

Pregnancy After Liver Transplant: Maternal and Perinatal Outcomes

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Abstract

Background: Liver transplantation is a life-saving and successful therapeutic procedure which is more and more frequent worldwide, also among women of reproductive age. Consequently, there is an increasing number of reports of pregnancy following liver transplantation, but doubts still exist regarding preconception counseling and the optimal method of managing pregnancy. The aim of this study was to report and evaluate pregnancy outcomes in women who had undergone liver transplantation.

Methods: We retrospectively analyzed female patients after orthotopic liver transplantation who reported pregnancy and were under medical care of a single transplant center.

Results: We identified 14 pregnancies in 10 women who had undergone liver transplantation (12 childbirths, one induced abortion due to fetal death in the first trimester, one pregnancy is still ongoing). Causes of transplantation include congenital or acquired disorders and the most common indication was autoimmune hepatitis (50%). The mean age at the point of transplantation was 28.5 (range 21–36), mean maternal age at pregnancy was 32 (range 26–43), and transplant-to-pregnancy interval was 4.07 years (range 1,5–7). The mean gestational week was 36.67 (range 31–40). Immunosuppression was maintained with combinations of prednisone (n=11), tacrolimus (n=13), and azathioprine (n=8) prior to and during pregnancy. Two pregnancies were unintended, so women took mycophenolate mofetil in the first weeks of gestation. Another two women stopped taking azathioprine due to increasing anemia. Maternal complications included increase of aspartate transaminase and alanine transaminase (n=2), anemia (n=4) and hyperthyroidism (n=2). Among the 12 childbirths, five (41,67%) were preterm. Only five women entered labor spontaneously, while seven (58,33%) had cesarean delivery.

Conclusions: Pregnancy after liver transplantation can achieve relatively favorable outcomes. It does not influence women's fertility and, during pregnancy, we report low rates of minor graft complications. A multidisciplinary team should be involved in contraceptive, fertility and consequently pregnancy counseling of female transplant recipients.

Background

Liver transplantation is a treatment for acute or chronic diseases, which is an effective life-saving procedure [1, 2, 3] and is increasingly performed all over the world. The number of liver transplants is also increasing among women of childbearing (reproductive) age [3, 4, 5]. Consequently, there is an increasing number of reports of pregnancy following liver transplantation but doubts still exist regarding preconception counseling and the optimal method of managing pregnancy.

Chronic organ failure disrupts the normal functioning of the gonads, so pregnancies are relatively rare. In women, this infertility results from a changed activity of the hypothalamus, and is associated with, among others, high levels of follicle stimulating hormone (FSH) or prolactin.

In the end stage of liver failure, women complain of irregular periods or their absence, very often they are infertile [3, 7, 8]. One of the effects of successful liver transplantation is the restoration of fertility and the ability to give birth to a healthy child in up to 97% of women [3, 7, 8].

Severe irreversible organ failure is associated with metabolic and endocrine disorders, often cachexia, loss of libido. A successful organ transplant one year after the procedure eliminates the negative effects of the disease, including the restoration of ovulation cycles [11, 12]. There is the possibility of having biological offspring. Many patients have this additional incentive and motivation to undergo numerous medical procedures related to transplantation. However, even in 30% of women, menstruation can return immediately after transplantation [14]. Therefore, it is very important to use effective contraception in organ recipients, because a necessary condition for a trouble-free pregnancy and delivery, and for the health of the fetus and newborn is a stable function of the transplanted organ. For this reason, it is recommended that a woman wait at least 12 months after transplantation until she begins conceiving a child.

Natural methods of contraception are not recommended due to their low effectiveness in preventing pregnancy in women with serious underlying diseases and using immunosuppressive drugs. Women with a liver transplant who have regular intercourse should use highly effective contraceptives. The use of hormonal contraceptives is most often recommended. In the early post-transplant period, the use of hormonal contraceptives may be of concern because of the potential interaction with calcineurin inhibitors, and uncontrolled fluctuations in drug levels may cause acute organ rejection [14]. An absolute contraindication to this type of contraception is unsatisfactory function of the transplanted organ or its rejection. It is important to systematically monitor the concentration of calcineurin inhibitors.

The first pregnancy in a liver recipient was reported in 1978, 15 years after the first successful liver transplant that took place in 1963 [11, 12, 13]. The European Liver Transplant Registry reports that approximately 75% of women who have had a liver transplant are of childbearing potential. Based on this information, an increase in the number of pregnancies in liver recipients can be expected [11].

Pregnancy after organ transplantation is a significant threat to the health of the mother, child and the further functioning of the transplanted organ. The best prognosis is to plan pregnancy in women with the lowest risk of rejection, while maintenance doses of immunosuppressants are used.

Pregnancy in a transplanted woman is a challenge for the interdisciplinary team of obstetrician-gynecologists, transplantologists, neonatologists and other specialists, depending on the patient's individual situation. Currently, there is no increase in the frequency of birth defects in the offspring of women who have undergone transplantation; however, the risk of low birth weight and prematurity and its complications remain a clinically significant problem.

Another important aspect to keep in mind when planning a pregnancy in a patient after a liver transplant is immunosuppressant medication she is taking. Most often, patients take the three-drug regimen: mycophenolate mofetil (MMF), tacrolimus and prednisone. The mycophenolate mofetil may cause

miscarriage in the first trimester of pregnancy; it is also responsible for numerous malformations in the fetus, for example: cleft lip and palate, microtia or lack of hearing channels. For this reason, MMF is absolutely contraindicated in pregnant women [14]. If a transplanted patient wishes to conceive a child, MMF must be discontinued approximately six weeks before conception.

This study analyzes maternal and perinatal outcomes in women with a liver transplant managed at the Department of Transplantation Medicine, Nephrology and Internal Medicine of the Medical University of Warsaw.

Methods

The aim of this study is to report and evaluate pregnancy outcomes in women who underwent liver transplantation.

We retrospectively analyzed medical records of 10 women who had undergone liver transplantation at the Department of General and Transplantation Surgery and were under further care of the doctors of the Department of Transplantation Medicine, Nephrology and Internal Medicine. The pregnancies were supervised at the Gynecology and Obstetrics Clinic of the Medical University of Warsaw. We qualified only those patients about whom full data were obtained. In our center, autoimmune diseases are treated with triple immunosuppression: prednisone, tacrolimus, mycophenolate mofetil. If there is information about a planned pregnancy at least six weeks before conception, immunosuppression is modified, and azathioprine is included. We extracted data on: details of the liver transplantation and graft health before and after pregnancy, immunosuppressive therapy and liver function, comorbidities, pregnancy-related outcomes (such as mode of conception and number of fetuses), maternal complications such as maternal death, graft rejection or failure, way of ending pregnancy, date of delivery: weight, length and number of points on the APGAR scale of the child after delivery.

We also obtained data on long-term follow-up of both mother and infant where possible.

Results

Maternal Characteristics

We identified 14 pregnancies in 10 women who had undergone a liver transplant - 12 childbirths and one induced abortion due to fetal death in the first trimester. The 14th pregnancy is still ongoing, one of our patients has once again decided to become a mother and is now in her second pregnancy. The patient is currently in the third trimester of pregnancy, the pregnancy is proceeding without complications. Due to incomplete data, we did not include this (14th) pregnancy in the statistics.

The mean age at the point of transplantation was 28.5 (range 21–36), mean maternal age at pregnancy was 32 (range 26–43), and transplant-to-pregnancy interval was 4.07 years (range 1.5–7). Causes of transplant include congenital or acquired disorders described in Table 1. The most common indication for

liver transplantation was autoimmune hepatitis (50%). The patient with HCV had no active infection at the time of pregnancy.

All of the pregnancies were conceived naturally. There were no twin pregnancies. Immunosuppression was maintained with combinations of prednisone (n=11), tacrolimus (n=13), and azathioprine (n=8) prior to and during pregnancy. Two pregnancies were unintended, so women took mycophenolate mofetil in the first weeks of gestation. Another two women stopped taking azathioprine due to increasing anemia. Maternal complications included increase of aspartate transaminase and alanine transaminase (n=2), anemia (n=4), hyperthyroidism (n=2), leukopenia and thrombocytopenia (n=1), asymptomatic leukocyturia (n=1) and erythrocyturia (n=1). One of the patients with hyperthyroidism had AIH and the other Wilson's disease – it is rather a coincidence.

One patient was found to have an active HBV infection during pregnancy. In accordance with the guidelines, treatment with tenofovir was started in the third trimester (the only drug approved for the treatment of pregnant women). The child received anti-HBs globulin, was vaccinated on the first day and has no HBV DNA.

Laboratory results are presented in Table 2.

Pregnancy outcomes

There were no maternal deaths. Among the 12 total childbirths, five (41,67%) delivered preterm, with a range between 31 and 36 weeks of gestation. The degree of anemia had no effect on preterm labor. Meanwhile, the general gestational age was 36.67 (range 31–40). Only five women entered labor spontaneously, while seven (58.33%) presented cesarean delivery. A high cesarean rate was not influenced by the high frequency of preterm birth. In fact, analyzing a subgroup of seven patients that delivered at term revealed a high rate of elective cesarean (four cases, 57.14%) with obstetric indications. Only one woman breastfed her child. It was the patient's choice after consultation with gynecologists. Previous recommendations ruled out the possibility of breastfeeding after transplantation. After delivery, lactation was stopped. Gynecologists' research on the concentration of tacrolimus in breast milk showed it to be minimal. Although there are still no clear guidelines for breastfeeding, if the mother wants to breastfeed, there are no absolute contraindications.

Neonatal outcomes

There were no major congenital malformations (one infant was diagnosed with tricuspid regurgitation). The average weight at birth was 2,775.83 g (range 1,140–3,600 g) and the average length was 51.33 cm (range 38–58 cm). Five of 12 neonates (41.67%) demonstrated low birth weights, which were defined as less than 2,500 g. The lowest birth weight occurred in a newborn weighing 1,140 g, who was born in 31 Hbd and diagnosed with intrauterine hypotrophy. There were seven female and five male newborns. Clinical characteristics at birth were stable, with an Apgar score > 8 in almost all newborns. Three infants

required assisted breathing (CPAP – Continuous Positive Airway Pressure), with a subsequent progressive improvement of the clinical conditions. There were no neonatal deaths.

Children outcomes

We should also pay attention to the long-term development of liver transplant patients' children. We looked at all 12 children of our patients. The average age of children is 6.08 years (range 1–14 years). All children develop harmoniously, with proper psychomotor development and no intellectual retardation in school-age children, who do not stand out from their peers. The mother of one of the children reports that the child is very lively, to the point of being hyperactive. One child was diagnosed with attention-deficit hyperactivity disorder (ADHD), but the child's mother had a similar personality. One child was born with one kidney, the other is healthy, the baby's health functions are proper. One child had a patent Botall's duct. One child was diagnosed with tricuspid regurgitation (3mm) after delivery, fortunately the deficit was overgrown and no surgery was needed. Now, seven years later, valvular regurgitation is 1mm. Both children are under constant supervision of a cardiologist and their development is normal.

Discussion

Women with chronic liver disease have a very low chance of conceiving and carrying a pregnancy. It is caused by irregular menstrual cycles and often no menstruation at all. Liver transplantation gives women a chance to become mothers. It was noticed that even six weeks after transplantation, female fertility returns. Almost 90% of female recipients have regular periods one year after the liver transplant [11, 15].

The latest research shows that with the proper functioning of the transplant, a woman can give birth to a healthy child. It is recommended that a woman should wait at least one year (preferably two years) after the transplant to begin trying to get pregnant. If conception occurs in the first year after transplantation, there is a high risk of prematurity and rejection in the organ recipient.

According to The US National Transplantation Pregnancy Registry (NTPR) in 2006, only 58% of pregnancies in women after liver transplantation ended with the birth of a live child; according to the data from 2012, the percentage of these cases increased to 77% [11, 12]. In our study, the percentage of live births was as high as 92.3%. There was only one spontaneous miscarriage in the first trimester of pregnancy, and no stillbirths.

Despite the ever increasing number of pregnant transplant recipients, little is known about the course of pregnancy and complications in women after liver transplantation. For this reason, these women should be assigned to the high-risk pregnancy group and should be under constant care of an interdisciplinary team composed of doctors of various specialties. Fetal development should be monitored with equal care, as well as the mother's health and the function of the transplanted organ.

In our study, the mean transplant-to-pregnancy interval was 4.07 years. Other studies have noted a wide range of graft rejections from 0–17% [7, 16, 19, 20]. In our study, patients were not diagnosed with acute

rejection episodes (0%).

It is important that women who have had a liver transplant during pregnancy and in the postpartum period are exposed to many complications. Common complications include hemorrhage, the need for blood transfusions, hypertension, gestational cholestasis, and hypertension.

The most common complication in pregnant women after liver transplantation is anemia. It is associated with both the long-term use of immunosuppressive drugs and the physiology of pregnancy itself [11]. In our study, 40% of the women surveyed suffered from anemia during pregnancy.

Blood transfusions were required in three cases. Anemia was a big problem in our patients, the values of hemoglobin and erythrocytes in laboratory results were statistically significantly decreased ($p < 0.05$).

In two women (20%) an increased activity of aspartate transaminase and alanine transaminase was observed; hyperthyroidism was also observed in 20% of women; likewise, leukopenia and thrombocytopenia were observed in 20% of women, while 10% suffered from asymptomatic leukocyturia and erythrocyturia. We do not see a relationship between hyperthyroidism and the fact that the patients underwent liver transplantation or pregnancy. It is probably a coincidence.

Additional risk factors for the course of pregnancy may include the mother's age, her medical history with multiple surgical interventions, and the mother's underlying disease.

The next stage of our work was the analysis of the results for fetuses and newborns born to women after liver transplantation.

Many authors mention prematurity and inhibition of intrauterine growth as the most common complications. In our study group, 41.67% of children were born prematurely, and 8.33% ($n = 1$) had intrauterine hypotrophy.

In immunosuppressive treatment regimens, several drugs with different mechanisms of action (usually 2 or 3) are combined. These drugs include: calcineurin inhibitors (tacrolimus, tacrolimus with modified release, tacrolimus with extended release (LCPT)), mycophenolates (mycophenolate sodium, mycophenolate mofetil), glucocorticosteroids, drugs inhibiting cell division (azathioprine) and mTOR inhibitors (sirolimus). The most common regimen used in the treatment of a vascularized organ transplant patient is calcineurin inhibitor + mycophenolate + glucocorticosteroid [21, 22].

Pregnancy is not a reason to discontinue immunosuppressive therapy. Organ recipients must take immunosuppressants throughout pregnancy to prevent organ rejection and loss. A patient expecting a baby can safely use drugs such as glucocorticosteroids, tacrolimus, azathioprine or cyclosporine A. However, mycophenolates and mTOR inhibitors are contraindicated. [21, 22].

In our center, autoimmune diseases are carried out with triple immunosuppression: encorton, tacrolimus and mycophenolate mofetil. If there is information about a planned pregnancy at least six weeks before

the pregnancy, the immunosuppression to azathioprine is modified.

The conducted study was limited by a small number of patients (n = 10), but in the group subjected to detailed analysis, we did not observe an increased risk of birth defects in the fetus. The results of our study confirm that the immunosuppressants used (prednisone, tacrolimus, azathioprine) do not adversely affect the fetus.

Due to postoperative wounds and adhesions, vaginal delivery is preferred in women after transplantation. However, there is now an increasing trend towards cesarean delivery, which is also reflected in transplant patients. All cesarean sections in our study group accounted for as much as 58.33% of all deliveries, and all of them had obstetric indications.

Fetal development should be monitored with equal care, as well as the mother's health and the function of the transplanted organ.

Also of interest is the fact that the our patents' children develop properly after several years of observation. They do not stand out from their peers both in terms of growth and intellectual development.

Conclusions

In conclusion, pregnancies after liver transplantation have a good chance of being successful. Nevertheless, pregnancy in female recipients is much riskier than in the general population of healthy women. Therefore, the issue of fertility and maternity planning should be widely discussed with the patient and her partner. A pregnant patient and her child should be looked after by a multidisciplinary team to ensure their safety as much as possible. The long-term health status of liver transplant recipients and their babies should continue to be assessed.

List Of Abbreviations

FSH - follicle stimulating hormone

MMF - mycophenolate mofetil

AIH – autoimmune hepatitis

CPAP – Continuous Positive Airway Pressure

ADHD - attention-deficit hyperactivity disorder

NTPR - National Transplantation Pregnancy Registry

LCPT - tacrolimus with extended release

Declarations

Ethics approval and consent to participate: This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the Bioethics Committee of Medical University of Warsaw who determined that our study did not need ethical approval. A Bioethics Committee's official statement of ethical approval was granted from the Bioethics Committee of Medical University of Warsaw. All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all subjects.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions:

I Marzec: Data collection and management, Data analysis, Manuscript writing and editing

A Słowakiewicz: Data collection and management, Data analysis, Manuscript writing and editing

J Gozdowska: Project development, Data collection and management, Data analysis, Manuscript editing

O Tronina: Data collection and management

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Tables

Indication	Number of patients
Autoimmune hepatitis (AIH)	5
Wilson's disease	3
Budd–Chiari syndrome	2
HCV	1

	PRE-PREGNANCY	PRE-LABOUR	POST-LABOUR	P
WBC (G/l)	5.91	7.40	5.35	NS
RBC (T/l)	4.63	3.57	3.74	<0.05
HGB (mg/dl)	13.03	11.17	11.51	<0.05
PLT (G/l)	209.62	159.25	198.25	NS
Glucose (mg/dl)	82.08	82.00	83.18	NS
ALT (U/l)	30.69	30.08	22.83	NS
AST (U/l)	25.92	25.58	19.25	NS
Bilirubin (mg/dl)	0.55	0.50	0.47	NS
GGT (U/l)	21.23	12.10	20.50	NS
Albumin (g/dl)	4.41	3.22	3.92	NS