Digestive and Liver Disease 54 (2022) 669–675

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Safe pregnancy after liver transplantation: Evidence from a multicenter Italian collaborative study

Salvatore Stefano Sciarrone[a], Alberto Ferrarese[a], Debora Bizzaro[a], Sofia Volpato[b], Francesca Maria Donato[c], Federica Invernizzi[c], Laura Trespidi[d], Ilaria Giuditta Ramezzana[d], Alfonso Wolfango Avolio[e], Erida Nure[e], Marco Maria Pascale[e], Stefano Fagiuoli[f], Luisa Pasulo[f], Manuela Merli[g], Lucia Lapenna[g], Pierluigi Toniutto[h], Ilaria Lenci[i], Roberto Di Donato[j], Nicola De Maria[k], Erica Villa[k], Alfonso Galeota Lanza[l], Simona Marenco[m], Sherrie Bhoori[n], Laura Mameli[o], Umberto Cillo[p], Patrizia Boccagni[p], Francesco Paolo Russo[a], Patrizio Bo[q], Erich Cosmi[b], Patrizia Burra[a,*]

[a] *Multivisceral Transplant Unit, Department of Surgery Oncology and Gastroenterology, University of Padua, Via Giustiniani 2, Padua 35128, Italy*
[b] *Gynaecology and Obstetrics Unit, Department of Women's and Children's Health, University of Padua, Via Giustianini 3, Padua 35128, Italy*
[c] *Division of Gastroenterology, Maggiore Hospital and IRCCS Foundation, Via Francesco Sforza 35, Milan 20122, Italy*
[d] *Gynaecology and Obstetrics Unit, Department of Women's and Children's Health, Fondazione Ospedale Maggiore, Via Francesco Sforza 35, Milan 20122, Italy*
[e] *Liver Unit, Department of Surgery, Agostino Gemelli Hospital, Catholic University, Largo Agostino Gemelli 8, Rome 00168, Italy*
[f] *Gastroenterology, Hepatology and Liver Transplantation Unit, ASST Papa Giovanni XXIII, Piazza OMS 1, Bergamo 24127, Italy*
[g] *Gastroenterology, Department of Clinical Medicine, Sapienza University of Rome, Via di Grottarossa 1015, Rome 00189, Italy*
[h] *Internal Medicine, Department of Medical Area, University of Udine, via Palladio 8, Udine 33100, Italy*
[i] *Hepatology and Liver Transplant Unit, Department of Medicine, Policlinico Tor Vergata, Viale Oxford 81, Rome 00133, Italy*
[j] *Department of Digestive Disease and Internal Medicine, Azienda Ospedaliero-Universitaria di Bologna Policlinico S.Orsola-Malpighi, Via Giuseppe Massarenti 11, Bologna 40138, Italy*
[k] *Department of Internal Medicine, Gastroenterology Unit, Azienda Ospedaliero-Universitaria Policlinico di Modena, Largo del Pozzo 71, Modena 41124, Italy*
[l] *Hepatology Unit, Cardarelli Hospital, Via A. Cardarelli 9, Naples 80131, Italy*
[m] *Department of Internal Medicine, Gastroenterolgy Unit, Ospedale Policlinico San Martino, Largo Rosanna Benzi 10, Genova 16132, Italy*
[n] *Department of Surgery and Oncology, Istituto Nazionale Tumori IRCCS, Via Giacomo Venezian, 1, Milan 20133, Italy*
[o] *Liver and Pancreas Transplant Center, Azienda Ospedaliera Brotzu Piazzale Ricchi 1, Cagliari 09134, Italy*
[p] *Hepatobiliary Surgery and Liver Transplantation Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Via Giustiniani 2, Padua 35128, Italy*
[q] *Gynaecology and Obstetrics Unit, Cittadella Hospital, Via Riva dell'Ospedale, Cittadella 35013, Italy*

ARTICLE INFO

Article history:
Received 22 June 2021
Accepted 18 August 2021
Available online 5 September 2021

Keywords:
Pregnancy outcomes
Liver transplantation
Infertility
Immunosuppression

ABSTRACT

Background: Women who have undergone liver transplantation (LT) enjoy better health, and possibility of childbearing. However, maternal and graft risks, optimal immunosuppression, and fetal outcome is still to clarify.
Aim: Aim of the study was to assess outcomes of pregnancy after LT at national level.
Methods: In 2019, under the auspices of the Permanent Transplant Committee of the Italian Association for the Study of the Liver, a multicenter survey including 14 Italian LT-centers was conducted aiming at evaluating the outcomes of recipients and newborns, and graft injury/function parameters during pregnancy in LT-recipients.
Results: Sixty-two pregnancies occurred in 60 LT-recipients between 1990 and 2018. Median age at the time of pregnancy was 31-years and median time from transplantation to conception was 8-years. During pregnancy, 4 recipients experienced maternal complications with hospital admission. Live-birth-rate was 100%. Prematurity occurred in 25/62 newborns, and 8/62 newborns had low-birth-weight. Cyclosporine was used in 16 and Tacrolimus in 37 pregnancies, with no different maternal or newborn outcomes. Low-birth-weight was correlated to high values of AST, ALT and GGT.

* Corresponding author.
E-mail address: burra@unipd.it (P. Burra).

https://doi.org/10.1016/j.dld.2021.08.013

Conclusion: Pregnancy after LT has good outcome; however, maternal complications and prematurity may occur. Compliance with the immunosuppression is fundamental to ensure the stability of graft function and prevent graft-deterioration.

1. Introduction

Pregnancy in patients with cirrhosis is uncommon; in fact, approximately 30–50% of females with chronic liver disease report amenorrhea [1–3]. Liver transplantation (LT) has evolved as a universally accepted treatment for patients with end-stage liver disease and graft and patient survival rates have improved steadily over the last 2 decades, with current 5-year survival rates reported to be in excess of 70%, long-term survival being expected in the majority of recipients [4–7]. The focus of medical care has therefore broadened to incorporate factors that have an impact on quality of life [8–10].

For female transplant recipients of childbearing age, the desire for a family often arises and involves questions regarding fertility and the safety of pregnancy for the mother, graft and fetus [11]. Pregnancy is often successful after LT, despite the potentially toxic effects of immunosuppressive drug therapy, however fetal and maternal features should be regularly assessed during pregnancy [4]. The first successful pregnancy following LT was reported in 1978, with a healthy boy delivered at 40.5-weeks' gestation, weighing 2400 g, with both the mother and baby in excellent health 1 year after delivery [11]. Subsequent to this, many case series have been reported [12–14], which have expanded our knowledge regarding the safety and outcomes of pregnancy following LT. Overall, the outcomes are largely favorable [15]. However, data suggest that pregnancy in LT recipients can be associated with unpredictable graft deterioration, an increased risk of pre-eclampsia, infections, and diabetes in the mother [16,17]. For the fetus, prematurity and low birth weight with the potential for long-term disability exists [18]. Acute cellular rejection (ACR) has been reported to complicate between 10 and 17% of patients in the gestational period [11–13,19] and 3 to 12% of patients in the postpartum period [11,12]. Graft loss directly related to ACR in pregnancy appears to be rare, with the majority of episodes controlled by immunosuppression (IS) augmentation or intravenous steroids. Regarding non–graft-related maternal complications, the incidence of pre-eclampsia and eclampsia are increased with rates of between 14 and 23% [11,13,20]. Other maternal risks include bacterial and viral infections (27%) and gestational diabetes (5%) [20]. Fetal outcomes are largely acceptable with a live birth rate of 73% reported by the England National Transplant Pregnancy Registry but with 30% of neonates born prematurely and 30% with low birth weight [21].

Distinguishing the minority of LT recipients who are at risk of the above serious adverse effects during pregnancy from those who are likely to have an uneventful pregnancy remains challenging. This makes tailoring preconception counselling to the individual quite difficult and interpretation of outcomes not always reproducible due to data derived from a largely heterogeneous cohort of women. Combining this with the fact that much uncertainty remains regarding the effect of IS on fetal outcomes, more data are needed in this unique cohort of patients. The aim of this study is to report the Italian experience of pregnancy in LT recipients by assessing safety, possible complications (in women, fetuses, grafts and newborns) and outcomes of pregnancy for the mother, fetus and grafts. We report on the maternal complications encountered during pregnancy including diabetes, hypertension, renal dysfunction, pre-eclampsia, and their impact on fetal outcomes, including the live birth rate, gestational week, birth weight, Apgar score and admission to intensive care unit. The national survey on pregnancy in LT recipients was performed under the auspices of the Italian Association for the Study of the Liver (AISF) Permanent Transplant Committee (PTC).

2. Patients and methods

2.1. Survey and data collection

In 2019 a survey on pregnancy in LT recipients was sent to all 21 Italian LT centers; we received data back from 14 centers, while 7 did not have female recipients who had become pregnant in their database. The survey was designed in accordance between the AISF-PTC, a representative from the College of Liver Surgeons of the Italian Society of Organ Transplantation and the obstetricians of the Gynecology and Obstetrics Unit, Department of Women's and Children's Health, Padua University Hospital. The survey consisted of questions related to the patients who had pregnancy after LT in each center, between 1990 and 2018.

Each center included women who experienced pregnancy after LT, identifying them in their own database with all transplanted patients and eventually by physician recollection. The electronic database of each center contains all patient data obtained during the different types of hospital access (outpatient, ordinary hospitalization, urgent hospitalization, etc.), after acquiring informed consent from the people involved. The pregnancy data, together with the other pre- and post-natal data were retrospectively extrapolated for the analysis. All patients who had their prenatal care at the LT center or who received care at peripheral hospitals were included in the study.

Data collected by each center were shared with the coordinator group (Multivisceral Transplant Unit, University of Padua). The collected data covered maternal age, indication for LT, interval between LT and conception, and baseline IS. Maternal complications during pregnancy, including hypertension, pre-eclampsia, gestational diabetes, sepsis and renal failure, along with specific hepatological complications including ACR and graft loss defined according to common clinical practice were recorded. Data on gestational duration, birth weight, live birth rate, and congenital abnormalities were also recorded. Finally, long-term survival in both mother and child was evaluated.

2.2. Schedule of outpatient visits

Despite there being no specific guidelines about the management of pregnancy after LT in Italy, in all centers, the cases are usually presented by transplant hepatologists during a multidisciplinary meeting with obstetricians and transplant surgeons, once the pregnancy is known with update during and after pregnancy. The transplant hepatologists and obstetricians regularly follow patients before and after delivery.

The pregnancy status was communicated to the LT center by the patient herself, and confirmed by the reference obstetrician who followed the patient. Upon receipt of this notification, a visit with the transplant hepatologist and the obstetrician, and also transplant surgeon whenever indicated, is scheduled within one month. Subsequently, a multidisciplinary follow-up is organized at the end of each trimester of pregnancy or is foreseen in case of problems reported by the patient, to agree on the management of

Table 1
Indications for liver transplantation.

Indication for LT	(%)
Viral cirrhosis	10 (16.1%)
Wilson's disease	10 (16.1%)
PBC/PSC	8 (12.9%)
Biliary atresia	7 (11.3%)
Caroli disease	3 (4.8%)
DILI	3 (4.8%)
Autoimmune hepatitis	2 (3.2%)
Alcohol-related	1 (1.6%)
Others	18 (29%)

PBC primary biliary cholangitis; PSC: primary sclerosing cholangitis; DILI: drug induced liver injury

IS regimen and evaluation of liver graft function. After the delivery, both, the transplant hepatologist and the obstetrician performed an outpatient visit within 1,2 months after childbirth; thereafter the patient continues with the normal intervals indicated for her pathology and health status.

2.3. Statistical analysis

Values for continuous variables are presented as median (range). Categorical-nominal variables are presented as frequencies. For group comparisons, quantitative variables were compared using Student's *t*-test and categorical variables using χ^2. The cumulative progression free survival rate was calculated using Kaplan-Meier method. The relationship between two variables was determined using Pearson's correlation analysis. A *P* value of <0.05 was considered to be of statistical significance.

All statistical analysis were performed using the SPSS statistical software package, version 21 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patients

Sixty-two conceptions occurred in 60 LT recipients between 1990 and 2018 in Italy. 60 out of 62 pregnancies (97%) were through natural conception, while 2 (3%) derived from *in vitro* fertilization (IVF) and embryo transfer technique. The indications for LT are summarized in Table 1. Median age at conception was 31 years (range 16–40 years) and the median interval between LT and conception was 8 years (range 1–31). Overall, 59 women had one conception (of whom one was a twin pregnancy), and one woman had 2 pregnancies.

3.2. Immunosuppressant regimes

Fourteen patients out of 60 were in therapy with mycophenolate mofetil (MMF). Due to its potential teratogenic effect on the fetus [22], MMF was discontinued when women programmed the conception or immediately after the confirmation of pregnancy, 6 patients were on Tacrolimus and 8 patients were on Cyclosporine immunosuppressive therapy. Overall, during pregnancy, the main immunosuppressant regimens were: Tacrolimus in 37 out of 62 pregnancies (60%), Cyclosporine in 16 out of 62 (26%), whereas in the remaining 9 (13%), IS regimen was the following: cyclosporine and corticosteroids in 4, Everolimus and Azathioprine in 2, Cyclosporine and Azathioprine in 1, Tacrolimus and Everolimus in 1, Tacrolimus and Azathioprine in 1. However, Azathioprine and Everolimus were discontinued within the first trimester of pregnancy due to their potentially dangerous effects on the fetus [4] and the recipients maintained monotherapy with Tacrolimus and Cyclosporine. The dosage of Tacrolimus or Cyclosporine was adjusted according to blood levels, and according to the trimester of pregnancy, since there is a risk of reduced levels due to a physiological blood dilution and weight gain during pregnancy.

3.3. Maternal outcomes

During pregnancy, 4 cases with medical complications were recorded: 1 recipient experienced a severe form of gestational diabetes without ketoacidosis that required hospital admission and medical treatment; 2 recipients developed infectious complications requiring hospitalization, due to cholangitis at 30 weeks of gestation in 1 case, and urinary tract infection at 32 weeks of gestation in another with recovery after antibiotic therapy; and 1 case experienced pre-eclampsia during the third trimester, resolved with an urgent caesarean section in the 37th week of gestation. No fetal damage or graft dysfunction were reported in those 4 cases.

However, a fatal case of acute onset of lymphoma 6 months after delivery was reported. The Kaplan Maier curve with representation of overall maternal survival is reported in Fig. 1A.

3.4. Graft function

During pregnancy, none of the patients experienced graft rejection. Only a case of mild increase of transaminases after the withdrawal of the MMF was recorded; however liver biopsy was not required with normalization of liver function tests by increasing immunosuppression. In all LT recipients, liver function and renal function assessed in each trimester remained substantially stable (Table 2) apart from 4 cases in whom abnormalities of AST, ALT, and GGT were recorded until the delivery and completely recovered after the delivery. One was the case described above with mild increase of transaminases after the withdrawal of MMF. In one patient, the transaminases increased due to reactivation of the autoimmune hepatitis probably as a consequence of poor compliance with IS. The third patient experienced ascending cholangitis (having a Roux-en-Y anastomosis). In one case, biliary sludge was diagnosed. The patient underwent magnetic resonance imaging investigation detecting no intrahepatic stenosis nor stones. Pharmacological therapy with ursodeoxycholic acid was carried out, with a progressive normalization of the laboratory values. The biopsy was not done.

3.5. Delivery

The median delivery time was 38 weeks of gestation, with the earliest delivery at 25 weeks and the latest at 40 weeks. 32 out of 62 deliveries (52%) occurred through a caesarean section, 20 out of 62 (32%) through natural delivery, 8 patients (13%) needed labor induction. Data from two deliveries were not available. No complications were recorded during delivery. No miscarriage was observed in the entire cohort. Data about delivery are reported in Table 3.

3.6. Fetal outcomes

Among the 62 newborns, including a pair of twins, the live birth rate was 100% (62/62), 25 out of 62 (40%) were classified as premature, while 35 (56.4%) were classified as born at term (Table 3).

A patient had an unstoppable labor; she delivered a vital fetus at 25 weeks of gestation, who died from pulmonary complications 2 days after delivery. The Kaplan Maier curve with representation of overall maternal survival is reported in Fig. 1B.

The median weight of newborns was 2.9 Kg (1.05–3.5) and 48 out of 62 (77%) had a weight greater than 2.5 Kg. Newborn low

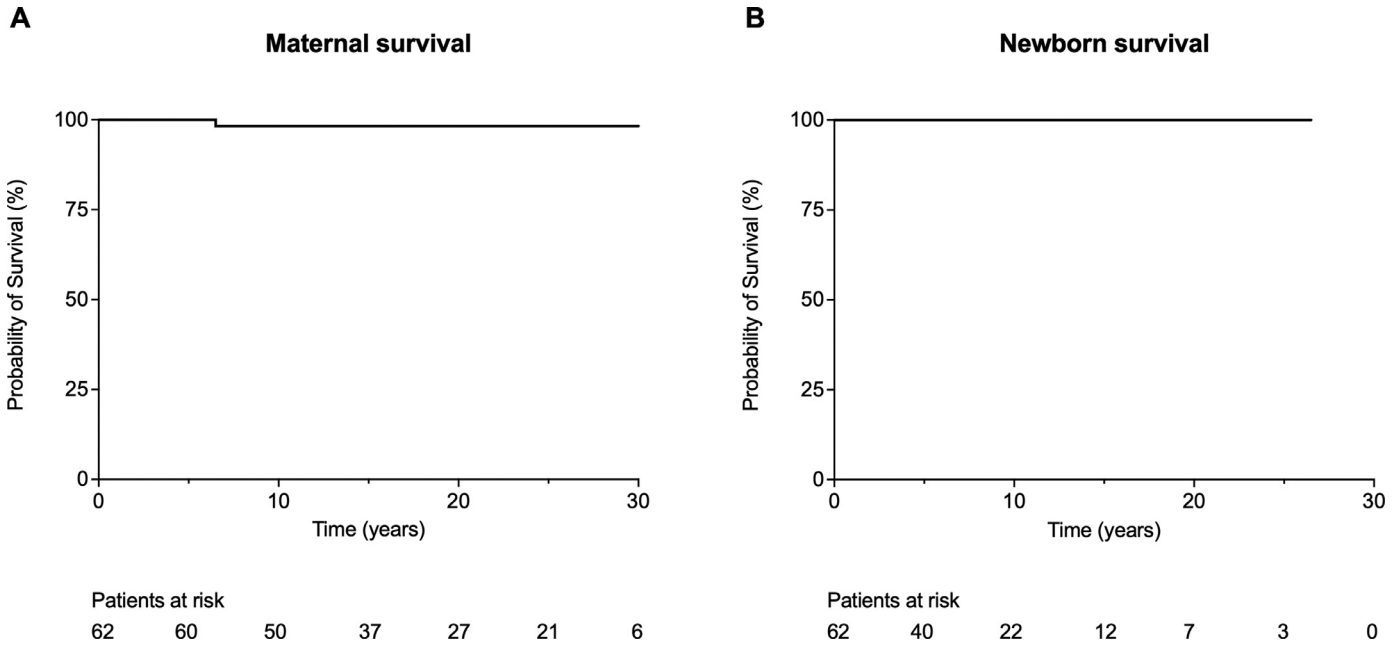

Fig. 1. Kaplan-Meier curve for overall survival. (A) Mother survival (years from LT) (B) newborns survival.

Table 2
Biochemical parameters of mothers during pregnancy. Data are reported as median (range).

	1st Trimester	2nd Trimester	3rd Trimester
AST (U/L) (nv 10 –35)	19.5 (9–91)	21 (8–182)	25 (12–242)
ALT (U/L) (nv 10 – 40)	20 (7–116)	20 (7–217)	21.5 (8–248)
GGT (U/L) (nv 55)	22 (5–431)	14.5 (5–248)	14 (4–367)
ALP (U/L) (nv 40–120)	69.5 (7–232)	77 (18–245)	129 (31–526)
Total Bilirubin (mg/dL) (nv 0.2–1.2)	0.8 (0.2–1.8)	0,7 (0.3–3)	0.8 (0.3–4.5)
BUN (mg/dL) (nv 21–40)	24.5 (2.8–67)	26 (10–109)	24 (8–75)
Creatinine (mg/dL) (nv 0.5–1.2)	0.7 (0.3–1.6)	0.7 (0.34–1.7)	0.7 (0.4–1.7)
INR (nv 0.7–1.1)	1 (0.7–1.21)	1 (0.8–9.6)	1 (0.86–1.2)

AST: aspartate transaminase; ALT: Alanine transaminase; GGT: gamma-glutamyltransferase; ALP: alkaline phosphatase; BUN: Blood Urea Nitrogen; INR: International Normalized Ratio; NV: normal values

Table 3
Delivery and newborns characteristics.

Median delivery time	
Weeks (range)	38 (25–40)
Delivery modality	
Physiological delivery	20 (32.3%)
Caesarean section	32 (51.6%)
Induction delivery	8 (12.9%)
Newborns characteristics	
Median weight (range), Kg	2.9 (1.05–3.5)
Weight >2.5 Kg	48 (77.4%)
ICU admission	5 (8.1%)
Apgar >8	53 (85.5 %)
Breastfeeding	11 (17.7%)

ICU intensive care unit

birth weight significantly correlated with abnormalities of mother's liver enzymes ($p < 0.01$) (Table 4).

Apgar score in 53 out of 62 newborns (85.5%) was >8 and only 5 out of 62 (8%) newborns needed intensive care because of respiratory insufficiency.

Regarding breastfeeding, 11 mothers, all of them on Tacrolimus and Corticosteroids (18%), decided to proceed with it (Table 3).

4. Discussion

Since the goal of transplantation is not only to ensure patient survival, but also to offer the level of health they expected, a good balance must be achieved between functional efficacy of the graft and the patient's psychological and physical integrity [8]. This includes for female transplant recipients of childbearing age, the possibility of having a safe pregnancy for the mother, graft and fetus.

It is well-known that data from case-control studies and meta-analyses indicate increased obstetric complications in women and increased risk for newborns after LT [1–4,23].

However, pregnancy outcomes are satisfactory overall. Immunosuppression, abdominal surgery, mother's age, and potential comorbidities are all risk factors in post transplantation pregnancies [6]. No guidelines based on strong evidence are currently available for pregnancy after LT despite important information being derived from National Transplant Pregnancy Registries [21]. A single-center experience publicised by Sivaprasadan et al., demonstrated that in majority of patients, pregnancy after LT can have favorable outcomes for the mother, foetus, and allograft. But confirm that there is still a lack of consensus regarding the optimal time of conception after LT, with most guidelines recommending a wait period of one to two years after transplantation to have a stable level of

Table 4
Correlation between mothers' graft function in the three trimesters of pregnancy and newborn birth weight.

	Weight		*P* value	CI	CI
AST 1st Trimester	>2.5 (Kg)	-3.423	.001	-2.697.624	-702.376
	<2.5 (Kg)	-3.306	.009	-2.854.862	-545.138
ALT 1st Trimester	>2.5 (Kg)	-2.877	.006	-4.185.288	-744.257
	<2.5 (Kg)	-2.657	.026	-4.557.994	-371.552
GGT 1st Trimester	>2.5 (Kg)	-3.399	.001	-11.530.878	-2.961.564
	<2.5 (Kg)	-1.492	.179	-18.713.674	-4.221.232
AST 2nd Trimester	>2.5 (Kg)	-3.065	.003	-4.721.446	-985.076
	<2.5 (Kg)	-1.501	.176	-7.323.140	1.616.618
ALT 2nd Trimester	>2.5 (Kg)	-2.897	.006	-6.304.552	-1.144.361
	<2.5 (Kg)	-1.624	.146	-9.088.513	1.639.600
GGT 2nd Trimester	>2.5 (Kg)	-3.759	.000	-7.618.588	-2.314.189
	<2.5 (Kg)	-1.624	0.01	-7.618.588	-2.314.189
AST 3rd Trimester	>2.5 (Kg)	-3.322	.002	-9.239.373	-2.262.293
	<2.5 (Kg)	-1.498	.193	-15.556.801	4.055.134
ALT 3rd Trimester	>2.5 (Kg)	-2.431	.019	-10.024.890	-936.777
	<2.5 (Kg)	-1.433	.208	-15.129.088	4.167.421
GGT 3rd Trimester	>2.5 (Kg)	-2.115	.040	-11.000.151	-261.388
	<2.5 (Kg)	-1.687	.144	-13.841.797	2.580.258

CI Confidence Interval

IS and minor probability of infection [24]. Similarly, a recent systematic review and meta-analysis including 38 studies with 1131 pregnancies among 838 LT recipients, reported that pregnancy after LT is feasible and safe, but does carry an increased risk of both maternal and fetal complications [25]. In this meta-analysis the optimal time interval to pregnancy of LT seems to be a minimum of 2 years. An interval of 4 years provides the highest rates of live birth and lowest rates of miscarriage.

In our cohort, the time of conception after LT was 8 years (range, 1 year to 31 years).

There are some studies reporting a significant increase of the risk of ACR in pregnancies occurring within 1 year of LT [26–28]. This increased risk has been attributed to instability in immunosuppressive drug use independently of pregnancy and an increased risk of infection [4]. Moreover, during pregnancy there are two other variables to consider (1) the immunomodulation of the organs that permit development of the fetus and (2) the high distribution volume of drugs.Therefore, a careful monitoring of immunosuppressive medications is recommended, and the lowest possible dose needed to prevent rejection should be used, in order to avoid potential adverse effects on mother and fetus. Maintenance of pre-conception immunosuppression is recommended, with the exception of Mycophenolic acid products and Azathioprine, which should be discontinued before conception a due to their teratogenic risks including developmental toxicity, intrauterine death, and malformations [22,29].

In our cohort, 37 recipients (60%) were on Tacrolimus, and 25 (40%) were on Cyclosporine therapy (4 in combination with steroids), and no differences were seen in terms of renal function, liver function or other complications or fetus outcome. Azathioprine, Everolimus and MMF were discontinued in prevision or at the confirmation of pregnancy in 17 women, without signs of relevant graft damage. In our cohort we did not record any episode of rejection, suggesting an adequate level of immunosuppressive drugs, due to a proper follow-up and compliance by recipients.

Regarding infectious complications, only 2 cases out of 60 recipients (3.3%) experienced infections, cholangitis and urinary tract infection treated with antibiotic therapy. Antibiotics are widely prescribed during pregnancy as the most important method for treating and preventing infections. It is estimated that one in five pregnant women in Europe is prescribed at least one antibiotic during pregnancy; in the United States, the rate is double [30,31]. Nevertheless, prescription of antibiotics should be carefully considered on an individual basis, weighing its benefits versus drawbacks for both the fetus and the mother. It has been shown that administration of certain antibiotics (Gentamicin and Meropenem) is linked to a significantly higher rate of neonatal necrotizing enterocolitis [32], although antibiotic treatment is also associated with a reduced rate of lung complications and major cerebral abnormalities, relative to non-antibiotic treated controls [33].

In general, overall renal and liver function remained satisfactory during the three trimesters and comparable to the value before the pregnancy.

Metabolic complications may occur during pregnancy, in our cohort we reported a case of diabetes and a case of pre-eclampsia; in the first case the complications occurred in the second trimester and did not influence the timing of delivery, in the second case the complication required a caesarean section at 37 weeks of gestation, the immunosuppression in this case was switched from Tacrolimus to low-dosage corticosteroids.

The King's College Hospital study reported a 14% incidence of pre-eclampsia, which might be associated with the vasoconstrictor effects of calcineurin inhibitors, long-term corticosteroid use, and increased renal dysfunction [34].

Importantly, in nearly 30 years from the first case of pregnancy after LT in Italy, maternal survival was excellent, with unfortunately one death out of 60 cases, due to an acute onset of lymphoma, probably immunosuppression-related. In fact, despite lower incidence of leukemias and lymphomas in women than in men, there is little evidence of associations with pregnancy factors and lymphoma [35] in healthy women. Pregnancy-related hormonal or immunological changes seem to have only a minor influence in the etiology of leukemias. However, one study did find a slight tendency towards reduced risk of chronic myeloid leukemia with higher parity [36] and another reported short-term protection against acute myeloid leukemia with pregnancy [37]. On the other hand post-transplant lymphoproliferative disorders (PTLD) occur in 1–20% of organ recipients following transplantation. PTLD risk factors include recipient pre-transplant Epstein-Barr virus (EBV) negative serostatus, type of transplant, intensity of immunosuppression, and age. PTLD treatment may require reduction of immunosuppression, radiation, surgical excision, monoclonal antibodies, interferon-alpha, and chemotherapy [33,38].

According to the National Transplant Pregnancy Register data, the live birth rate after transplantation is 73%, whereas the level for premature birth and low birth weight is 30% [21]. The study from King's College Hospital reported a live birth rate of 73%, prematurity rate of 31%, a low birth weight rate of 19%, and a very

low birth weight rate of 10% without any congenital abnormalities. The authors reported that higher levels of prematurity and low birth weight compared to the general population was maybe associated with immunosuppressants, increased preeclampsia and eclampsia, iatrogenic causes, acute cellular rejection, and maternal comorbidities [26]. In another study by Sobotka et al., specific complications more likely to occur in LT recipients compared with the general population include miscarriage (3.2% vs 0.8%, $p = 0.001$), intrauterine growth restriction (5.6% vs 2.1%, $p = 0.001$), postpartum haemorrhage (5.8% vs 2.7%, $p = 0.001$), hypertension (35.1% vs 9.5%, $p = 0.001$), preeclampsia (17.8% vs 4.1%, $p = 0.001$), and venous thromboembolism (3.9% vs 0.4%, $p = 0.001$)[23]. The premature birth rate in our study was 40%, higher than cases reported in the literature, but also premature birth at 35–38 weeks with an acceptable weight. One premature birth occurred at 25 weeks and died from pulmonary complications.

In contrast to the literature, no miscarriage was observed in our study, and the live birth rate was 100%; on the contrary, several reviews in the literature report a median miscarriage score of 12.9, and 2.3% of intrauterine fetal death, in contrast with our study [39].

In another study neonatal asphyxia was observed in 1 newborn with a low birth weight (less than 2500 g) and intracranial hemorrhage in another newborn with very low birth weight (less than 1500 g) [40]. In our study, one newborn had an exceptionally low birth weight (less than 1500 g) without further complications, but was a twin pregnancy, so is in line with the general population. Interestingly in our cohort the increased level of AST, ALT and GGT was significantly associated with low weight at birth, therefore the lower fetal growth was correlated significantly with graft function ($p < 0.01$).

The time from LT did not influence the fetus development, in our cohort. However the National Transplant Pregnancy Register does not recommend pregnancy in the first year after transplantation [20]. As reported before in this article the main condition that influences the outcome of pregnancy is the optimal function of the graft and stable immunosuppression level, so optimal time to pregnancy post-transplantation has not been indicated.

Interestingly in a study by Lim et al. [41], the fetus development was also related to renal function of the mother, evidence that is not confirmed in our study.

Regarding anomalies and malformation in newborns, Coscia et al. investigated 57 women with pregnancies after LT and identified anomalies in five newborns. They reported a maternal age of less than 21 years in all five cases. The birth defects were reported as two cases of multiple anomalies, one of total venous anomalous return, one of pyloric stenosis, and one of hypospadias, a total of 2 cases out of 57 pregnancies (3.5%) [42].

Jain et al. described tracheoesophageal fistula and valvular heart disease in one baby and unilateral non-functional cystic kidney and accessory mammary tissue in another [13]. Nagy et al. reported small membranous ventricular septal defect in two babies of three mothers receiving tacrolimus therapy and bilateral hydrocele in one baby, together with hypospadias in the baby of another mother receiving cyclosporine [15]. Kainz et al. reported the development of neonatal congenital malformation in 4 of 100 pregnancies in patients receiving tacrolimus therapy [43]. No congenital anomaly was observed in any neonate in our study. The limited patient number in this study may have influenced this. However, as also emphasized in several recent studies, the risk of congenital anomaly after LT is similar to that for the healthy population [6].

LT accompanied by immunosuppressive therapies does not constitute an additional risk for the development of congenital anomalies. Deshpande et al. subjected the data for 450 pregnancies in 306 women undergoing LT to metanalysis. They reported 346 live births (76.9%), 70 miscarriages (15.6%), 28 abortions (6.2%), 4 still births (0.9%), and 2 ectopic pregnancies (0.4%) [17]. Caesarean delivery was higher among patients who had received LT compared to the general population, which we confirmed in our study. Breastfeeding rate was extremely low, perhaps for the immunosuppression therapy of the mother, but a recent study demonstrates how safe it is for newborns; in fact, the concentrations of Cyclosporine, Tacrolimus and Corticosteroids in breast milk two hours after assumption were negligible [9,10,44,45].

Finally, for LT recipients with infertility, few recent reports confirm the safety and efficacy of IVF, but the patients should be counselled on the potential increased risks of ovarian hyperstimulation syndrome, obstetric cholestasis, and prematurity [46]. Indeed, for those women who experienced infertility after LT the success rate of IVF in terms of clinical pregnancy and live birth rates in women with liver disease and post-LT may be comparable to known rates in the general population. However, the ideal IVF regimen remains to be defined. Further, the independent risk of IVF on maternal, infant, and liver-related outcomes in women with liver disease remains unclear [46,47].

Due to the relevance and few data published on this topic, it is needed to develop large international prospective cohorts able to accurately define both liver and IVF exposures and outcomes [47].

A limitation of our study is the lack of some data such as the blood levels of immunosuppression during pregnancy. Moreover, we are aware that several articles have recently been published on the same topic [3,23,46,48] and that the originality of the work might not be so evident at an international level. However, we would like to highlight its relevance at a single country level, being the first time that data on post-transplant pregnancies have been collected in Italy, since 1990, when LT activity began. One strength of our study is certainly the number of Italian transplant centers that collaborated with us, sharing their data about pregnancy after LT. We contacted all 21 LT centers in Italy and the only 7 centers that could not accept, did so because they did not have female recipients who had become pregnant in their database, meaning that all the other LT centers contributed. The proposal to assess post-transplant pregnancy outcomes across Italy was approved by the Permanent Transplant Commission of the Italian Association for the Study of the Liver, and by the representative from the College of Liver Surgeons of the Italian Society of Organ Transplantation. We think that the contribution of representatives of two scientific societies is important for a paper of this type. Furthermore, we had discussions with the obstetricians of the Gynecology and Obstetrics Unit, Department of Women's and Children's Health, Padua University Hospital, in order to organize the collection of data, balancing the experience of transplant hepatologists and surgeons and transplant obstetricians. This collaboration gave us a complete evaluation of this clinical situation. Another remarkable point of strength is the long interval, up to 30 years from the first case of pregnancy, which demonstrated that pregnancy after LT is relatively safe both for mothers and newborns. Indeed, in 30 years we reported only one maternal and one newborn death, and these data reinforce the strength of LT as a definitive curative treatment for patients with end stage liver disease, also providing them with the possibility to procreate, when it was not possible before transplant.

5. Conclusion

In conclusion, we found that, in the Italian cohort of post-LT patients, pregnancies have successful outcomes in the majority if an optimal graft function is reached. Considering the possible complications (e.g., concomitant chronic conditions and immunosuppressive drugs), pregnancy outcomes are reassuringly favorable. However, pregnancy in these individuals should therefore be carefully considered, planned, and monitored in a multidisciplinary setting, including input from an experienced obstetrician and transplant

physician. For the health of the transplanted patient and the fetus, we strongly recommend to perform joint transplant hepatologist and obstetrician outpatient follow-up during pregnancy to balance the needs of the fetus with those of the transplanted patient.

Future research goals should include defining the impact of pregnancy on short-term and long-term graft function, optimizing screening during pregnancy, identifying LT-specific risk factors for pre-eclampsia and intrauterine growth retardation (IUGR), and determining the outcomes of IVF and mTOR inhibitors on pregnancy. Furthermore, the possibility of a safe pregnancy after LT is an important issue of women's quality of life after the intervention, the knowledge that despite transplantation there is the possibility of childbearing is an important psychological factor that could improve quality of life after LT.

Conflict of Interest

The authors declare that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding

The authors declare that no financial support was provided for the preparation of the manuscript.

References

[1] Borssen AD, Wallerstedt S, Nyhlin N, et al. Pregnancy and childbirth in women with autoimmune hepatitis is safe, even in compensated cirrhosis. Scand J Gastroenterol 2016;51:479–85.
[2] Cundy TF, Ogrady JG, Williams R. Recovery of menstruation and pregnancy after liver-transplantation. Gut 1990;31:337–8.
[3] Rahim MN, Long L, Penna L, et al. Pregnancy in liver transplantation. Liver Transpl 2020;26:564–81.
[4] Alisi A, Balsano C, Bernabucci V, et al. AISF position paper on liver transplantation and pregnancy women in hepatology group, Italian association for the study of the liver (AISF). Dig Liver Dis 2016;48:860–8.
[5] Seaberg EC, Belle SH, Beringer KC, et al. Long-term patient and retransplantation-free survival by selected recipient and donor characteristics: an update from the Pitt-UNOS liver transplant registry. Clin Transpl 1997:15–28.
[6] Alvaro E, Jimenez LC, Palomo I, et al. Pregnancy and orthotopic liver transplantation. Transpl Proc 2013;45:1966–8.
[7] Blume C, Sensoy A, Gross MM, et al. A comparison of the outcome of pregnancies after liver and kidney transplantation. Transplantation 2013;95:222–7.
[8] Tome S, Wells JT, Said A, et al. Quality of life after liver transplantation. A systematic review. J Hepatol 2008;48:567–77.
[9] Burra P, De Bona M. Quality of life following organ transplantation. Transpl Int 2007;20:397–409.
[10] Burra P. Sexual dysfunction after liver transplantation. Liver Transpl 2009;15:S50–SS6.
[11] Walcott WO, Derick DE, Jolley JJ, et al. Successful pregnancy in a liver transplant patient. Am J Obstet Gynecol 1978;132:340–1.
[12] Christopher V, Al-Chalabi T, Richardson PD, et al. Pregnancy outcome after liver transplantation: a single-center experience of 71 pregnancies in 45 recipients. Liver Transpl 2006;12:1138–43.
[13] Jain AB, Reyes J, Marcos A, et al. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. Transplantation 2003;76:827–32.
[14] Lim KB, Schiano TD. Long-term outcome after liver transplantation. Mt Sinai J Med 2012;79:169–89.
[15] Nagy S, Bush MC, Berkowitz R, et al. Pregnancy outcome in liver transplant recipients. Obstet Gynecol 2003;102:121–8.
[16] Laifer SA, Darby MJ, Scantlebury VP, et al. Pregnancy and liver-transplantation. Obstet Gynecol 1990;76:1083–8.
[17] Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes of liver transplant recipients: a systematic review and meta-analysis. Liver Transpl 2012;18:621–9.
[18] López-Cepero R, de la Vega A, Lynch L. Pregnancy after liver transplantation. Bol Asoc Med P R 2013;105:9–13.
[19] Mohamed-Ahmed O, Nelson-Piercy C, Bramham K, et al. Pregnancy outcomes in liver and cardiothoracic transplant recipients: a UK national cohort study. PLoS ONE 2014;9:e89151.
[20] Rayes N, Neuhaus R, David M, et al. Pregnancies following liver transplantation–how safe are they? A report of 19 cases under cyclosporine A and tacrolimus. Clin Transpl 1998;12:396–400.
[21] Armenti VT, Radomski JS, Moritz MJ, et al. Report from the national transplantation pregnancy registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2004:103–14.
[22] Pérgola PE, Kancharla A, Riley DJ. Kidney transplantation during the first trimester of pregnancy: immunosuppression with mycophenolate mofetil, tacrolimus, and prednisone. Transplantation 2001;71:994–7.
[23] Sobotka LA, Mumtaz K, Hinton A, et al. Pregnancy in liver transplantation recipients is associated with increased complications and healthcare utilization. Am J Gastroenterol 2021;116:560–7.
[24] Sivaprasadan S, Mathew JS, Surendran S, et al. Pregnancy after liver transplantation: outcomes from a single-center experience. J Clin Exp Hepatol 2020;10:329–33.
[25] Valentin N, Guerrido I, Rozenshteyn F, et al. Pregnancy outcomes after liver transplantation: a systematic review and meta-analysis. Am J Gastroenterol 2021;116:491–504.
[26] Rupley DM, Janda AM, Kapeles SR, et al. Preconception counseling, fertility, and pregnancy complications after abdominal organ transplantation: a survey and cohort study of 532 recipients. Clin Transpl 2014;28:937–45.
[27] Riely CA. Contraception and pregnancy after liver transplantation. Liver Transpl 2001;7:S74–SS6.
[28] Parolin MB, Rabinovich I, Urbanetz A, et al. [Sexual and reproductive function in female liver transplant recipients]. Arq Gastroenterol 2004;41:10–17.
[29] Deshpande NA, Coscia LA, Gomez-Lobo V, et al. Pregnancy after solid organ transplantation: a guide for obstetric management. Rev Obstet Gynecol 2013;6:116–25.
[30] Kuperman AA, Koren O. Antibiotic use during pregnancy: how bad is it? BMC Med 2016;14:91.
[31] Roberts DJ, Celi AC, Riley LE, et al. Acute histologic chorioamnionitis at term: nearly always noninfectious. PLoS ONE 2012;7:e31819.
[32] Raba AA, O'Sullivan A, Semberova J, et al. Are antibiotics a risk factor for the development of necrotizing enterocolitis-case-control retrospective study. Eur J Pediatr 2019;178:923–8.
[33] Kenyon SL, Taylor DJ, Tarnow-Mordi W, et al. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. Lancet 2001;357:979–88.
[34] Westbrook RH, Yeoman AD, Agarwal K, et al. Outcomes of pregnancy following liver transplantation: the King's college hospital experience. Liver Transpl 2015;21:1153–9.
[35] Troisi R, Bjorge T, Gissler M, et al. The role of pregnancy, perinatal factors and hormones in maternal cancer risk: a review of the evidence. J Intern Med 2018;283:430–45.
[36] Lambe M, Hsieh C, Tsaih S, et al. Childbearing and the risk of Hodgkin's disease. Cancer Epidemiol Biomark Prev 1998;7:831–4.
[37] Ekstrom K, Wuu J, Hsieh CC, et al. Childbearing and the risk of leukemia in Sweden. Cancer Causes Control 2002;13:47–53.
[38] Everly MJ, Bloom RD, Tsai DE, et al. Posttransplant lymphoproliferative disorder. Ann Pharmacother 2007;41:1850–8.
[39] Zullo F, Saccone G, Donnarumma L, et al. Pregnancy after liver transplantation: a case series and review of the literature. J Maternal-Fetal Neonatal Med 2021;34:3269–76.
[40] Parhar KS, Gibson PS, Coffin CS. Pregnancy following liver transplantation: review of outcomes and recommendations for management. Can J Gastroenterol Hepatol 2012;26:621–6.
[41] Lim TY, Gonsalkorala E, Cannon MD, et al. Successful pregnancy outcomes following liver transplantation is predicted by renal function. Liver Transpl 2018;24:606–15.
[42] Coscia LA, Constantinescu S, Moritz MJ, et al. Report from the national transplantation pregnancy registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2009:103–22.
[43] Kainz A, Harabacz I, Cowlrick IS, et al. Analysis of 100 pregnancy outcomes in women treated systemically with tacrolimus. Transpl Int 2000;13(Suppl 1):S299–300.
[44] Nyberg G, Haljamae U, Frisenette-Fich C, et al. Breast-feeding during treatment with cyclosporine. Transplantation 1998;65:253–5.
[45] Osadchy A, Koren G. Cyclosporine and lactation: when the mother is willing to breastfeed. Ther Drug Monit 2011;33:147–8.
[46] Rahim MN, Theocharidou E, Yen Lau KG, et al. Safety and efficacy of *in vitro* fertilisation in patients with chronic liver disease and liver transplantation recipients. J Hepatol 2021;74:1407–15.
[47] Flemming JA, Velez MP. The ART of medicine: counselling women with liver disease about assisted reproductive technology. J Hepatol 2021;74:1283–5.
[48] Gong X, Li J, Yan J, et al. Pregnancy outcomes in female patients exposed to cyclosporin-based versus tacrolimus-based immunosuppressive regimens after liver/kidney transplantation: a systematic review and meta-analysis. J Clin Pharm Ther 2021;46:744–53.