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REVIEW ARTICLE

Pregnancy after liver transplantation: a case series and review of the literature

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ABSTRACT

Objective: To evaluate maternal and perinatal outcomes in pregnant women after liver transplantation with a case series and literature systematic review.

Methods: This was a single-center case-series study performed at University of Naples Federico II. All consecutive women with liver transplantation who reported pregnancy at our institution were included in a dedicated database. In addition, a systematic literature review was performed, including case series, population-based studies, and national registries, including maternal and perinatal outcomes of pregnant women with liver transplant. Studies with fewer than 10 cases and surveys were excluded. The primary outcome was perinatal death, defined as either stillbirth (defined as intrauterine fetal death after 20 weeks of gestation) or neonatal death (death of a live-born infant within the first 28 d of life).

Results: During the study period, two women who underwent liver transplantation had a pregnancy in our Institution. Both of them underwent liver transplantation for biliary atresia at 1 year of age. One of them received cyclosporin as immunosuppressive regime during pregnancy, while the other one received tacrolimus. Both of them had a pregnancy with no major complications and delivered by cesarean section at term a baby with normal weight. One of them developed thrombocytopenia. Seventeen articles were included in this systematic review. Preterm birth at less than 37 weeks of gestations occurred in 279 women (33.6%). One-hundred women (14.9%) experienced preeclampsia, and 206 women (49.2%) delivered by cesarean delivery. Graft rejection related to pregnancy occurred in 73 women (8.3%). 117 women (12.9%) experienced miscarriage, and 22 (2.3%) IUFD. Fifty-two women (9.52%) underwent elective I-TOP. 195 fetuses (33.4%) were LBW. Eight neonatal deaths were recorded (1.3%).

Conclusion: The maternal and perinatal outcome is usually favorable, but with an increased risk of preeclampsia, preterm birth, and perinatal morbidity and mortality. However, appropriate counseling about risks and complications is essential but women shouldn't be advised against pregnancy.

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Intensive care; liver; maternal mortality; neonatal; preeclampsia; transplantation; ultrasound

Introduction

Liver transplantation is a life-saving and successful therapeutic procedure in acute liver failure and end-stage liver disease [1,2]. Liver transplantation is increasing worldwide, and there is also a striking increase among women of reproductive age [3,4].

Liver transplantation should be considered in any patient with end-stage liver disease in whom the procedure would extend the life expectancy beyond what the natural history of the underlying disease would predict [5–56]. Patients should be selected if expectancy survival is 1 year or less in absence of transplantation or if the patient has an unacceptable quality of life due to liver disease [57].

Optimal patients' selection is essential due to the constant organs shortage. Priority on the waiting list is based on the Child-Pugh Turcotte classification and MELD (Model For End-Stage Liver Disease) score. However, the final decision for graft allocation is based on multiple parameters [57].

Reproductive function is often severely compromised in the setting of end-stage liver disease, characterized by menstrual irregularity, amenorrhea, and infertility in half of the women [7,58].

Successful liver transplantation is able to restore the menstrual cycle and function in 97% of female patients, meaning childbearing potential is also restored [59].

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In the USA alone, ~14,000 women of childbearing age are currently liver transplantation recipients, and another 500 women will undergo this procedure annually [60].

Since the first successful pregnancy following liver transplantation reported in 1978 by Walcott et al. [5], several studies have been published [6–21], including case report [5], case series [6–14], surveys [15,16], population-based studies [17], and registries [18–21], including the National Transplantation Pregnancy Registry from the USA [18–20], and the UK Transplant Pregnancy Registry [21]. The maternal and perinatal outcome is usually favorable, but with an increased risk of preeclampsia, preterm birth, and perinatal morbidity and mortality [22,23].

The aim of this study was to evaluate maternal and perinatal outcomes in pregnant women after liver transplantation with a case series and literature review.

Materials and methods

Study design, search strategy, and study selection

This was a single-center case-series study performed at the University of Naples Federico II (Naples, Italy). All consecutive women with liver transplantation who reported pregnancy at our institution between January 2010 and December 2018 were included in a dedicated database.

In addition, a systematic literature review was performed according to a protocol recommended for systematic review [24]. The review protocol was designed *a priori* defining methods for collecting, extracting and analyzing data. The research was conducted using Medline, Embase, Scopus, Web of Sciences, and ClinicalTrial.gov as electronic databases. The articles were identified with the use of a combination of the relevant heading term, keywords, and word variants for: "liver transplant," "liver transplantation" and "pregnancy," from the inception of each database to January 2019. A review of articles also included the abstracts of all references retrieved from the search.

Case series, population-based studies, and national registries, including maternal and perinatal outcomes of pregnant women with a liver transplant, were included in the systematic review. Studies with fewer than 10 cases were excluded to avoid publication bias. Case reports and surveys were excluded.

Primary and secondary outcomes

The primary outcome was preterm birth at less than 37 weeks of gestation. The secondary outcomes were maternal outcomes, including maternal death, cesarean delivery, preeclampsia, gestational diabetes mellitus (GMD), and graft rejection related to pregnancy (i.e. during pregnancy or in the postpartum period); and neonatal outcomes, including intrauterine growth restriction (IUGR) (i.e. ultrasound estimated fetal weight <10th percentile for gestational age), intrauterine fetal death (IUFD) (i.e. fetal death after 20 weeks of gestation), miscarriage (i.e. pregnancy loss before 20 weeks of gestations), elective termination of pregnancy (I-TOP), low birth weight (LBW) (i.e. neonatal birth weight at less than 2500 g), and neonatal deaths (i.e. death of a live-born infant within the first 28 d of life).

Data extraction and risk of bias assessment

For the systematic review, two authors (FZ, GS) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full-text copies of those papers were obtained and the same reviewers independently extracted relevant data regarding study characteristics and pregnancy outcomes. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author (VB).

Quality assessment of the studies included in the systematic review was performed using the Newcastle-Ottawa Scale (NOS) [25]. According to NOS, each study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure and the demonstration that outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of assessment of the outcome of interest, length, and adequacy of follow-up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability [25].

Statistical analysis

Data are shown as means, or as number (percentage). Univariate comparisons of dichotomous data were

Table 1. Characteristics of the cases from University of Naples Federico II.

	Case 1	Case 2
Age at transplant (year)	1	1
Indication for transplant	Biliary Atresia	Biliary Atresia
Age at conception (year)	31	21
Transplant-pregnancy interval (year)	30	20
Immunosuppressive regimen in pregnancy	Cyclosporin	Tacrolimus
Postpartum graft function	Optimal	Optimal
Graft rejection related to pregnancy	None	None
Previous pregnancy	None	None
IVF	None	None
Number of fetuses	Singleton pregnancy	Singleton pregnancy

IVF: *in vitro* fertilization.

Table 2. Outcomes of the cases from University of Naples Federico II.

	Case 1	Case 2
Stillbirth	None	None
Neonatal death	None	None
Miscarriage	None	None
I-TOP	None	None
PTB < 37 weeks	None	None
Mode of delivery	Planned cesarean delivery at 39 weeks	Planned cesarean delivery at 39 weeks
Reason for cesarean delivery	Maternal request	Breech presentation
IUGR	None	None
Preeclampsia	None	None
Diabetes mellitus	None	None
PPH	None	None
VTE	None	None
Thrombocytopenia	Yes, 80,000 PLT/mm^3	None
NICU	None	None
Birth weight	3050 g	3300 g
Congenital anomalies	None	None

I-TOP: induced termination of pregnancy; PTB: preterm birth; IUGR: intrauterine growth restriction; NICU: admission to neonatal intensive care unit; PPH: postpartum hemorrhage; VTE: venous thromboembolism.

performed with the use of the chi-square test with continuity correction. Comparisons between groups were performed with the use of the T-test to test group means by assuming equal within-group variances.

A p-value $<.05$ was considered to indicate statistical significance.

The systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [26], while the case series was reported following the STROBE guidelines [27].

Results

Case-series

During the study period, two women who underwent liver transplantation had a pregnancy. Table 1 shows the characteristics of the two women. Both of them underwent liver transplantation for biliary atresia at 1 year of age. One of them received cyclosporin as immunosuppressive regime during pregnancy, while the other one received tacrolimus. Both pregnancies were spontaneous singleton gestations.

Table 2 shows the outcomes of the included pregnancies. Both of them had a pregnancy with no major complications and delivered by planned cesarean section at term a baby with normal weight. One of them developed thrombocytopenia with 80,000/mm^3 platelets at the time of delivery.

Systematic review

Study selection and study characteristics

Figure 1 shows the flow diagram (PRISMA template) of information derived from reviewing of potentially relevant articles. Forty-six articles were identified as relevant [5–21,28–56]. Twenty-eight studies were excluded, of which, 24 were case reports or studies with fewer than 10 cases [5,6,28–44,46,50–53], 2 were surveys [15,16], 2 were duplicates [18,19] of the National Transplantation Pregnancy Registry (NTPR) [20], and one because it also included women with kidney transplant [47]. Therefore 17 articles were included in this systematic review [7–14,17,20,21,45,48,49,54–56].

Table 3 shows the quality assessment of the included studies according to NOS. Most of the

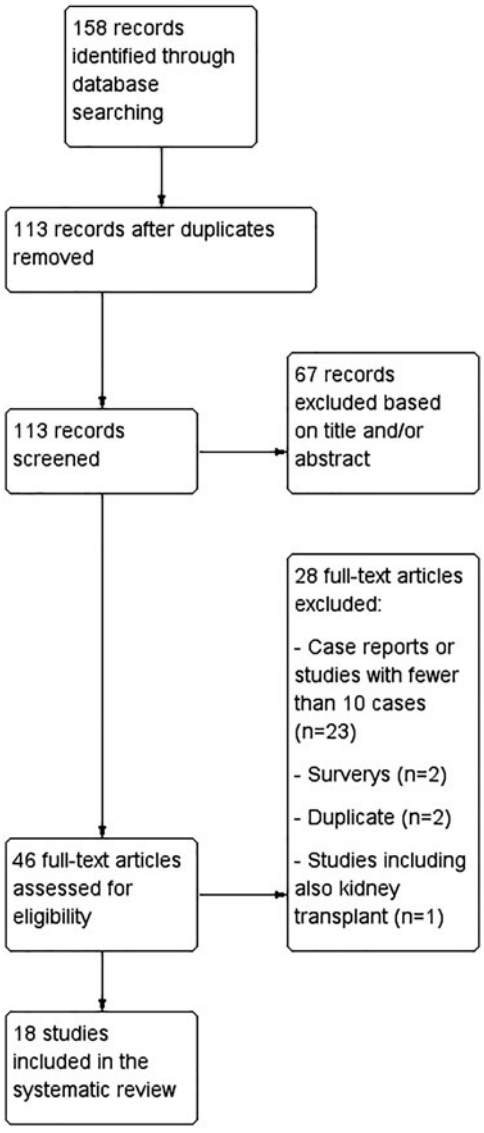

Figure 1. Flow diagram of studies identified in the systematic review. (PRISMA template [preferred reporting items for systematic reviews and meta-analyses]).

included studies were judged as low risk of bias in selection, comparability, and outcome.

Table 4 shows the characteristics of the included studies. Out of the 18 included studies, one was a population-based study [17], two were national registry [20,21], and the others were case series.

Synthesis of results

Tables 5 and 6 show maternal and neonatal outcomes. Preterm birth at less than 37 weeks of gestations occurred in 279 women (33.6%). One-hundred women (14.9%) experienced preeclampsia, and 206 women (49.2%) delivered by cesarean delivery. Graft rejection related to pregnancy occurred in 73 women (8.3%).

Table 3. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS).

	Selection	Comparability	Outcome
Scantlebury 1990 [8]	*	**	*
Ville 1993 [49]	*	***	**
Jain 1997 [10]	***	***	**
Patapis 1997 [11]	***	***	***
Wu 1998 [13]	**	**	**
Rayes 1998 [48]	*	*	***
Raakow 2001 [14]	***	***	***
Jain 2003 [9]	***	*	***
Nagy 2003 [12]	***	***	***
Christopher 2006 [7]	**	***	***
Coffin 2010 [17]	**	*	***
UK transplant registry 2007 [21]	***	***	***
NTPR 2010 [20]	***	***	***
Jabiry-Zieniewicz 2011 [45]	***	*	**
Westbrook 2015 [56]	***	***	***
Akarsu 2016 [54]	**	**	***
Baskiran 2017 [55]	***	***	***

Studies can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

117 women (12.9%) experienced miscarriage, and 22 (2.3%) IUFD. 52 women (9.52%) underwent elective I-TOP. 195 fetuses (33.4%) were LBW. Eight neonatal deaths were recorded (1.3%).

Comment

Main findings

Our case-series included two women who had a pregnancy after liver transplantation. Both of our patients received orthotopic liver transplantation at 1 year of age for congenital biliary atresia after having undergone a previous intervention of Kasai portoenterostomy. Biliary atresia, indeed, remains one of the most untreatable hepatic diseases of early infancy [61]. The transplant–pregnancy interval was 20 years for one patient and 30 years for the other patient. The immunosuppressive regimen was different, one was treated with cyclosporin the other with tacrolimus, no significative differences in fetal and maternal outcomes were reported according to different chronic immunosuppressive therapy. The systematic review included 18 studies for a total of 713 patients and 948 pregnancies. The overall pregnancy outcome was quite poor, with about 15% rate of preeclampsia, 34% of preterm birth, and 50% of cesarean delivery.

One prior review has been published on the topic in 2012 [62]. Parhar et al. [62] included studies with less than 10 cases and did not report all outcomes of interest. Moreover, they did not include studies published after 2011. The strengths of our study included a large number of included studies and included

Table 4. Literature review: summary table of study characteristics.

	Study design	Location	Sample size
Scantlebury 1990 [8]	Case-series	Pittsburgh, USA	17 women (19 pregnancies)
Ville 1993 [49]	Case-series	Clamart, France	19 women (19 pregnancies)
Jain 1997 [10]	Case-series	Pittsburgh, USA	21 women (21 pregnancies)
Patapis 1997 [11]	Case-series	Birmingham, UK	15 women (27 pregnancies)
Wu 1998 [13]	Case-series	Hanover, Germany	16 women (22 pregnancies)
Rayes 1998 [48]	Case-series	Berlin, Germany	16 women (19 pregnancies)
Raakow 2001 [14]	Case-series	Berlin, Germany	19 women (21 pregnancies)
Jain 2003 [9]	Case-series	Rochester, NY, USA	37 women (49 pregnancies)
Nagy 2003 [12]	Case-series	New York, USA	29 women (38 pregnancies)
Christopher 2006 [7]	Case-series	London, UK	45 women (71 pregnancies)
Coffin 2010 [17] MOLTO CONUSO	Population-based	Calgary, Canada	206 pregnancies
UK transplant registry 2007 [21]	National registry	London, UK	16 women (18 pregnancies)
NTPR 2010 [20]	NTPR registry	Philadelphia, PA, USA	125 women (215 pregnancies)
Jabiry-Zieniewicz 2011 [45]	Case-series	Warsaw, Poland	36 women (39 pregnancies)
Westbrook 2015 [56]	Case-series	London, UK	79 women (117 pregnancies)
Akarsu 2016 [54]	Case-series	Izmir, Turkey	15 women (21 pregnancies)
Baskiran 2017 [55]	Case-series	Malatya, Turkey	18 women (26 pregnancies)

NTPR: National Transplation Pregnancy Registry; IUFD: intrauterine fetal death.

Table 5. Literature review: summary table of maternal outcomes.

	Maternal death	Cesarean delivery	Preeclampsia	GDM	PTB	Graft rejection related to pregnancy
Scantlebury 1990 [8]	0/17	13/19 (68.4%)	6/19 (31.5%)	N/A	11/20 (55%)	1/17 (5.9%)
Ville 1993 [49]	0/19	5/10 (50%)	2/19 (10.6%)	1/19 (5.3%)	6/10(31.6%)	2/19(10.5%)
Jain 1997 [10]	0/21	12/27 (44.4%)	N/A	N/A	15/27 (55.5%)	N/A
Patapis 1997 [11]	0/15	N/A	5/29 (17.2%)	N/A	N/A	2/27(7.4%)
Wu 1998 [13]	0/16	7/23 (30.4%)	3/23 (13%)	N/A	3/23 (13%)	1/23(4.3%)
Rayes 1998 [48]	0/16	7/13 (54%)	5/16 (31.3%)	N/A	5/13 (38.6%)	0/16
Raakow 2001 [14]	0/19	10/21 (47.6%)	9/21 (42.8%)	N/A	4/21 (19.0%)	0/21
Jain 2003 [9]	1/37 (2.7%)	22/49 (46.9%)	1/49 (2.0%)	N/A	15/49 (30.6%)	1/49 (2.0%)
Nagy 2003 [12]	0/29	11/24 (45.8%)	5/24 LB (20.8%)	9/24 (37.5%)	7/24 (29.2%)	4/24 (16.7%)
Christopher 2006 [7]	0/45	28/71 (40%)	9/70(13%)	1/70 (1.4%)	24/51(47.0%)	14/70 (20.0%)
Coffin 2010 [17] MOLTO CONUSO	0/206	(37.7%)	34/206 (16.5%)	5/206 (2.4%)	56/206 (27.3%)	10/206 (4.9%)
UK transplant registry 2007 [21]	0/16	N/A	N/A	N/A	4/8 (50%)	N/A
NTPR 2010 [20]	N/A	N/A	N/A	N/A	80/217 (36.8%)	19/217 (8.8%)
Jabiry-Zieniewicz 2011 [45]	0/36	31/39 (79.5%)	3/39 (7.7%)	0/39	12/39(30.8%)	3/39 (7.7%)
Westbrook 2015 [56]	0/79	36/85 (42.3%	16/117(13.7%)	8/115 (7.0%)	26/83 (31.3%)	17/115 (14.8%)
Akarsu 2016 [54]	0/15	15/21 (71.4%)	0/22	0/22	5/21(23.8%)	0/15
Baskiran 2017 [55]	0/18	9/17 (53,0%)	2/18 (11.1%)	2/18 (11.1%)	6/17(35.3%)	1/18 (5.5%)
Total	1/604 (0.2%)	206/419 (49.2%)	100/672 (14.9%)	26/491 (5.3%)	279/829 (33.6%)	73/876 (8.3%)

NTPR: National Transplation Pregnancy Registry; N/A: data not available; GDM: gestational diabetes mellitus; PTB: preterm birth at less than 37 weeks.

Table 6. Literature review: summary table of neonatal outcomes.

	IUGR	IUFD	Miscarriage	I-TOP	Low Birth weight	Neonatal death
Scantlebury 1990 [8]	N/A	0/20	0/20	N/A	12/20 (60.0%)	0/20
Ville 1993 [49]		0/19	4/19 (21.1%)	3/19(15.8%)	1/10 (10%)	0/10
Jain 1997 [10]	N/A	0/27	0/27	N/A	15/27 (55.5%)	2/27 (7.4%)
Patapis 1997 [11]	N/A	0/27	5/27 (18.5%)	7/27(25.9%)	N/A	0/27
Wu 1998 [13]	N/A	0/23	0/23	N/A	7/23(30.4%)	0/23
Rayes 1998 [48]	N/A	0/19	4/19 (21.1%)	2/19 (10.5%)	4/13 (30.8%)	0/19
Raakow 2001 [14]	N/A	0/21	7/21(33.3%)	N/A	6/21 (28.6%)	1/21 (4.8%)
Jain 2003 [9]	N/A	0/49	0/49	N/A	21/49 (42.9%)	2/49 (4.08%)
Nagy 2003 [12]	4/24 (16.7%)	0/24	4/38 (10.5%)	10/38 (26.3%)	N/A	0/24
Christopher 2006 [7]	N/A	1/71 (1.4%)	13/71 (18.3%)	6/71 (8.5%)	15/51 (29.4%)	N/A
Coffin 2010 [17]	10/206 (4.8%)	3/206 (1.4%)	10/206 (4.9%)	N/A	N/A	N/A
UK transplant registry 2007 [21]	N/A	0/16	5/16 (31.3%)	N/A	N/A	N/A
NTPR 2010 [20]	N/A	4/217 (1.8%)	39/217 (18.0%)	12/217 (6.1%)	77/217 (35.5%)	2/217 (0.9%)
Jabiry-Zieniewicz 2011 [45]	N/A	0/40	0/40	0/40	8/40 (20.0%)	0/40
Westbrook 2015 [56]	N/A	0/115	20/115 (17.4%)	12/115 (10.4%)	24/83 (29.0%)	0/85
Akarsu 2016 [54]	N/A	0/22	0/22	N/A	4/21 (19.0%)	1/22 (4.6%)
Baskiran 2017 [55]	N/A	3/26 (11.5%)	6/26 (23.1%)	N/A	4/17 (23.3%)	0/26
Total	14/230 (6.1%)	22/942 (2.3%)	117/907 (12.9%)	52/546 (9.52%)	198/592 (33.4%)	8/594 (1.3%)

NTPR: National Transplation Pregnancy Registry; IUFD: intrauterine fetal death; IUGR: intrauterine growth restriction; I-TOP: induced termination of pregnancy.

Table 7. Summary of risks related to immunosuppression during pregnancy.

	Side effects	FDA rating
Calcineurin inhibitors*	Diabetes, hypertension, preeclampsia, renal dysfunction, neonatal hyperkalemia	C
Azathioprine	Fetal thrombocytopenia, anemia and leucopenia, neonatal sepsis, preterm birth, low birth weight	D
Corticosteroids	Hypertension, diabetes, fetal adrenal insufficiency	B
Mycophenylate mofetil	Early pregnancy loss, fetal malformation**	D

*Including cyclosporine and tacrolimus; **including cleft lip and palate, microtia, absence of auditory canals.

women. No prior reviews were as large and comprehensive. The case series was limited by the number of low numbers of included women.

Implications

After the first successful pregnancy in a liver transplant women in 1978, much evidence has accumulated on the course, outcome, and management strategies of pregnancy following liver transplantation. Generally, liver transplantation restores sexual function and fertility as early as a few months after transplant. Pregnancy outcomes are fair, with an increased rate of preterm birth and pregnancy-induced hypertension and preeclampsia. Immunosuppression therapy should be reviewed during pregnancy, and the risks and benefits of each medication discussed with the couple. Calcineurin inhibitors, steroids, and azathioprine are considered to be safe and appropriate choices (Table 7). Due to the theoretical risk of altered drug metabolism and general immunosuppressive state of pregnancy, graft function and immunosuppression should be closely monitored. Regarding the mode of delivery, although vaginal delivery is a very reasonable option, data from the literature shows that almost half of the women delivered by cesarean section.

Conclusions

The maternal and perinatal outcome is usually favorable, but with an increased risk of preeclampsia, preterm birth, and perinatal morbidity and mortality. However, appropriate counseling about risks and complications is essential but women shouldn't be advised against pregnancy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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