection and graft loss attributable directly to the pregnancy remain unclear.

Age and Interval

The mean maternal age was 28.6 years for LT recipients, and the mean interval between transplantation and pregnancy was 4.8 years. There were 3 studies with a mean maternal age < 29 years and 3 studies with a mean maternal age ≥ 29 years; 2 studies did not report the mean maternal age (Table 1). Higher live birth rates were seen in studies of older women; we report this with the strong caveat that these are study-level inferences and not patient-level inferences (Table 3). There was only 1 study with a study mean interval less than 2 years, 3 studies with a study mean interval of 3 to 4 years, and 3 studies with a study mean interval greater than 4 years (Table 1). Outcomes have been stratified by the study mean interval, again with the caveat that these represent study-level inferences and not patient-level inferences (Table 3).

DISCUSSION

Representing 450 pregnancies in 306 LT recipients, this international, systematic review of 8 studies from 4 countries confirms that successful pregnancies are viable in LT recipients. The live birth rate for post-LT pregnancies exceeded the rate for the US general population (76.9% versus 66.7%), and the chance of miscarriage was lower for LT recipients versus the US general population (15.6% versus 17.1%). Although post-LT pregnancies were found to be viable, the risk of post-LT obstetrical complications was high: proportions higher than the US averages for nonterminated pregnancies were reported for pre-eclampsia (21.9%), cesarean section delivery (44.6%), and preterm births (39.4%). However, all these complication rates were lower than the rates for post-KT pregnancies (27.0% for pre-eclampsia, 56.9% for cesarean section delivery, and 45.6% for preterm births). This could suggest differences in post-transplant obstetrical care, a selection bias, or transplant organ-specific risks (rather than immunosuppression-specific risks). Overall, the aggregate LT recipient cohort delivered in the late preterm category (36.5 weeks, similar to KT recipients at 35.6 weeks) and at a normal birth weight (2866 g, unlike KT recipients at 2420 g). However, the mean gestational age and the mean birth weight were significantly greater in the LT recipient cohort versus the KT recipient cohort.

Although there is no established optimal interval between LT and pregnancy, reports from the National Transplantation Pregnancy Registry and the American Society of Transplantation recommend that LT recipients wait a minimum of 1 year before conception to stabilize graft function and the immunosuppression dosage.³²⁻³⁴ One study strongly advocates that LT recipients wait a minimum of 2 years to ensure best maternal and fetal outcomes.⁹ Although there was only 1 study with a mean transplant-pregnancy interval less than 2 years, the rates of hypertension, pre-eclampsia, cesarean sections, and preterm births for this interval were greater than those for any intervals longer than 3 years. Although these findings cannot be applied to the individual level and are limited to a few studies, they are indeed consistent with the current clinical recommendations. Whether or not the initial 2-year interval immediately after LT is in fact a period particularly sensitive to high-risk maternal-fetal complications merits further investigation, and so do the physiological and pharmacological reasons behind this sensitivity.

Several limitations, including patient overlap between the studies, differences in the classification criteria, and reporting biases in the studies, merit discussion. First, although multiple reports of the same LT recipient cohorts were purposefully excluded to prevent overlapping (ie, counting the same patient twice if she appeared in more than 1 study), it was not possible to take this precaution with the studies involving registry analyses. It is possible that some LT recipients and pregnancies may have been counted multiple times (particularly those from US^{9,26,27,29} and UK studies^{3,31}). Second, the diagnostic distinction between pre-eclampsia and hypertension may vary with the geographic location. It was unclear whether gestational hypertension was reported as a unique entity apart from hypertension, so all reports of hypertension were grouped together. It was also unclear whether abortions were performed for therapeutic or contraceptive reasons. Finally, the included registries were all voluntary, and this potentially introduced a selection or reporting bias into the studies that were analyzed.

In conclusion, live birth outcomes are possible among LT recipients, and this favorable trend is consistent on the international level. LT recipients have relatively healthy newborn outcomes and deliver term and normal birth weight babies. However, special attention should be given to obstetric complications such as hypertension, pre-eclampsia, and preterm delivery. The high incidence of these complications supports the high-risk classification of post-LT pregnancies. This systematic review confirms that it is necessary for a multidisciplinary team to be involved in the monitoring and counseling of LT recipients both before and during pregnancy. More case and center reports are necessary so that information can be gathered on post-LT pregnancy outcomes and complications to improve the clinical management of pregnant LT recipients. Continued reporting to active registries is highly encouraged at the center level.

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