ASSISTED REPRODUCTIVE TECHNOLOGY USE AMONG FEMALE LIVER TRANSPLANT RECIPIENTS

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Background: Infertility is not uncommon among female liver transplant (LT) recipients. It is estimated that over 10% of LT recipients are currently of reproductive age or younger. With a growing number of transplant recipients considering pregnancy, the need for accurate counseling and available treatment options has become increasingly relevant.
Objective: The purpose of this study was to evaluate pregnancy and transplant outcomes among female LT recipients who conceived with and without assisted reproductive technologies (ART).
Materials and Methods: The data were collected by the Transplant Pregnancy Registry International (TPRI) through surveys and medical records. Categorical variables were compared by the Chi-squared test or Fisher's exact test and continuous variables were compared using Wilcoxon rank sum test. We followed recipients from the date of pregnancy-transplant (defined as the LT that was functioning at the time of the first assisted or unassisted pregnancy) until graft loss, mortality, or censorship on the last contact date. We used log-rank tests and parsimonious Cox regression model to compare risk of graft loss by pregnancy type adjusting for conception age, indication for transplant, and body mass index (BMI). All analyses were performed using Stata 17.0.
Result(s): Of 357 female LT recipients in the TPRI, 38 recipients reported using ART, including 17 recipients conceiving through ovulation induction medications alone, 4 with intrauterine insemination (IUI), and 17 with *in vitro* fertilization (IVF). There was a total of 48 pregnancies and 54 outcomes. Pregnancy outcomes were: 35 live births (65%), 15 spontaneous abortions, and 2 ectopic. Pregnancies were complicated by chronic hypertension (22%), preeclampsia (13%), gestational diabetes (17%), and cholestasis (11%). Among recipients using ART, data as median (IQR): maternal age at conception 32 years (30-37), gestational age 37 weeks (34-38), and birth weight 2863 g (1786-3169). Cesarean delivery rate was 37%. Among live births using ART, child follow-up was a median age of 4.9 years with 100% children reported as being healthy and developing well. Congenital defects were seen in 3 newborns, including renal agenesis, club foot, and septal defect. Maternal follow-up was a median of 6.4 years with 92% reporting adequate graft function. Two recipients using ART died, one due to primary sclerosing cholangitis 8 years post-transplant and one due to unknown graft failure 24 years post-transplant. Overall, cumulative incidence of graft failure/mortality was 7.7% at 10 years (7.8% among those with only unassisted pregnancies vs 6.6% among those with at least 1 ART pregnancy, log-rank p-value=0.14). In a parsimonious model, ever having had an assisted pregnancy with a functioning LT was associated with a lower but not statistically significantly different risk of graft failure/mortality when compared to only unassisted pregnancies (aHR 0.75 [95% CI 0.23-2.48], p=0.64).
Conclusion(s): Successful pregnancies via ART were reported among female LT recipients with 65% of pregnancies resulting in livebirth. There was no significant difference of graft failure among female LT recipients conceiving via ART versus without. Female liver transplant recipients who pursue fertility assistance should not be discouraged from utilizing ART.
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References:
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Table 1A: Characteristics of LT Recipients Achieving Pregnancy with and without ART.

Characteristics	Unassisted n = 319	Assisted n = 38	p-value
Conception age, years, median (IQR)	28 (24, 32)	32 (30, 37)	**<0.001**
White Race, n (%)	213 (67)	30 (79)	0.13
BMI, median (IQR)	23 (21, 27)	23 (21, 26)	0.89
Successful Pregnancy Prior to First Transplant, n (%)	76 (24)	10 (38)	0.69
Etiology of Liver Disease, n (%)			0.47
Metabolic/Genetic	110 (34)	14 (37)	
Autoimmune	84 (26)	11 (29)	
Drug/Toxin	30 (9)	2 (5)	
Viral/Fulminant Hepatitis	29 (9)	1 (3)	
Ischemic/Vascular	11 (3)	2 (5)	
Cancer	5 (2)	2 (5)	
Other/Cryptogenic/Unknown	50 (16)	6 (16)	
Age at First Transplant, median (IQR)	22 (16, 28)	22 (16, 31)	0.60
Total Number of Transplants, median (IQR)			0.63
One	271 (85)	31 (82)	
Two	33 (10)	6 (16)	
>Two	14 (4)	1 (3)	
Gravida, n (%)			0.52
One	128 (40)	13 (34)	
Two	102 (32)	11 (29)	
>Two	89 (28)	14 (37)	
Transplant-to-Conception, years, median (IQR)	4.1 (1.7, 11.7)	3.8 (5.3, 15.3)	**<0.001**

Table 1B: Characteristics of Female Liver Transplant Recipients Achieving Pregnancy by ART Method.

Characteristics	Unassisted n = 319	IVF n = 17	IUI n = 4	Meds alone n = 17	p-value
Conception age, years, median (IQR)	28 (24, 32)	32 (32, 36)	33 (30, 35)	31 (28, 38)	**<0.001**
White Race, n (%)	213 (67)	12 (71)	4 (100)	14 (82)	0.62
BMI, median (IQR)	23 (21, 27)	23 (21, 25)	22 (21, 25)	26 (23, 30)	0.31
Successful Pregnancy Prior to First Transplant, n (%)	76 (24)	3 (18)	0 (0)	7 (41)	0.33
Etiology of Liver Disease, n (%)					0.59
Metabolic/genetic	110 (34)	7 (41)	2 (50)	5 (29)	
Autoimmune	84 (26)	6 (35)	0 (0)	5 (29)	
Drug/Toxin	30 (9)	0 (0)	0 (0)	2 (12)	
Viral/Fulminant Hepatitis	29 (9)	0 (0)	0 (0)	1 (6)	
Ischemic/Vascular	11 (3)	1 (6)	0 (0)	1 (6)	
Cancer	5 (2)	1 (6)	0 (0)	1 (6)	
Other/Cryptogenic/Unknown	50 (16)	2 (12)	2 (50)	2 (12)	
Age at First Transplant, median (IQR)	22 (16, 28)	22 (15, 26)	20 (11, 26)	23 (18, 32)	0.57
Total Number of Transplants, median (IQR)					0.54
One	271 (85)	12 (71)	4 (100)	15 (88)	
Two	33 (10)	4 (24)	0 (0)	2 (12)	
>Two	14 (4)	1 (6)	0 (0)	0 (0)	
Gravida, n (%)					0.17
One	128 (40)	7 (41)	2 (50)	4 (24)	
Two	102 (32)	6 (35)	2 (50)	3 (18)	
>Two	89 (28)	4 (24)	0 (0)	10 (59)	
Transplant-to-Conception, years, median (IQR)	4.1 (1.7, 11.7)	2.3 (6.4, 15.8)	1.4 (6.4, 21.9)	7.5 (3.5, 12.4)	**0.004**

Table 2: Maternal Outcomes of Recipients Achieving Pregnancy with or without ART.

Characteristics	Unassisted n = 818	Assisted n = 54	p-value
Diabetes, n (%)			
Pregestational	38 (5)	8 (15)	**0.007**
Gestational	82 (10)	9 (17)	0.090
Postpartum	37 (5)	8 (15)	**0.005**
Hypertension, n (%)			
Chronic	135 (17)	12 (22)	0.35
Postpartum	148 (18)	8 (15)	0.59
Preeclampsia	119 (15)	7 (13)	0.20
Cholestasis of Pregnancy, n (%)	72 (9)	6 (11)	0.81
Type of gestation, n (%)			**<0.001**
Singleton	764 (93)	43 (80)	
Twin	34 (4)	10 (19)	
Pregnancy Outcome, n (%)			0.14
Live Birth	595 (73)	35 (65)	
Miscarriage	175 (21)	15 (28)	
Currently Pregnant	14 (2)	0 (0)	
Ectopic	5 (1)	2 (4)	
Stillbirth	10 (1)	0 (0)	
Termination	19 (2)	2 (4)	
Placental/Cord Problems, n (%)	75 (9)	3 (6)	0.33
Cesarean Section, n (%)	262 (32)	20 (37)	0.23

Table 3: Neonatal Outcomes of LT Recipients with or without using ART Methods.

Characteristics	Unassisted n = 521	Assisted n = 35	p-value
Gestational age, weeks, median (IQR)	37.9 (36, 39)	37.0 (34, 38)	0.081
Birth weight, grams, median (IQR)	2927.1 (2431, 3317)	2863.3 (1786, 3169)	0.15
Congenital Defects, n (%)	30 (6)	3 (9)	0.64
Neonatal Death, n (%)	3 (1)	0 (0)	1.00
Child Follow-Up, years, median (IQR)	8.0 (3.5, 15.3)	4.9 (2.7, 10.3)	**0.035**
Healthy & Developing Well, n (%)	496 (95)	35 (100)	0.64

Table 4: Long Term Outcomes after LT with First Reported Pregnancy Achieved with or without ART.

Characteristics	Unassisted n = 384	Assisted n = 38	p-value
Adult Follow-Up, years, median (IQR)	9.7 (4.2, 17.3)	6.4 (3.6, 10.5)	0.09
Rejection During Pregnancy, n (%)	20 (5)	2 (5)	1.00
Graft Loss After Pregnancy, n (%)	9 (2)	1 (3)	1.00
Adequate Graft Function Currently, n (%)	302 (79)	35 (92)	0.24
Maternal Mortality, n (%)	60 (16)	2 (5)	0.10

Figure 1. Time to graft failure or mortality in LT recipients achieving pregnancy with and without ART.