PREGNANCY IN LIVER RECIPIENTS – MANAGEMENT AND OUTCOME. REVIEW.

Krzysztof Jaroń1, Monika Bieniasz2, Agnieszka Dobrowolska-Redo3, Julia Zaręba-Szczudlik3, Joanna Kacperczyk3, Aneta Malinowska-Polubiec3, Artur Kwiatkowski2, Ewa Romejko-Wolniewicz2

1. Students’ Scientific Group affiliated to 2nd Department of Obstetrics and Gynecology, First Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
2. Department of General and Transplantation Surgery, Medical University of Warsaw, Warsaw, Poland
3. 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Warsaw, Poland

#Corresponding author: Monika Bieniasz MD, PhD, e-mail: monicabien@o2.pl. Department of General and Transplantation Surgery, Medical University of Warsaw, Nowogrodzka St 59, p.o. box 02-006 Warsaw, Poland, phone number: + 48 22 502 14 70, fax: + 48 22 502 21 55

RUNNING TITLE Pregnancy in liver recipients

KEYWORDS liver transplantation, pregnancy, transplant recipients, breastfeeding, complications, premature birth

WORD COUNT 1839

CONFLICT OF INTERESTS no conflicts of interest

ABSTRACT
Possession of the offspring and experiencing maternity is desired by many women, including solid-organ transplant recipients. The number of women post liver transplantation (LT) in reproductive age in the USA is approximately 14,000 and raises up to 500 more new cases each year. Moreover, 1/3 of LTs is performed in women of reproductive age. It is necessary to emphasize that pregnancy after LT is a high risk pregnancy, yet it does not increase the risk of graft rejection. In 2017 the first case of woman giving birth to a healthy child after ABO-incompatible LT was described. A period of 1-2 years between LT and conception is considered safe. Complications of pregnancy such as increased risk of hypertension, preeclampsia or gestational diabetes are more frequent among liver recipients than in general population. Increased risk of low birth weight, preterm birth and graft rejection were reported if the conceiving took place within the first year after transplantation. Choosing the right lifestyle, contraceptives and preventing drug interactions are pivotal tasks for the gynaecologist at the time. Management of patients wishing to become pregnant after LT should be based on the lowest effective dose of immunosuppressant. Calcineurin inhibitors and glucocorticosteroids are currently recommended in this group of patients.
BACKGROUND

The first pregnancy after liver transplantation (LT) took place in 1978. Patient gave birth one year after the surgery to a healthy newborn, weighing 2400 g [1, 2]. Since then, the number of women deciding to become pregnant has been gradually increasing, as does the number of transplantations. Deshpande NA et al. estimated in 2011 that the number of women post liver transplantation in reproductive age in the USA is approximately 14 000 and raises up to 500 more new cases each year [3]. Moreover, 1/3 of LTs is performed in women of reproductive age (18-49 years old) [4].

Fertility

Liver is a multifunctional organ responsible for various physiological processes, including maintenance of fertility. It is, therefore, not surprising that women suffering from liver failure have problems conceiving. The reason is usually a dysfunctional hypothalamic-pituitary-ovarian axis, caused by increased serum level of testosterone and estradiol resulting in ovulation inhibition [1]. Hormonal balance and fertility may be restored after LT as, on average, 80% of women up to 8 weeks after surgery report normal menstruations and libido return [1].

Graft Survival

Pregnancy does not increase the risk of graft rejection [4]. The best prognosis of graft survival in women was reported in the Japanese population with majority (97%) of live donor transplantations [4]. Typically, 5-year survival after liver transplantation is over 70% [2, 5].

However, Kanazaki Y. et al. also demonstrated a 10-year survival rate of 70% [4]. Various studies report hepatic rejection rate in 10-17% of pregnancies [6]. All the more interesting is the work of Higashi et al. published in 2017, describing the case of a 39-year-old woman who gave birth to a healthy child after ABO-incompatible liver transplantation [7].

The current state of knowledge does not specify whether the risk of graft rejection is correlated with the indications for LT. Acute cellular rejection (ACR) during pregnancy occurs in 13-17% of cases [5, 8]. Unfortunately, the mechanism by which transplant rejection occurs during pregnancy is unknown. Therefore, it is necessary to monitor the activity of liver enzymes during its duration, as their growth may be the first sign of ACR [9].

Accompanying complications

Pregnancy after LT is a high risk pregnancy. Complications of pregnancy such as increased risk of hypertension, preeclampsia or gestational diabetes are more frequent among liver recipients than in general population [4]. The increased risk of diabetes can be related to chronic steroid therapy. Maternal complications following LT include: risk of impaired renal function, increased risk of recurrent respiratory and urinary tract infections, increased risk of miscarriage [4]. Complications to the child include lower birth weight and the risk of prematurity [1, 2, 10].

Therefore, blood pressure during pregnancy should be closely monitored [4]. Fetal ultrasound performed once a month allows the assessment of child’s growth and well-being. IgM antibody detection against Toxoplasma gondii and Herpes simplex virus in seronegative women) in each trimester is recommended [11].

Contraception

Choosing the right lifestyle, contraceptives and preventing drug interactions are pivotal tasks for the gynecologist care within the first year post transplantation. As unsuccessful and even opposed are periodic abstinence and coitus interruptus for contraception purpose [3]. Condoms provide safe barrier protection against sexually transmitted diseases. They should be recommended to patients who do not have permanent partners [12]. Intravaginal therapeutic systems, while allowing to avoid drug interactions and having high efficacy, may increase the risk of infection [13]. Contraindications for oral or transdermal contraception are the same as for the general population [4]. When choosing contraception, it should be kept in mind that tacrolimus (TAC) is metabolised by CYP3A5, whereas cyclosporine A (CsA) by CYP3A4 [4, 14, 15]. Although there are some authors who did not notice significant cardiovascular complications in their patients, increased thromboembolic risk or transplant rejection risk while concomitantly using oral contraceptives were reported [13, 16].

Preconception care

Undoubtedly, the decision to become pregnant should be considered and consulted with the transplantologist and gynecologist regarding patient’s age, time since transplantation and type of applied immunosuppression [3]. 9-12 month period between LT and conceiving is considered safe [2]. However, some authors recommend gap prolongation to over 2 years, claiming better prognosis for mother and child [17]. Low birth weight, increased preterm births, or transplant rejection were reported if the conceiving took place within the first year after LT [3]. The mean time after conception is about 4.8 years and the average age of patients is 28.6 years [3].

According to the recommendations of the American Society of Transplantation, an informed decision to conceive after LT can be made when the following conditions are met (Table 1) [12].

Systematic monitoring of the aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase levels and blood coagulation system parameters is necessary even if the patient does not present any symptoms of liver dysfunction. Platelet count and fibrinogen level monitoring is important especially for the purpose of postpartum hemorrhage prophylaxis [16]. Additional attention should be paid to the possibility of intrahepatic cholestasis of pregnancy (ICP) in liver transplant recipients. It may be difficult to differentiate ICP from graft rejection.

Management

Treatment of patients wishing to become pregnant after LT should be based on the lowest effective dose of immunosuppressant [4]. Calcineurin inhibitors such as cyclosporine and tacrolimus belong to the category C drugs and are not teratogenic. TAC is a drug preferred by most transplant centres. Cyclosporine and TAC pass through the placenta [4, 14].
TAC binds to erythrocytes in 85-95% [14]. From 2 months after LT, blood TAC concentration should be 8-10 ng/ml in a two-way immunosuppressive regimen. In the case of triple therapy, the recommended TAC concentrations in whole venous blood are approximately 5 ng/ml [18]. Reports of miscarriage, premature births and inhibition of intrauterine growth are generally associated with drug overconcentration in whole venous blood in the range of 8.5-9.9 ng/ml [4, 13]. In turn, the dose reduction to 1.3-4.6 mg/ml as in Kanzaki Y’s et al. study, resulted in an increase in ACR to 38% [9]. In addition, CYP3A7 in fetus is 50% of CYP-450, and is replaced by CYP3A4 only after delivery. In addition, CYP3A7 in fetus has, respectively, 29% and 18% catalytic capacity as compared to CYP3A4 and CYP3A5 [18]. In the studies of Zheng et al. mother’s whole venous blood TAC concentration was 9.0±3.4 ng/ml and 6.6±1.8 ng/ml in venous blood of the umbilical cord, constituting 71±18% (range 45-99%). TAC concentrations in the umbilical vein plasma was 23±11% (range 12-44%) of the drug concentration in mother’s plasma [15].

For patients receiving treatment based on calcineurin inhibitors, it is essential to monitor renal function and drug concentrations due to increased creatinine clearance during pregnancy [4]. It has been demonstrated that the use of CsA increases the risk of renal failure, hypertension and preeclampsia [3], as does the graft loss over 2 years compared to TAC [6].

Short-acting glucocorticoids such as methylprednisolone, prednisone, prednisolone belong to category B and are metabolised by the placental enzyme 11 beta-hydroxysteroid dehydrogenase. The ratio of the drug concentration in umbilical blood to maternal blood is 1:10, which means that the fetus receives 10% of mother’s dose [4, 19]. Research performed on animal models proved that administration of glucocorticoids (Prednisone, Prednisolone, Methylprednisolone) during pregnancy increased the risk of orofacial cleft, intrauterine growth restriction and decreased birth weight in the newborn. According to the United States Food and Drug Administration, at present there is no evidence that either prednisone or methylprednisolone is teratogenic in humans [4, 19].

Azathioprine (AZA) is category D drug. Therefore, the use of AZA during pregnancy or breastfeeding is controversial (4). It crosses the placental barrier, but the absence of fetal enzymes converting it to active metabolites seems to have a protective effect in this case [21]. Cases of both intrauterine growth restriction (IUGR) and births of healthy children following AZA intake are reported [4]. AZA dose reduction from 32 week of gestation can prevent leuko- and thrombocytopenia. In addition, maintaining a leukocyte count of more than 7500 per mm³ in the mother, in most cases, protects the foetus from leukopenia [22]. During such therapy, the monitoring of the patient and the foetus is crucial to its success.

Mycophenolate mofetil (MMF) is a teratogenic drug (category D), forbidden in pregnancy. The mechanism of action which is based on the inhibition of purine formation significantly increases the risk of intrauterine death and birth defects, i.e. cleft lip and palate malformations, as described in the Sifonis study [4, 23].

Sirolimus and everolimus (m-TOR inhibitors) are contraindicated during pregnancy and should be discontinued 12 weeks prior to planned procreation. Conversion to calcineurin inhibitors is recommended [4]. Due to the small amount of research on these drugs they are currently classified as category C. However, there are also studies showing the effectiveness of such therapy in pregnancy with positive results for the mother and the foetus [16, 17].

Childbirth

No significant contraindications to vaginal birth in liver transplant recipients were reported [2]. They are the same as for the general population. Nevertheless, a tendency is noticeable, as in case of healthy women, to end pregnancy by the caesarean section. Frequency of this procedure oscillates within 30-63% of pregnancies after LT [6]. In studies of Jabiry-Ziemińwicz et al., there was no statistically significant difference between vaginal birth and caesarean section in terms of: fetal weight (2.828 vs. 2.830 g), maternal age at birth (21.3 vs. 22.4 years) and gestational age (36.7 vs. 37.1 week of gestation) [16]. Due to increased risk of perinatal infection, antibiotic (penicillin or cephalosporin) and a single dose of glucocorticosteroids are recommended. After pregnancy, a regimen of treatment based on immunosuppressant serum concentrations is modified [11].

Breastfeeding

The American Society of Transplantation does not perceive breastfeeding during immunosuppression as contraindicated if monitoring of drug concentration in infant’s body is possible [12]. In studies of mothers receiving cyclosporine, drug concentration in breast milk 2 hours after administration was 50-227 ng/ml, with concentration in infant’s whole vein blood was lower than 30 ng/ml [24]. For patients receiving TAC twice a day at a dose of 1.5 mg, the concentration of drug in breast milk 6 h post administration was on average 0.93 ng/ml, and the daily milking was 32.0 ng, corresponding to 0.059% of the mother’s dose converted to kg of body weight (54.4 mg/kg/day) [15]. During a 3-month treatment, this value is 0.14 µg/kg/day, which is 0.3% of the mother’s dose converted to kg of the body weight [15]. Bramham et al. concluded that breastfed babies did not have higher TAC concentrations in free venous blood than those fed artificially [18].

The American Academy of Paediatrics recommends prednisolone and prednisone as safe drugs in breastfeeding, although they can be found in breast milk in low concentrations. No side effects associated with this have been observed [4]. In most recommendations, breastfeeding during MMF, AZA and mTOR inhibitors intake is contraindicated [6].

CONCLUSION

Adequate cooperation between transplantologist and gynaecologist, together with patient’s compliance - systematic drug use and recommended lifestyle, make it possible for women with liver transplantation to be
optimistic about their ability to have healthy children in future.

CITE THIS AS

ABBREVIATIONS

ACR – acute cellular rejection
ALT – alanine aminotransferase
AST – aspartate aminotransferase
CsA – cyclosporine A
ICP – of intrahepatic cholestasis of pregnancy
IUGR – intrauterine growth restriction
LT – liver transplantation
TAC – tacrolimus

REFERENCES


LIST OF THE TABLES

Tab. 1. Conditions required for safe conception in liver recipients – Recommendations of the American Society of Transplantation [12].
**TAB. 1. CONDITIONS REQUIRED FOR SAFE CONCEPTION IN LIVER RECIPIENTS – RECOMMENDATIONS OF THE AMERICAN SOCIETY OF TRANSPLANTATION [12]**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Proper functioning of the graft (monitored by the level of activity of liver enzymes: AST, ALT)</td>
</tr>
<tr>
<td>2.</td>
<td>Normal liver image found in abdominal ultrasound</td>
</tr>
<tr>
<td>3.</td>
<td>No acute infection which may adversely affect the graft or fetus</td>
</tr>
<tr>
<td>4.</td>
<td>Normal levels of immunosuppressive drugs in the blood</td>
</tr>
<tr>
<td>5.</td>
<td>No episodes of acute rejection within the year preceding the decision to conceive</td>
</tr>
</tbody>
</table>