



Pregnancy After Liver Transplant: Neonatal Outcomes and Long-Term Maternal Follow-up

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ABSTRACT

Background. Today, women who have undergone liver transplantation enjoy better health, so they encounter more frequently the possibility of living pregnancy. Many questions about the safety of pregnancy are pending. This study analyzes pregnancy outcomes in women with a liver transplant managed at Policlinico Universitario "A.Gemelli."

Results. We identified 17 childbirths in 13 women who had undergone a liver transplant. Causes of transplant include congenital or acquired disorders. The mean age at transplant was 22 ± 9 years, mean maternal age at delivery was 33 ± 5 years, and transplant-to-pregnancy interval was 12 ± 6 years. The mean gestational week was 36.1 ± 3.5 . All women had normal liver function after pregnancy. Immunosuppressive therapy before and during pregnancy included tacrolimus ($n = 8$), cyclosporine ($n = 5$) and mycophenolate mofetil ($n = 1$). No maternal death was registered. Maternal complications included increase of aspartate transaminase and alanine transaminase, graft deterioration requiring liver retransplantation, increase of bile acids ($n = 1$), itch ($n = 1$), and anemia ($n = 1$). Twelve women had a high adherence to an immunosuppressive regimen during pregnancy. A woman with poor compliance continued therapy with mycophenolic acid during pregnancy, showing preterm birth (25th week) with fetal respiratory failure. Another woman continued therapy with tacrolimus during breastfeeding without adverse effects.

Conclusion. Liver transplant does not influence women's fertility; during pregnancy, we report low rates of minor graft complications and no major issues. There are no adverse effects on babies. An evaluation by a multidisciplinary team is recommended. Compliance to an immunosuppressive regimen is fundamental to ensure the stability of graft function and to prevent graft deterioration in pregnancy. Moreover, it is suggested to avoid teratogenic drugs, such as mycophenolic acid.

THANKS to medical innovations, the number of successful liver transplants is increasing worldwide. Transplant statistics, as regularly reported from the Transplant National Center (Italy), indicate that 1094 patients in 2015 had undergone a liver transplant. As 31.7% of all liver transplant recipients are women, transplant physicians increasingly see pregnancies in their periodic follow-up [1]. A recent systematic review described the outcomes of 450 pregnancies in 306 liver transplant recipients and showed that although pregnancy complications such as miscarriages, preterm birth, preeclampsia, and cesarean deliveries were

lower than with renal transplants, they were still significantly higher than the general population [2]. As experience with the management of pregnancies in women following liver

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transplantation around the world continues to grow, it is hoped that pregnancy outcomes continue to improve [3]. To this end, the purpose of our study is to describe the experience of the Liver Transplantation Unit at “Fondazione Policlinico A. Gemelli”-UCSC in Rome.

MATERIALS AND METHODS

We retrospectively analyzed all patients who had undergone a transplant at the Liver Transplantation Unit at “Fondazione Policlinico A. Gemelli”-UCSC in Rome from 1991 to 2015. Then, we reviewed medical records and extracted data on: maternal demographics; details on the liver transplantation and graft health; immunosuppressive therapy and liver function at the onset of pregnancy; comorbidities; pregnancy-related outcomes (such as mode of conception and number of fetuses); maternal complications such as maternal death, graft rejection or failure; deterioration of liver function; gestational diabetes mellitus; hypertensive disorders of pregnancy including preeclampsia (elevated blood pressure after 20 weeks of gestation with proteinuria or in the absence of proteinuria but with the association of thrombocytopenia, impaired liver function, new-onset renal insufficiency, pulmonary edema, new-onset cerebral, or visual symptoms); gestational hypertension (elevated blood pressure after 20 weeks of gestation in the absence of proteinuria or other systemic findings); and chronic hypertension with superimposed preeclampsia. We also recorded fetal/neonatal data and outcomes including: mode of delivery, small for gestational age (defined as birth weight under the 10th percentile for gestational age), preterm births (defined as < 37 weeks of gestation), presence of congenital malformations, and admission to the neonatal intensive care unit. We also obtained data on long-term follow-up of both mother and infant where possible.

RESULTS

Maternal Characteristics

We identified 13 women who had 18 pregnancies following liver transplantation between 1990 and 2015. Among these, 17 were term-pregnancies, while 1 patient had an abortion.

The mean age at transplant was 22 ± 9 years, while the mean maternal age at delivery was 33 ± 5 years and the mean transplant-to-pregnancy interval was 12 ± 6 years. One pregnancy was conceived following assisted reproductive technique (in vitro fertilization). There were no twin pregnancies. The characteristics of these pregnancies, as well as the indications for transplantation and immunosuppressants used at the time of conception and during pregnancy, are described in Table 1. Three women (23%) had other significant comorbidities predating pregnancy such as diabetes ($n = 2$) and chronic hypertension ($n = 2$). All patients increased the frequency of routine check-ups (or outpatient follow-ups) in order to keep the immunosuppressant blood levels low, without graft risk. Maternal complications included: increase of aspartate transaminase and alanine transaminase from the eighth week of pregnancy ($n = 1$), increase of bile acids ($n = 1$), itch ($n = 1$), and anemia requiring blood transfusion ($n = 1$). A patient with difficult socioeconomic conditions continued to take mycophenolic acid during pregnancy. She underwent liver transplantation in another country and was lost to

Table 1. Liver Transplant Patients' Characteristics

Indication for Transplantation	
S. Crigler-Najjar	2
PSC	1
S. Caroli	2
HBV, HCV	2
S. Byler	1
ALF	2
S. Alagille	1
S. Wilson	2
Cryptogenic	1
Mean age at transplant	22 ± 9 y
Mean maternal age at delivery	33 ± 5 y
Mean transplant-to-pregnancy interval	12 ± 6 y
Immunosuppressive therapy	
Tacrolimus	8
Cyclosporine	5
Mycophenolate mofetil	1

ALF, autoimmune liver failure; HBV, hepatitis B virus; HCV, hepatitis C virus; PSC, primary sclerosant cholangitis; S, syndrome.

transplant follow-up due to her frequent moving. She came to our attention for obstetric complications during the 24th gestational week.

Pregnancy Outcomes (Table 2)

There were no maternal deaths. Among the 17 total pregnancies, 9 (52.9%) delivered preterm, with a range between 25 and 36 weeks of gestation; meanwhile, the general gestational age at the delivery was 36.1 ± 3.5 weeks. Only 3 women entered labor spontaneously, while 14 (82.4%) presented cesarean delivery on account of hypertensive disorders of pregnancy including preeclampsia and hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome ($n = 9$) and fetal wellbeing concerns or growth restriction ($n = 5$). It is noteworthy that patients with hypertensive disorders were promptly evaluated and treated by a devoted gynecologist so that they did not present clinical sequelae after delivery. A high cesarean rate was not influenced by the high frequency of preterm birth. In fact, analyzing a subgroup of 8 patients that delivered at term, it maintained a high rate of elective cesarean (6 cases, 75%) with obstetric indications.

Neonatal Outcomes

There were no congenital malformations. The average weight at birth was 2960 grams. Clinical characteristics at birth were stable, with an Apgar score > 7 in almost all

Table 2. Pregnancy Outcomes

	36 ± 3 wk
Pregnancy Total Mean Duration	n/tot (%)
Preterm birth (25-36 wk)	9/17 (52.9)
Elective cesarean section	14/17 (82.4)
Maternal hypertensive disorders	9/14
Fetal disorders	5/14

newborns. One infant, born from the patient taking mycophenolic acid, was small for gestational age and needed admission to the neonatal intensive care unit on account of respiratory and neuromotor failure, with a subsequent progressive improvement of the clinical conditions. There were no neonatal deaths. There was a case of natural breastfeeding of the child together with use of tacrolimus by the patient, without the onset of neonatal complications.

Long-Term Maternal Outcomes

Maternal follow-up was made by a medical multidisciplinary group formed by a hepatologist, a transplant surgeon, and a gynecologist specialized in risky pregnancies. Follow-up had a median of 5.4 years (range, 0.5-15 years). We found 1 case of transplant loss and 1 case of diabetes mellitus type II. The former patient had deterioration of graft function. The indication at the first transplant was Crigler-Najjar type I syndrome. About 21 weeks after delivery, her liver enzymes were found elevated on routine testing. She was started on IV steroids for a presumed diagnosis of graft rejection. The liver enzymes continued to increase. A diagnosis of rejection for previous inadequate compliance to the pharmacologic therapy was made. For this reason, she underwent a liver transplant 43 weeks after delivery (22 weeks after onset of hypertransaminasemia). Afterward, the patient was hospitalized 3 times: the first time with a diagnosis of chronic rejection, treated pharmacologically, and the second and third times for a biliar stenosis, treated with the insertion and then with a substitution of percutaneous biliar drainage. The other patient was diagnosed with diabetes mellitus type II 10 years after delivery, without deterioration of graft function or other liver complications.

DISCUSSION

The number of patients who are undergoing solid organ transplants is increasing, as is their quality of life and, for female patients, chance of pregnancy [4]. It is noted that 8% of liver transplant recipients are women of reproductive age and 5% are in pediatric age, most of whom will enter in reproductive age and will consider the possibility of pregnancy [13].

It is noteworthy that women with advanced liver disease have compromised reproductive function, with menstrual irregularities, amenorrhea, and infertility in about half the cases [5-7].

On the other hand, immunosuppression, abdominal surgery, advanced maternal age, and comorbidities are all factors that may place abdominal transplant recipients at risk during pregnancy [8].

In a work of Deshpande, recipients of kidney transplants have the possibility of a pregnancy that is viable even if high rates of obstetric complications (as hypertension, preeclampsia and gestational diabetes) and high-risk delivery outcomes (cesarean section, preterm birth, and low birth weight) are registered, in comparison with the general population [9]. In a successive study about liver transplantation,

the same group study showed that the live birth rate for pregnancies after liver transplantation exceeded the rate for the US general population and the chance of miscarriage was lower for liver recipients versus the US general population. Although postliver transplantation pregnancies were found to be viable, the risk of obstetrical complications was high; proportions higher than the US averages for non-terminated pregnancies were reported for preeclampsia, cesarean section delivery, and preterm births [2].

However, data about European countries are not available [10], above all about the Italian context.

For this reason, a retrospective research was conducted at the Liver Transplantation Unit of "Fondazione Policlinico A. Gemelli"-UCSC in Rome to analyze pregnancy outcomes in women who have received a liver transplant.

The aim of our study is to evaluate, first of all, modalities of conception to understand how important health care should be for the success of maternal project. In our population, only 1 pregnancy out of 16 began thanks to a medical procedure, an in vitro fertilization. Instead, the majority of them had a natural beginning; this is a proof that patients can conceive without many major postsurgery issues.

Another fundamental aspect is the rate of graft-related complications during the pregnancy. This is important to evaluate the feasibility of a project of maternity in liver transplant patients, with a subtle balance among hepatic function, immunosuppressive therapy, and gestational needs.

It is noteworthy that even the problems that the pregnancy may have suffered due to the transplant have been considered.

After the onset of gestation, we must consider the presence of another human being, the fetus, who becomes part of a life and a medical project of which the health system has the imperative to take care. For this reason, in our institute, patients expressing a desire for pregnancy during outpatient follow-up are included in a multidisciplinary surveillance program. This scheme includes an evaluation carried out by a group of clinicians formed by a hepatologist and a transplant surgeon, who know the patient's clinical history even before liver transplantation, supported by an obstetrician gynecologist and, subsequently, a neonatologist.

This program is the result of our assistance standard, not applied in all Italian or international institutions [11,12]. We wanted to evaluate our strategy feasibility and, eventually, success to justify an economic and care commitment and to standardize an assistance protocol.

In our population, major maternal complications during pregnancy included increase of aspartate transaminase and alanine transaminase from the eighth week of pregnancy ($n = 1$), increase of bile acids ($n = 1$), itch ($n = 1$), and anemia requiring blood transfusion ($n = 1$).

Furthermore, pregnancy-related complications were preeclampsia and HELLP syndrome (detected in 9 patients), as reported in other studies [13,14]. There were no major

clinical sequelae in all of these clinical cases, thanks to the continuous multidisciplinary evaluation that allowed for specific treatments.

Regarding fetus clinical conditions, we found good clinical characteristics in the majority of the population, with an Apgar score > 7 in all babies, except in a single one, the son of a patient who continued to independently take mofetil-mycophenolate during pregnancy, with a confirmation of the collateral effects [15], unlike other immunosuppressive drugs [16,17]. Because of respiratory and neuromotor failure, he was transferred to the ICU for support that stabilized his clinical condition. For this reason, no deaths were recorded among newborns.

The neonatologist's presence in the medical group ameliorated all patients prognosis thanks to the application of intensive assistance before the onset of clinical complication.

Outcome improvements in maternal and fetal clinical conditions are in line with the data in the literature [2–17] and reflect a need for clinical assistance standardization made up of a multidisciplinary medical group in which transplant clinicians (internist and surgeon) are supported by obstetrician and neonatologist specialists to provide patients the capacity to make plans and make their life more normal, the purpose of any medical activity.

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