Pregnancy in Liver Transplantation

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Pregnancy after liver transplantation (LT) is increasingly common and is a frequent scenario that transplant physicians, obstetricians, and midwives encounter. This review summarizes the key issues surrounding preconception, pregnancy-related outcomes, immunosuppression, and breastfeeding in female LT recipients. Prepregnancy counseling in these patients should include recommendations to delay conception for at least 1-2 years after LT and discussions about effective methods of contraception. Female LT recipients are generally recommended to continue immunosuppression during pregnancy to prevent allograft rejection; however, individual regimens may need to be altered. Although pregnancy outcomes are overall favorable, there is an increased risk of maternal and fetal complications. Pregnancy in this cohort remains high risk and should be managed vigilantly in a multidisciplinary setting. We aim to review the available evidence from national registries, population-based studies, and case series and to provide recommendations for attending clinicians.

Liver Transplantation 26 564–581 2020 AASLD.
Received September 29, 2019; accepted December 26, 2019.

Preconception

FERTILITY BEFORE LIVER TRANSPLANTATION

Pregnancy in patients with cirrhosis was previously uncommon but is now increasing in frequency.[1,2] This relates to increased awareness and demand from patients as well as improved clinical care, prepregnancy counseling, and methods of assisted conception.

Abbreviations: ACR, acute cellular rejection; AIH, autoimmune hepatitis; BW, birth weight; CMV, cytomegalovirus; COC, combined oral contraceptive; eGFR, estimated glomerular filtration rate; FBC, full blood count; FDA, US Food and Drug Administration; FSH, follicle-stimulating hormone; GD, gestational diabetes; GnRH, gonadotropin-releasing hormone; HIV, human immunodeficiency virus; IUD, intrauterine device; IUGR, intrauterine growth restriction; KT, kidney transplantation; LBR, live birth rate; LBW, low birth weight; LFT, liver function test; LH, luteinizing hormone; LT, liver transplantation; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; NTPR, National Transplantation Pregnancy Registry; PIH, pregnancy-induced hypertension; U&E, urea and electrolytes.

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Approximately 30%-50% of females with chronic liver disease report amenorrhea.[3,4] The prevalence of amenorrhea appears to be higher in patients with established cirrhosis compared with those with cholestatic disorders, which are more likely to present with menorrhagia. The etiology of liver disease, nutritional status, and metabolic/endocrine dysfunction all play roles in the pathogenesis of amenorrhea.

Hypothalamic function and the release of gonadotropin-releasing hormone (GnRH) are influenced by several factors. Malnutrition itself can cause hypothalamic hypogonadotrophic amenorrhea. Cirrhosis can independently affect hypothalamic function as well. Hepatic encephalopathy may influence the hypothalamic release of GnRH through effects on growth hormone and the adrenal axis.[5,6] Disruption of the hypothalamic-pituitary axis in conjunction with impaired hepatic metabolism of sex hormones, portosystemic shunting of weak androgens, and peripheral aromatization of androgens leads to hormonal imbalance (Fig. 1). The initial stages of liver disease can be associated with increased estrogen levels. However, the estrogen balance in more advanced disease is less clear, with some studies suggesting that estradiol levels are low.[7]

Rates of alcohol-related liver disease, including alcoholic hepatitis, in women of childbearing age is increasing in the United States and other parts of the

world.[8,9] Alcohol can influence the hypothalamic-pituitary axis and directly alter ovarian function, as demonstrated by the absence of corpora lutea and the impaired development of follicles in a histological study on ovaries in women who died of alcohol-related cirrhosis.[10] This can lead to features of primary gonadal failure with low estradiol levels and blunted GnRH release.

Studies have demonstrated variable changes in follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol, and progesterone before and after liver transplantation (LT).[7,11] A systematic review, of which only 4/12 studies included women, showed that estradiol and prolactin levels are elevated prior to LT and decrease afterward.[12] FSH and LH tend to increase after LT. Larger studies are required to understand the exact hormonal mechanisms involved.

FERTILITY AND SEXUAL FUNCTION AFTER LT

Menstruation can occur as early as the first month after transplantation with 70%-95% of recipients experiencing normalization within a year.[3,4,7,13] This implies that fertility is promptly restored after LT, likely due to the rebalancing of sex hormones. Alterations in pituitary function as a result of feedback mechanisms also reverse.

An imbalance between progesterone and estrogen may explain persistent anovulation in female LT recipients (Fig. 2). Consequently, relative hyperestrogenic states contribute to an increased risk of gynecological pathologies, eg, uterine bleeding from endometrial hyperplasia. Progesterone has been shown to reduce vaginal bleeding in LT recipients.[14]

Michael A. Heneghan and Mussarat N. Rahim are recipients of funding from the Sidney Orpin Bequest, a King's College Hospital charity. Michael A Heneghan is the recipient of a European Association for the Study of the Liver registry grant for pregnancy-related liver disease.

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View this article online at wileyonlinelibrary.com.

DOI 10.1002/lt.25717

Sexual dysfunction is complex. Factors such as age, social circumstance, drug side effects, and disturbances in sexual desire can all reduce sexual activity. A number of these factors improve after LT, but there is still a proportion of patients who experience problems after LT.[11,15] Sorrell et al. showed that female recipients who failed to recover sexual function had issues with self-worth as a result of unemployment, continued health problems, changes in body image, and depression.[15]

TIMING OF PREGNANCY

In those patients in whom fertility is restored, most experts would recommend waiting at least a year, and some even 2 years, after LT before planning a pregnancy.[16,17] The reasons for this include more predictable graft function, complete postoperative healing, lower levels of immunosuppression, lower risks of opportunistic infections, and reduced rates of acute cellular rejection (ACR) during this phase of transplantation.

The National Transplantation Pregnancy Registry (NTPR) is a questionnaire-based US registry investigating pregnancy outcomes in solid organ transplant recipients. A report from 2009 demonstrated that a transplant-to-conception interval of >2 years was associated with reduced rates of low birth weight (LBW), rejection, and graft loss. Risks for these outcomes were highest in women conceiving within 6 months of LT.[18] Additionally, 1 single-center study reported only 1 successful live birth in 7 out of 38 pregnancies conceived within 12 months of LT. Consequently, the authors recommended delaying conception for at least 2 years after LT.[19]

Another single-center study of 71 pregnancies reported no difference in the live birth rate (LBR) between their early group (conceived within first year of LT) and late group (conceived >1 year after LT). However, they observed increased rates of prematurity, LBW, and ACR in the early group. On the basis of these findings, the authors recommended delaying pregnancy for at least a year after LT.[20]

Higher-risk patients, ie, those with recent ACR, erratic graft function, or graft failure, are more likely to encounter poorer pregnancy outcomes. As such, it is appropriate to delay pregnancy in these patients and to have a period of observation prior to conception, eg, 3-6 months. Careful prepregnancy counseling and multidisciplinary input during this time with a medical obstetrician is advisable.

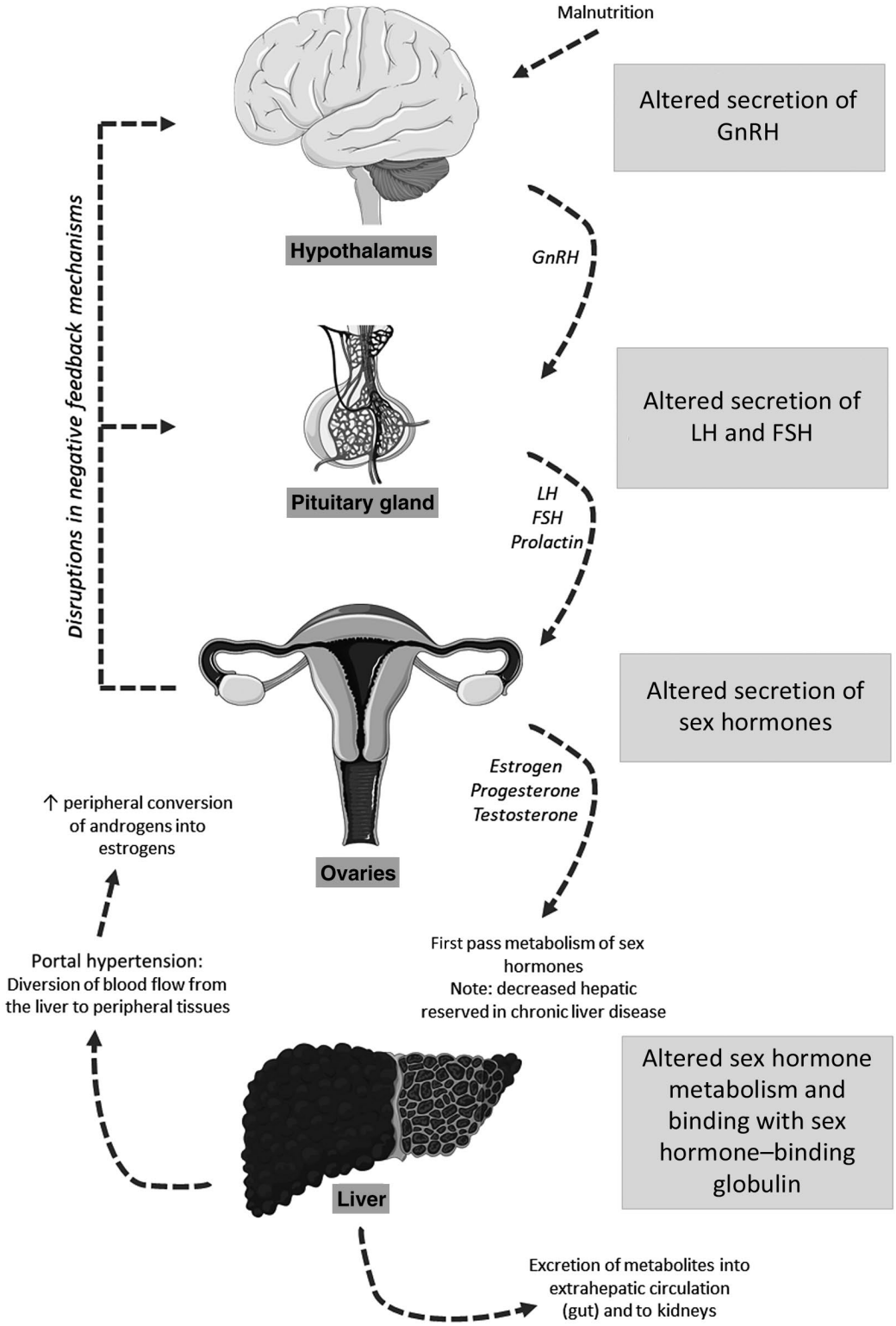

FIG. 1. The hypothalamic-pituitary axis in a female with chronic liver disease.

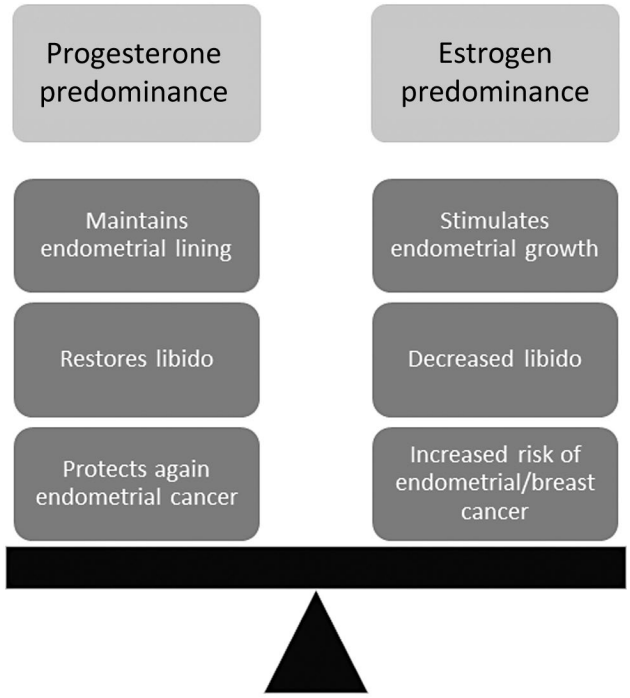

FIG. 2. Schematic representation of estrogen-progesterone imbalance.

MODE OF CONTRACEPTION

In post-LT recipients where pregnancy should be delayed or the patient wishes to defer starting a family, appropriate methods of contraception should be discussed. The ideal method of contraception for female LT recipients is unknown. Many women will be seeking safe, effective, and reversible options (Table 1). Female sterilization or partner vasectomy can be considered in patients who have completed their family.

Intrauterine devices (IUDs) may have reduced efficacy in immunosuppressed patients, secondary to reduced anti-inflammatory effects locally within the uterus. In a case series on the use of IUDs in kidney transplantation (KT) recipients, 3 (2 copper-IUDs, 1 unspecified) out of 5 patients reported unplanned pregnancies.[21]

Some advocate that IUDs should be avoided in immunocompromised patients due to an increased risk of infectious complications, although this assertion is based on old case reports.[21,22] Interestingly, the use of IUDs is effective and widely accepted in human immunodeficiency virus (HIV)–infected women.[23] Although the American Society of Transplantation does not recommend IUDs as first-line contraception in transplant recipients, it remains an area of controversy because IUDs can be an effective approach in many women. Further studies are required to determine efficacy in the posttransplant setting.

A systematic review on contraceptive use in KT/LT recipients reported no unplanned pregnancies or major biochemical abnormalities during the follow-up of patients using low-dose oral or transdermal hormonal therapy. However, discontinuation did occur in 2 patients (due to thrombophlebitis and graft dysfunction), and modification of antihypertensive therapy was required in some.[21] Additionally, a retrospective study examining 15 patients on combined oral contraceptives (COCs) or a transdermal patch found no clinical or biochemical abnormalities during follow-up, while maintaining 100% efficacy.[24] The United Kingdom Medical Eligibility Criteria for Contraceptive Use recommends the use of progesterone-only therapies in organ transplant recipients because the benefits usually outweigh the theoretical risks.[25]

ASSISTED CONCEPTION

There are various reasons why a female LT recipient may have difficulties getting pregnant, eg, abdominal adhesions, primary reproductive pathologies, or etiology of liver disease. Patients should be encouraged to discuss these issues with their transplant physician. After addressing reversible factors, they should be referred to a specialist if necessary. Although not without risk, in vitro fertilization in female LT recipients has previously resulted in successful pregnancies.[26,27] Fertility preservation techniques, cryopreservation of oocytes, surrogacy, and adoption are other options to be considered.[28]

PREPREGNANCY COUNSELING

Counseling of female transplant recipients wishing to become pregnant and supervision of a subsequent pregnancy requires expert discussions in a multidisciplinary setting, particularly as concomitant chronic disease and immunosuppressants pose potential risks. Optimal timings of pregnancy should also be discussed.

Prepregnancy counseling is not always possible in women who undergo emergency transplantation for drug-induced, viral-induced, or autoimmune-induced liver failure. However, in these cases, counseling should occur early in the posttransplant phase, ideally before discharge.

All women due to start mycophenolate mofetil (MMF) must receive contraceptive counseling and have a negative pregnancy test before starting therapy.

TABLE 1. Contraceptive Options After LT

Contraceptive Method	Advantages	Disadvantages	Recommendation
Barrier methods	No contraindication in LT recipients No drug-drug interactions Low cost	Noncompliance Higher failure rates	Recommended (if efficacy issues discussed)
Male condom	Protection against most sexually transmitted infections	15% failure rate	
Female condom		21% failure rate	
Cervical cap		Requires fitting by health care professional	
Diaphragm		16% failure rate Increased risk of urinary tract infections	
IUDs	Long lasting Low failure rate Reversibility No drug-drug interactions	Theoretical risk of ineffectiveness and infective complications	Not fully recommended (although poor evidence to support this)
Hormonal contraception	Low failure rate Reversibility	No protection against sexually transmitted infections Multiple contraindications, eg, migraines, venothromboembolism, stroke, smokers, and so on Possible reduced efficacy of immunosuppressive medications	Individualized to patient, decision based on risk versus benefit profile Hypertension must be well controlled
Estrogen/progestin (combined) pill	Less irregular bleeding Reduced risk of endometrial and ovarian cancer	May interfere with immunosuppressive medications via cytochrome P450 system, eg, hepatotoxic effect Possible cholestasis Increased risk of cervical cancer	
Patch		Possible increased risk of venothromboembolism	
Vaginal ring	No first pass liver metabolism		
Progestin-only pill	5% failure rate	Liver metabolism	
Depot medroxyprogesterone acetate	2% failure rate No liver metabolism	Irregular bleeding Amenorrhea Weight gain Delayed return to fertility Decreased bone mineral density	
Etonogestrel implant	<1% failure rate No liver metabolism No decrease in bone mineral density	Similar to depot medroxyprogesterone acetate	

NOTE: Adapted from McKay et al.[16]

Patients should ideally use 2 methods of contraception for at least 4 weeks before initiating MMF, during treatment, and for 12 weeks after discontinuation.

Risk of Immunosuppression During Pregnancy

As part of prepregnancy counseling, the effect of immunosuppression on mother and fetus should be discussed with the patient. The benefits of immunosuppressive therapy to maintain adequate graft function during pregnancy usually outweigh the possible risks associated with fetal exposure. Stable doses of immunosuppression before and during pregnancy are key in preventing problems in the mother as well as in the fetus. Maintenance of preconception immunosuppression is generally recommended, except for MMF. Once pregnant, we recommend that clinicians enroll patients into an appropriate registry.

CORTICOSTEROIDS

Approximately 10% of the maternal corticosteroid dose reaches the fetus. Older studies have suggested an association between corticosteroid use in the first trimester and cleft lip/palate abnormalities.[29,30] However, these studies used high-dose corticosteroids (mean, 30 mg) and had several confounding factors. Newer studies have not demonstrated evidence of teratogenicity, thereby establishing the safe use of corticosteroids during pregnancy.[31,32] Prolonged or repeated administration of systemic corticosteroids during pregnancy may be associated with intrauterine growth restriction (IUGR), although short courses (eg, to aid fetal lung maturation) in threatened preterm deliveries are likely to be safe.[33-35]

AZATHIOPRINE

Although azathioprine crosses the placenta, the fetal liver lacks inosinate pyrophosphorylase, an enzyme required to convert azathioprine into its active metabolites.[36] Azathioprine has good safety data for use in human pregnancies.[37] It has been associated with dose-related myelosuppression in the fetus, although maintaining the mother's white cell count >7500 mm^{-3} appears to minimize this risk.[38] Lymphopenia, hypogammaglobulinemia, and thymic hypoplasia have been reported in children born to mothers on azathioprine. However, these changes appear to reverse after birth with no longterm consequences.[17,39] In clinical practice, most transplant physicians are comfortable continuing azathioprine during pregnancy if necessary.

CYCLOSPORINE

Cyclosporine readily crosses the placenta. Blood concentrations in the fetus range between 30%-60% of the mothers' concentration.[40,41] Current data do not indicate an increased risk of congenital malformations when compared with nonexposed patients. There is, however, a moderate risk of IUGR.[42-44]

Hepatic cytochrome P450 enzymes can be inhibited during pregnancy, and there may also be changes in drug distribution, renal dysfunction, and hepatic clearance during pregnancy. To prevent toxicity or underdosing, cyclosporine levels should be monitored during pregnancy.

TACROLIMUS

Pregnancy outcomes with tacrolimus-based immunosuppression have shown lower incidences of hypertension and pre-eclampsia when compared with cyclosporine-based therapy.[42,43,45] Nephrotoxicity and glucose intolerance during pregnancy may also be associated with tacrolimus-based therapy. Transient unexplained hyperkalemia in newborns of mothers taking tacrolimus have been noted, although this is reversible without need for treatment.[42] In a literature review of 83 pregnant LT/KT recipients treated with tacrolimus, the incidence of fetal malformations was 6%.[44] Other studies have demonstrated rates of 4%-5% in LT/KT recipients, which is comparable to the general population.[43,46] Overall, tacrolimus is deemed to be safe in pregnancy, but levels should be monitored closely by the transplant team. Target levels should be individualized based on history of rejection and concomitant disease.

MYCOPHENOLATE MOFETIL

MMF is contraindicated during pregnancy. Risks include spontaneous abortion (49%), stillbirth (2%), and structural anomalies (23%).[47] Kamarajah et al. reported 9 conceptions in 77 LT recipients while on MMF. The outcomes of these pregnancies included 6 live births (67%), 2 early miscarriages, and 1 maternal/fetal death in the first trimester from preexisting chronic graft rejection in the mother.[48] Sifontis et al. demonstrated the teratogenic effects in a study of 33 pregnancies in different organ transplant recipients with early exposure to MMF. There was a high incidence of malformations, including hypoplastic nails, shortened fifth fingers, microtia, and cleft lip/palate abnormalities.[49] Other reported malformations included the absence of auditory canals, Tetralogy of Fallot, and total anomalous pulmonary venous return.[19,49,50] It has been advocated that there may be a dose-related relationship with developmental toxicity.[47] The management of MMF exposure in the setting of unplanned pregnancies or patients who require adjunctive therapy is not clear.

MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS

There are limited data on the effects of mammalian target of rapamycin (mTOR) inhibitors (eg, sirolimus or everolimus) during pregnancy. The antiproliferative effect of these drugs could theoretically prevent the development of a fetus. A recent study reported a stillbirth at 25 weeks gestation in an LT recipient on sirolimus.[48] However, there have been numerous reports of

successful pregnancies with mTOR inhibitors.[47,49,51] Nonetheless, these drugs remain contraindicated during pregnancy, and we would recommend discontinuation prior to an attempted conception, although the exact interval has not been elucidated.

Table 2 classifies the risks of the most commonly used immunosuppressive agents in LT. The US Food and Drug Administration (FDA) pregnancy categories have been replaced with the Pregnancy and Lactation Labelling Rule. The original FDA categories were deemed too simplistic and misleading in terms of describing the degree of risk involved with each drug. The newer descriptive system is suggested to be better at aiding clinicians and patients with decision making.

Imaging of the Fetus During Pregnancy

During pregnancy, antenatal ultrasound scans should be performed in LT recipients as per local protocol. However, because of the increased risk of IUGR, we would recommend further growth scans at 28, 32, and 36 weeks' gestation. If IUGR is suspected, regular middle cerebral and umbilical artery Doppler ultrasounds can assess the risk of ensuing hypoxia.

Outcomes in Pregnancy Following Transplantation

Fetal deaths, antepartum admissions, and maternal/fetal complications are overall increased 2-3–fold in LT recipients.[52] The most significant complications include pregnancy-induced hypertension (PIH), pre-eclampsia, prematurity, and IUGR (Fig. 3). Pregnancy in a LT recipient should therefore be considered high risk and managed by an experienced obstetrician, transplant physician, and midwife. A complicated pregnancy may require delivery in a transplant center. See Fig. 4 for a proposed management plan for these patients.

Maternal Outcomes

MATERNAL DEATH

Overall, maternal deaths have not been reported to be higher in pregnant LT recipients when compared with the general population.[52-54] Death rates during pregnancy and the postpartum phase vary between 0% and 1%.[52,54-57] In the older studies quoting higher rates of maternal death (5%-17%), most deaths occurred more than a year postpartum and were unlikely to be related to the pregnancy.[19,20,43] A report from 2003 described 1 maternal death in the immediate postpartum phase where an infra-aortic arterial graft clotted during labor and led to a gangrenous graft, liver failure, and death before retransplantation.[43]

PREGNANCY-INDUCED HYPERTENSION

PIH is the development of new hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) in a pregnant woman after 20 weeks' gestation in the absence of proteinuria or new-onset hepatic/renal dysfunction. Coffin et al. reported the rate of PIH as 30% in a LT recipient group versus 9% in a control group.[52] Deshpande et al. reported a similar rate in their meta-analysis.[58] In certain patient series, the rates of PIH range between 16% and 23%.[19,20,59-61] This variance may be due to the inclusion of patients with chronic hypertension in some studies.

Deshpande et al. also demonstrated that the rates of PIH in LT recipients were lower than in KT recipients (54%).[58] This is likely due to the higher levels of immunosuppression required in KT recipients as well as an accepted reduction in kidney graft function over time and increased likelihood of vascular pathologies in these individuals.

The incidence of hypertension according to the type of immunosuppression is between 22% and 29% with corticosteroids, 63% and 73% with cyclosporine, and 47% and 54% with tacrolimus.[19,42,43,62,63] Cyclosporine may be related to higher rates of hypertension when compared with tacrolimus.

PRE-ECLAMPSIA

Pre-eclampsia is a pregnancy-specific hypertensive disorder that occurs after 20 weeks' gestation and is associated with new-onset proteinuria (≥300 mg/dL/day) with or without other multisystem involvement.[64] Rates of pre-eclampsia in the general US population have previously been reported as 4%.[52,58] Older studies in pregnant LT recipients have reported pre-eclampsia rates of 21%-26%,[19,58,62] whereas newer studies have reported rates of 7%-12%.[57,59,61,65,66]

TABLE 2. Immunosuppressive Drugs Commonly Used in LT Recipients and Their Effects on Pregnancy

Drug	Previous FDA Pregnancy Category*	Possible Effects on Mother	Possible Effects on Fetus	Safety in Breastfeeding
Corticosteroids	C	Hypertension GD Cushingoid symptoms Osteonecrosis Weight gain Dyslipidemia Infection Poor wound healing	Malformations (rate 4%) Increased rate of cleft palate abnormalities Premature rupture of membranes† Adrenal insufficiency IUGR	Yes (use lowest dose possible)
Azathioprine	D	Leukopenia Gastrointestinal side effects	Malformation (rate 7%) Preterm delivery‡ Anemia§ Leukopenia§ Thrombocytopenia§ Immune deficiency§ Infection†,§ (Usually normalize within a year) LBW‡ IUGR Thymic hypoplasia	No
Cyclosporine	C	Hypertension GD Pre-eclampsia Renal dysfunction	Malformation (rate 3%-5%) LBW IUGR	No
Tacrolimus	C	Hypertension GD Renal dysfunction Neurotoxicity	Malformation (rate 4%-6%) Pre-term delivery LBW IUGR Transient renal insufficiency (hyperkalemia)	Yes (but with caution and careful monitoring)
Mycophenolate mofetil	D	Leukopenia Gastrointestinal side effects	Malformation (rate 22%)—wide spectrum affecting cleft palate, ears, limbs, heart, esophagus, and kidneys Spontaneous abortion in the first trimester	No
mTOR inhibitors	C	Gastrointestinal side effects Mucositis Infection	Limited data In animal models, reduced fetal weight, delayed ossification of skeletal structures, but no teratogenicity known	No
OKT3 (murine monoclonal antibody)	C	Flu-like symptoms Allergic reaction	Unknown	Unknown
Antithymocyte globulin	Not assigned	Flu-like symptoms Leukopenia Allergic reaction	Unknown	Unknown

*Category A: Adequate and well-controlled studies have failed to demonstrate risk to the fetus in the first and later trimesters of pregnancy. Category B: Animal reproduction studies have failed to demonstrate risk to the fetus, and there are no adequate well-controlled studies in pregnant women. Category C: Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate well-controlled studies in humans. However, potential benefits may warrant use of the drug in pregnant women despite potential risks. Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†Catnach et al.[97] (1995).
‡American Academy of Pediatrics[98] (2012).
§Effect usually normalizes within a year.

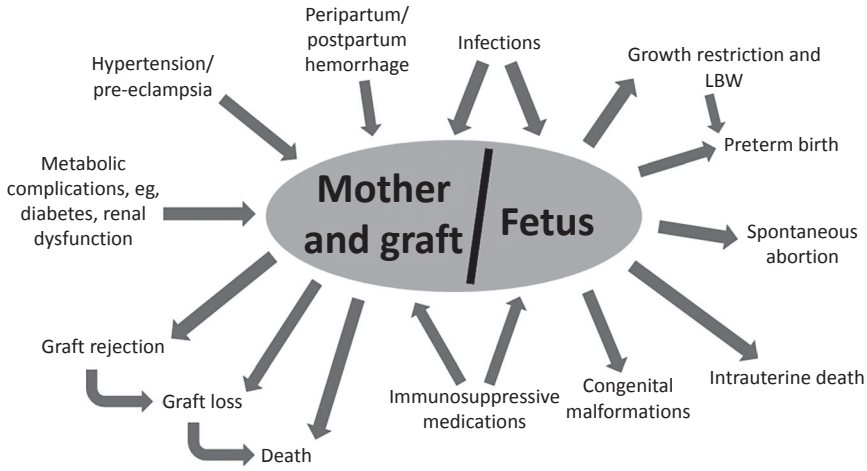

FIG. 3. The complex interplay between maternal, graft, and fetal outcomes.

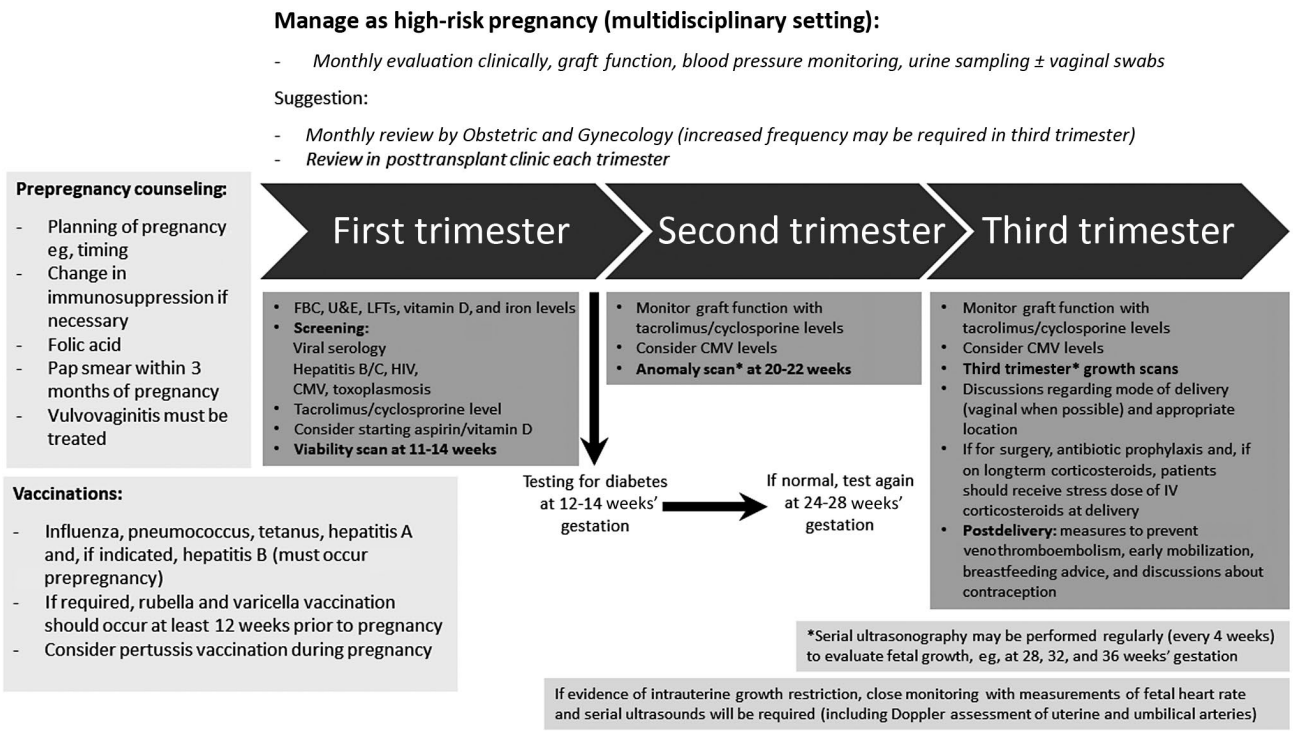

FIG. 4. Proposed management scheme of pregnancy after LT.

Rates may have improved over time as a result of better management of immunosuppression and risk factors (Table 3) associated with pre-eclampsia. Pre-eclampsia is the main contributing factor for preterm delivery in LT recipients.[47,57] The pathophysiology behind this is not entirely understood, although the vasoconstrictive effects of calcineurin inhibitors, chronic corticosteroid use, and increased incidence of baseline hypertension and renal dysfunction are important factors.

TABLE 3. Risk Factors for Pre-Eclampsia in Pregnant Females With No Previous LT

Risk Factor	Unadjusted Relative Risk*
Previous pre-eclampsia	8.4
Chronic hypertension	5.1
Previous GD	3.7
Multiple pregnancies	2.9
Pre-pregnancy BMI >30 kg/m^2	2.8
Antiphospholipid syndrome	2.8
Systemic lupus erythematosus	2.5
Previous stillbirth	2.4
Nulliparity	2.1
Pre-pregnancy BMI >25 kg/m^2	2.1
Previous placental abruption	2.0
Chronic kidney disease	1.8
Antiretroviral therapy	1.8
Maternal age >40 years	1.5
Previous IUGR	1.4
Maternal age >35 years	1.2

NOTE: Additional factors include ethnicity, smoking history, family history of pre-eclampsia, in vitro fertilization, other assisted reproductive technologies, and partner-related factors indicated by Wright et al.[99] (2015). Adapted from Bartsch et al.[100]
*Compared with pregnant women without the risk factor.

Vitamin D deficiency has been associated with an increased rate of pre-eclampsia, and therefore, supplementation is recommended from the first trimester.[67] Additionally, daily aspirin (if initiated ≤16 weeks' gestation) improves placental hemodynamics and reduces the risk of preterm (<37 weeks) pre-eclampsia (relative risk, 0.62) but not term pre-eclampsia (relative risk, 0.92).[68,69] To avoid the risk of nonresponse, our recommendation is to start 150 mg once per day from the first trimester.[70] Where this dose is not available, a dose of 162 mg once per day (81 mg tablets × 2) is also suitable. Aspirin should be discontinued at 36 weeks' gestation or at least a week before delivery.

REJECTION AND GRAFT LOSS

Pregnancy is viewed as a state of relative immunosuppression. Pregnant women do not necessarily have diminished systemic immunity; however, the uterus becomes an immunoprivileged site, with an increase in other tolerogenic mechanisms.[71] Fetal antigens that cross the maternoplacental barrier can induce a peripheral T cell response.

During pregnancy, a 3-4–fold rise in alkaline phosphatase is expected due to increased placental and bone isoenzyme production.[72,73] In the later stages of pregnancy, female sex hormones may inhibit the hepatic synthesis of gamma-glutamyl transpeptidase because decreased secretion and activity have been demonstrated in the second and third trimesters.[74] Overall, alanine aminotransferase and aspartate aminotransferase levels are thought to remain stable during pregnancy. Hypoalbuminemia, due to a hemodilution effect, is also common in pregnancy. Both total and free bilirubin have been shown to be lower, as has conjugated bilirubin during the second and third trimesters.[74] Markers of synthetic function, such as platelet count, prothrombin time, and the international normalized ratio, all remain within the normal range during pregnancy. These described changes have not been fully studied in the LT population.

In clinical practice, it can be difficult to determine the cause of new liver enzyme derangement, particularly a transaminitis, in a post-LT pregnant woman. Baseline prepregnancy graft function and liver enzymes need to be considered. The gestation at the time of liver derangement is important to note as well as the full clinical picture at the time, eg, tacrolimus levels, noncompliance, presence of hypertension with or without proteinuria. It is also vital to rule out viral causes. Liver biopsy can be considered in cases of uncertainty, particularly if it is likely to significantly impact management.

Rates of graft rejection in pregnant LT recipients can be highly variable between 0% and 20%.[19,20,45,52,55,61,62,65,75-78] Unfortunately, some of these studies did not employ uniform diagnostic criteria for ACR. The rate of ACR in the nonpregnant LT population is also unclear.[79] Rates of postpartum graft rejection range between 3% and 12%.[19,20,43,56,57,60] Rejection during pregnancy is likely secondary to a combination of factors: either voluntary discontinuation or reduction of immunosuppression or the effect of dilution caused by increased plasma volume during pregnancy. Those patients who develop ACR during pregnancy usually respond to a course of corticosteroids or reestablishment/augmentation of immunosuppression.[20,43,56] There may be a link between biopsy-proven ACR during pregnancy, recurrent rejection, and graft loss, although it is difficult to confirm a true causal relationship.[56]

Graft loss during pregnancy as a direct result of ACR is rare, but there are reports of graft loss after delivery due to recurrent autoimmune hepatitis (AIH) and chronic rejection.[43] Table 4 demonstrates the

TABLE 4. Rates of Rejection and Graft Loss During or After Pregnancies in LT Recipients

Reference	Number of Pregnancies	County of Origin	ACR Rate During Pregnancy (Percentage of All Pregnancies)	ACR Postpartum (Percentage of All Pregnancies)	Graft Loss Within 1 Year After Delivery	Graft Loss (Because of Chronic Rejection) on Longterm Follow-up
Patapis et al.[45] (1997)	29	United Kingdom	7%	Not reported	1 graft loss during pregnancy for irreversible rejection	Not reported
Coscia et al.[46] (2008)*	241	United States	8%	Not reported	Not reported	8% within 2 years of delivery
Deshpande et al.[58] (2012)	450	United States/United Kingdom/Poland/Italy	2%-17%	Not reported	Not reported	Up to 10.5% within 2 years of delivery
Álvaro et al.[55] (2013)	30	Spain	10%	Not reported	Not reported	Not reported
Blume et al.[66] (2013)	62	Germany	3%	10%	No graft loss	Not reported
Kubo et al.[60] (2014)	38	Japan	5%	8%	Not reported	Not reported
Coscia et al.[89] (2015)*	444	United States	4%	4%	Not reported	4% within 2 years of delivery
Mattila et al.[83] (2017)	25	Finland	8%	Not reported	Not reported	Not reported
Baskiran et al.[59] (2017)	26	Turkey	0% (1 case of chronic rejection)	Not reported	No graft loss	6%
Lim et al.[57] (2018)	162	United Kingdom	7%	5%	No graft loss	5%
Kamarajah 2019[48]	130	United Kingdom	8%	2%	Not reported	2%

*NTPR data.

rates of rejection and graft loss during pregnancy in different studies. Lim et al. reported that 9% of their cohort (8/93 patients) underwent retransplantation at a median of 42 months postpartum. Indications included chronic rejection, recurrent disease, and late hepatic artery thrombosis. In all cases, graft losses were not felt to be specifically related to the pregnancy.[57]

Other factors that may also be associated with graft loss include younger age at transplantation/conception, interval between transplantation and pregnancy, renal insufficiency, stage of graft disease, and the presence of portal hypertension.[20,56,57,80]

RENAL DYSFUNCTION

Christopher et al. described de novo renal impairment in 11% of their pregnant LT cohort.[20] Nagy et al. reported that 25% of their cohort had a creatinine of >1.3 mg/dL during pregnancy.[19] However, there are several studies that have not detected a significant decline in renal function during pregnancy.[43,81] Lim et al. demonstrated that a preconception estimated glomerular filtration rate (eGFR) of <90 mL/minute in LT recipients was associated with preterm delivery. They concluded that a progressive decline in eGFR during pregnancy predicted gestational length and outcome.[57]

GESTATIONAL DIABETES

Pregnancy is a physiological state of insulin resistance. Diabetogenic immunosuppressants, in conjunction with other risk factors, may induce gestational diabetes (GD). The rate of GD in pregnant LT recipients varies between 0% and 11%.[20,52,54,58,59,61,77,78] The variance may be due to sample size, ethnicity, and inclusion of patients with preexisting diabetes. In a North American population–based study, the GD rate in LT recipients was significantly higher than the nontransplanted group (8.6% versus 5.4%, respectively).[54] As an independent factor, it is not clear if the development of GD alters the course of pregnancy in LT recipients.

HEMORRHAGE

Rates of antepartum hemorrhage have been reported to be similar between LT recipients and the general population. However, postpartum hemorrhage has been reported as statistically more frequent in LT recipients when compared with controls (8% versus 3%, respectively).[52] This was corroborated in a population-based study that showed an increased requirement of blood

products after pregnancy in LT recipients.[54] This may be related to several factors: increased cesarean delivery rates, immunosuppression-related thrombocytopenia, and coagulation defects as a result of hypertensive disorders.

Pregnancy-related ruptures of splenic artery aneurysms have also been described in the LT population.[48,82,83] These aneurysms should ideally undergo intervention before pregnancy.

PREGNANCY-RELATED INFECTIONS

The frequency of infections acquired during pregnancy has been reported to be similar between LT recipients and the general population.[52,53] Christopher et al. reported an infectious complication rate of 11% (8/71 pregnancies). Of these patients, 3 were viral-related cases: 2 with parvovirus and 1 with cytomegalovirus (CMV) reactivation (treated with ganciclovir).[20] Genitourinary infections have been shown to be more prevalent during pregnancy in LT recipients compared with non-LT recipients (5.3% versus 1.4%, respectively).[54]

OTHER COMPLICATIONS

Pregnancy is a hypercoagulable state, which may increase the likelihood of thrombosis. However, in 1 study among 4 patients who underwent transplantation for Budd-Chiari, with the use of aspirin in the first and second trimesters and low-molecular-weight heparin in the third trimester, there was no recurrence during pregnancy.[59] Additionally, venothromboembolism does not appear to be more prevalent in pregnant LT recipients when compared with nontransplanted individuals.[52,54]

Anemia is one of the most common complications in pregnant LT recipients and is likely to be secondary to physiological changes during pregnancy, effects of immunosuppression, renal insufficiency, and iron deficiency. One population-based study suggested a prevalence of 23% in LT recipients.[54]

Finally, there have been reports of increased rates of cholestasis of pregnancy in LT recipients.[84,85] The risk of intrahepatic cholestasis of pregnancy has been shown to be significantly increased in those patients with hepatitis C infection, but whether this risk remains after LT has yet to be determined.[86] If there is suspicion of this condition, monitoring with bile acids during pregnancy will determine the risk to the fetus and may influence the time of delivery.[87]

Fetal Outcomes

LIVE BIRTH RATE

The LBR in pregnancies of LT recipients has consistently been quoted to be above 65%.[20,55,56,59,61,81] Desphande et al. reported an LBR of 77% (346/450 LT pregnancies). At the time, the LBR in the general US population was 67%.[58] Lim et al. demonstrated that the LBR has increased over the last 3 decades in their cohort, from 60% before 1997, to 70% between 1997 and 2006, to 84% between 2007 and 2016.[57] This improvement is likely secondary to more intensive specialist care during these high-risk pregnancies as well as the reduced rate of unplanned pregnancies.

SPONTANEOUS ABORTION

The rate of spontaneous abortions in LT recipients is thought to be in the region of 11%-19%.[19,20,45,56,78,81] Deshpande et al. reported a miscarriage rate of 16% versus 17% in the general population.[58] It is difficult to ascertain the true rates of medically induced abortions because they are not reported accurately. A recent systematic review reported a rate of 8%.[88]

STILLBIRTHS

Most studies have suggested a stillbirth rate of 0%-1.2% in pregnant LT recipients.[19,57,58] However, rates as high as 12% have been reported in some studies.[55,59] There are multiple risk factors for stillbirth: ethnicity, parity, previous stillbirth, infections, obesity, smoking, diabetes, hypertensive disorders, antepartum hemorrhage, placental abruption, IUGR, genetic defects, and obstetric cholestasis. According to NTPR data, the development of cholestasis during pregnancy in LT recipients is 6 times higher than the general population; however, adverse outcomes have not been demonstrated.[89]

PREMATURITY

Preterm birth rates are increased in LT recipients. Reported rates vary between 14% and 53%.[19,20,43,55,59-61,75,76,78,81] Deshpande et al. reported a rate of 39%, a rate much greater than the general US population (14%).[58] Prodromidou et al. reported

a preterm birth rate of 32% in 1079 pregnancies in a recently published systematic review.[88] The increased risk of prematurity may be related to the increased incidence of obstetric complications in LT recipients, eg, pre-eclampsia.

FETAL GROWTH RESTRICTION

Birth weight (BW) is intrinsically related to gestational age. One prospective patient series reported the mean BW percentile to gestational age in neonates of LT recipients, with 8.5% having a BW percentile of <25th and 60% having a BW percentile >50th.[43] In another study, the mean neonatal weight in the LT recipients was 2838 g (<34 weeks' gestation, 1897 g; 34-36 weeks' gestation, 2324 g; >37 weeks' gestation, 3125 g).[90] Deshpande et al. showed that the mean BW was significantly greater for LT recipients (2866 g) compared with KT recipients (2420 g) but that it was lower than the general US population (3298 g).[58]

IUGR is defined as a pathological process that inhibits the growth of a fetus and prevents it from reaching its full growth potential. Rates of IUGR in LT recipients vary between 5% and 20%.[19,55,60,61] This variance is likely due to inconsistent definitions of IUGR between studies. Certain studies have demonstrated that IUGR rates in LT recipients are statistically more frequent when compared with the general population.[55,61,63]

CONGENITAL INFECTIONS

Infections that can be transmitted transplacentally to the fetus include CMV, toxoplasmosis, herpes simplex virus, varicella, HIV, hepatitis B virus, and hepatitis C virus. The greatest risk of congenital infection is through primary CMV infection in the mother during pregnancy. However, recurrent CMV infection in the immunosuppressed female patient has also been reported to cause congenital CMV infection.[91] If untreated, this can lead to serious fetal complications, eg, hydrops fetalis, stillbirth, mental retardation, visual/hearing loss, prematurity, or death.[92] It is therefore important to monitor CMV levels during pregnancy in LT recipients when indicated.

CONGENITAL MALFORMATIONS

Congenital abnormalities are uncommon in the children of LT recipients. Rates range between 0% and 4%.[18,43,45,52,60,75,77] Older series have reported unusually high incidences of 10%-17%.[19,76] A recent population-based study also reported a slightly increased rate of congenital anomalies in LT recipients when compared with nontransplanted individuals, although the authors acknowledged that an earlier study (derived from the same database) did not show a statistical difference.[52,54] Contrastingly, Coffin et al. reported a malformation rate of 1.4% in 206 LT pregnancies (versus 0.6% in the nontransplanted group).[52] In 2006, the NTPR reported a malformation rate of 3%-5% in the general US population.[78]

Documented congenital anomalies in the neonates of female LT recipients include tracheoesophageal fistula, pyloric stenosis, ventricular septal defects, Tetralogy of Fallot, valvular disease, total anomalous pulmonary venous defect, cystic kidney, hydrocoeles, and hypospadias.[18,19,43,44,60,65] There is no consistent pattern of malformation, and it is difficult to ascertain if these are related to immunosuppression or genetic predisposition. In contrast, there are several studies that have not reported any congenital malformations in their LT cohorts.[20,52,56,59,61,77] Overall, it is felt that the malformation rate is no different between LT recipients and the general population.

LONGTERM FOLLOW-UP OF CHILDREN

Data on longterm pediatric outcomes are lacking. Small studies have reported appropriate physical and psychological development in the children of mothers who have previously undergone LT.[75,77] Neurological development of children born to LT recipients appear to be similar to that of children whose mothers have not undergone transplantation.[93]

Obstetric Outcomes

MODE OF DELIVERY

The rates of cesarean delivery in pregnant LT recipients varies between 20% and 63%.[19,20,43,45,52,55,56,59,60,75,76,78,81] Deshpande et al. reported a rate of 45%, which was significantly higher than the general US population (32%).[58] One study reported the indications for cesarean deliveries in their cohort of LT recipients, which included pre-eclampsia, placental abruption/previa, fetal distress, failure to progress, prolonged labor, ruptured membranes, and breach presentation.[43] This was corroborated by another study that showed that

71% of their pregnant LT recipients underwent cesarean deliveries, all due to obstetric indications. The length of stay in these patients was approximately 4 days longer than those who had vaginal deliveries, which were documented to be uneventful.[24] There are no specific contraindications to vaginal delivery in LT recipients. Hospitalization in a transplant center does not appear to change obstetric outcomes.[52]

OTHER OBSTETRIC COMPLICATIONS

Frequency of premature rupture of membranes (5.5%), placental previa (1.4%), and placental abruption (2.7%) have been reported to be similar between pregnant LT recipients and the general population.[52,54]

Transplantation During Pregnancy

The development of acute liver failure during pregnancy from conditions such as acute fatty liver of pregnancy, hemolysis, elevated liver enzymes and low platelets syndrome, drug overdose, AIH, or acute hepatitis B/E is very rare.[94,95] In pregnancy-induced liver failure, delivery is nearly universally recommended to treat the underlying liver condition; however, emergency LT may need to be considered in selected patients.[96]

Although most of the literature on this subject is based on case reports, fetal outcomes appear to be poor. Depending on the age of gestation and the viability of the fetus, continuation or termination of the pregnancy must be tactfully discussed with the patient. A multidisciplinary approach in a specialist transplant center with intensivists and transplant/obstetric surgeons and physicians is mandatory. It is difficult to recommend a gestation from which a live birth can be pursued. One of the youngest reported in the literature is a woman who was transplanted for AIH at 20 weeks' gestation, and the neonate delivered spontaneously at 28 weeks.[97]

Postpartum Phase

After pregnancy, the return to normal physiology leads to a period that warrants careful monitoring for maternal drug toxicity. It is therefore recommended that immunosuppressant levels are monitored postpartum, particularly if doses were changed during pregnancy. It can take several weeks for fluid retention to improve after delivery, so we would recommend repeating tacrolimus or cyclosporin level tests within a month of delivery. Women should receive regular follow-up in the first 3 months after delivery, although this does not necessarily have to be done in secondary/tertiary care.

BREASTFEEDING AND DRUG PASSAGE

In the past, it was strongly advocated that LT recipients should not breastfeed. However, international consensus has changed to the view that breastfeeding need not be an absolute contraindication.[16] Despite the lack of good-quality prospective studies, evidence is slowly accruing on the safety of breastfeeding from other disciplines, such as rheumatology, inflammatory bowel disease, and KT. Patients should be given the opportunity to weigh the potential risks of drug exposure and the benefits of breastfeeding, eg, reduced rates of allergies, celiac disease, infections, and colitis.[98]

Corticosteroids

Small amounts of corticosteroid are present in the breast milk of women on corticosteroid therapy. However, at low doses, the effects on the infant are negligible. The American Academy of Pediatrics has recommended relative safety of breastfeeding while on corticosteroids.[101] Prednis(ol)one doses up to 20 mg/day are not expected to cause adverse effects on the infant.[102]

Azathioprine

Low doses of azathioprine can be found in breast milk. Despite this, there are concerns regarding the longterm effects of drug exposure on immunosuppression, malignancy, and development in the infant. However, the detrimental effects of azathioprine on newborns have not been demonstrated in several studies.[37,102] The British Society of Rheumatology guidelines recommend that azathioprine is compatible with breastfeeding.[103]

Cyclosporine

Drug levels within breast milk can be highly variable regardless of the maternal cyclosporine dose. Small studies have shown low concentrations of cyclosporine in infants with no significant adverse events noted.[104] However, the American Academy of Pediatrics has recommended against breastfeeding with cyclosporine due to concerns regarding possible immunosuppression in the infant.[101]

Because of the lack of longterm detrimental effects on neonates, in clinical practice we do not discourage breastfeeding in patients on cyclosporine.

Tacrolimus

Older studies have suggested that tacrolimus content within breast milk is high, and so, mothers on tacrolimus should not breastfeed.[42] However, newer studies have determined that infant ingestion/exposure of the drug is very low, and therefore, it may be compatible with breastfeeding.[105,106]

There are minimal data on the safety of MMF and mTOR inhibitors in breastfeeding.

Breastfeeding in LT recipients remains a controversial topic, and further studies are required before definitive recommendations can be made. The benefits of combination feeding ("breast and bottle") and timing of feeding in relation to drug ingestion also need to be explored.

Conclusion

Despite increasing experience in the management of pregnancy in transplant recipients, these pregnancies remain high risk when compared with the general population. 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. Considering the possible complications (eg, concomitant chronic conditions and immunosuppressive drugs), pregnancy outcomes are reassuringly favorable. Although there are data from registries, population-based studies, case series and reports, there is a lack of good-quality randomized controlled trials on pregnancy in transplantation. This mandates the collection of accurate data through registries to obtain up-to-date and reliable data sets. Future research goals should include defining the impact of pregnancy on short-term and longterm graft function, optimizing screening during pregnancy, identifying LT-specific risk factors for pre-eclampsia and IUGR, and determining the outcomes of in vitro fertilization and mTOR inhibitors on pregnancy.

REFERENCES

1) Russell MA, Craigo SD. Cirrhosis and portal hypertension in pregnancy. Semin Perinatol 1998;22:156-165.
2) Danielsson Borssén Å, Wallerstedt S, Nyhlin N, Bergquist A, Lindgren S, Almer S, et al. Pregnancy and childbirth in women with autoimmune hepatitis is safe, even in compensated cirrhosis. Scand J Gastroenterol 2016;51:479-485.
3) Cundy TF, O'Grady JG, Williams R. Recovery of menstruation and pregnancy after liver transplantation. Gut 1990;31:337-338.
4) Mass K, Quint EH, Punch MR, Merion RM. Gynecological and reproductive function after liver transplantation. Transplantation 1996;62:476-479.
5) Van Thiel DH, Gavaler JS, Schade RR. Liver disease and the hypothalamic pituitary gonadal axis. Semin Liver Dis 1985;5: 35-45.
6) Llansola M, Ahabrach H, Errami M, Cabrera-Pastor A, Addaoudi K, Felipo V. Impaired release of corticosterone from adrenals contributes to impairment of circadian rhythms of activity in hyperammonemic rats. Arch Biochem Biophys 2013;536:164-170.
7) Jabiry-Zieniewicz Z, Kaminski P, Bobrowska K, Pietrzak B, Wielgos M, Smoter P, et al. Menstrual function in female liver transplant recipients of reproductive age. Transplant Proc 2009;41: 1735-1739.
8) Moon AM, Yang JY, Barritt AS, Bataller R, Peery AF. Rising mortality from alcohol-associated liver disease in the United States in the 21st century. Am J Gastroenterol 2020;115:79-87.
9) Singal AK, Arora S, Wong RJ, Satapathy SK, Shah VH, Kuo YF, Kamath PS. Increasing burden of acute-on-chronic liver failure among alcohol-associated liver disease in the young population in the United States. Am J Gastroenterol 2020;115:88-95.
10) Jung Y, Russfield AB. Prolactin cells in the hypophysis of cirrhotic patients. Arch Pathol 1972;94:265-269.
11) Burra P, Germani G, Masier A, De Martin E, Gambato M, Salonia A, et al. Sexual dysfunction in chronic liver disease: is liver transplantation an effective cure? Transplantation 2010;89:1425-1429.
12) Gariani K, Toso C, Philippe J, Orci LA. Effects of liver transplantation on endocrine function: a systematic review. Liver Int 2016;36:1401-1411.
13) De Koning ND, Haagsma EB. Normalization of menstrual pattern after liver transplantation: consequences for contraception. Digestion 2004;46:239-241.
14) Nicholas SL, Rulin MC. Acute vaginal bleeding in women undergoing liver transplantation. Am J Obstet Gynecol 1994;170:733-736.
15) Sorrell JH, Brown JR. Sexual functioning in patients with end-stage liver disease before and after transplantation. Liver Transplant 2006;12:1473-1477.
16) McKay DB, Josephson MA, Armenti VT, August P, Coscia LA, Davis CL, et al. Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. Am J Transplant 2005;5:1592-1599.
17) Blume C, Pischke S, Von Versen-Höynck F, Günter HH, Gross MM. Pregnancies in liver and kidney transplant recipients: a review of the current literature and recommendation. Best Pract Res Clin Obstet Gynaecol 2014;28:1123-1136.
18) Coscia LA, Constantinescu S, Moritz MJ, Frank A, Ramirez CB, Maley WL, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transplant 2009:103-122.
19) Nagy S, Bush MC, Berkowitz R, Fishbein TM, Gomez-Lobo V. Pregnancy outcome in liver transplant recipients. Obstet Gynecol 2003;102:121-128.
20) Christopher V, Al-Chalabi T, Richardson PD, Mulesan P, Rela M, Heaton ND, et al. Pregnancy outcome after liver transplantation: a single-center experience of 71 pregnancies in 45 recipients. Liver Transplant 2006;12:1138-1143.

21) Paulen ME, Folger SG, Curtis KM, Jamieson DJ. Contraceptive use among solid organ transplant patients: a systematic review. Contraception 2010;82:102-112.
22) Zerner J, Doil KL, Drewry J, Leeber DA. Intrauterine contraceptive device failures in renal transplant patients. J Reprod Med 1981;26:99-102.
23) Estes CM, Westhoff C. Contraception for the transplant patient. Semin Perinatol 2007;31:372-377.
24) Jabiry-Zieniewicz Z, Bobrowska K, Kaminski P, Wielgos M, Zieniewicz K, Krawczyk M. Low-dose hormonal contraception after liver transplantation. Transplant Proc 2007;39:1530-1532.
25) Kochhar S. UK medical eligibility criteria for contraceptive use. Independent Nurse 2016;2016:16-18.
26) Premuzic M, Vrcic H, Stanic P, Rustemovic N, Barisic D, Skegro M, et al. Successful pregnancy in a liver transplant patient after ovarian tubes removal resulting from in-vitro fertilisation: a case report. Liver Transplant 2012;18(suppl 1:S52).
27) Choi JM, Mahany EB, Sauer MV. Pregnancy after in vitro fertilization in a liver transplant patient. Reprod Med Biol 2013;12:69-70.
28) Ulug U, Mesut A, Jozwiak EA, Bahceci M. Successful pregnancy in a liver transplant recipient following controlled ovarian hyperstimulation and intracytoplasmic sperm injection. J Assist Reprod Genet 2005;22:311-313.
29) Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000;62:385-392.
30) Xiao WL, Liu XY, Liu YS, Zhang DZ, Xue LF. The relationship between maternal corticosteroid use and orofacial clefts-a meta-analysis. Reprod Toxicol 2017;69:99-105.
31) Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. CMAJ 2011;183:796-804.
32) Skuladottir H, Wilcox AJ, Ma C, Lammer EJ, Rasmussen SA, Werler MM, et al. Corticosteroid use and risk of orofacial clefts. Birth Defects Res A Clin Mol Teratol 2014;100:499-506.
33) Gur C, Diav-Citrin O, Shechtman S, Arnon J, Ornoy A. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. Reprod Toxicol 2004;18:93-101.
34) Bloom SL, Sheffield JS, Mcintire DD, Leveno KJ. Antenatal dexamethasone and decreased birth weight. Obstet Gynecol 2001;97:485-490.
35) McKinlay CJD, Crowther CA, Middleton P, Harding JE. Repeat antenatal glucocorticoids for women at risk of preterm birth: a Cochrane Systematic Review. Am J Obstet Gynecol 2012;206:187-194.
36) Nørgård B, Pedersen L, Fonager K, Rasmussen SN, Sørensen HT. Azathioprine, mercaptopurine and birth outcome: a population-based cohort study. Aliment Pharmacol Ther 2003; 17:827-834.
37) Casanova MJ, Chaparro M, Domènech E, Barreiro-De Acosta M, Bermejo F, Iglesias E, et al. Safety of thiopurines and Anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. Am J Gastroenterol 2013;108:433-440.
38) Cleary BJ, Källén B. Early pregnancy azathioprine use and pregnancy outcomes. Birth Defects Res A Clin Mol Teratol 2009;85:647-654.
39) Angelberger S, Reinisch W, Messerschmidt A, Miehsler W, Novacek G, Vogelsang H, Dejaco C. Long-term follow-up of babies exposed to azathioprine in utero and via breastfeeding. J Crohns Colitis 2011;5:95-100.
40) Flechner SM, Katz AR, Rogers AJ, Van Buren C, Kahan BD. The presence of cyclosporine in body tissues and fluids during pregnancy. Am J Kidney Dis 1985;5:60-63.
41) Venkataramanan R, Koneru B, Paul Wang CC, Burckart GJ, Caritis SN, Starzl TE. Cyclosporine and its metabolites in mother and baby. Transplantation 1988;46:468-469.
42) Jain A, Venkataramanan R, Fung JJ, Carlton Gartner J, Lever J, Balan V, et al. Pregnancy after liver transplantation under tacrolimus. Transplantation 1997;64:559-565.
43) Jain AB, Reyes J, Marcos A, Mazariegos G, Eghtesad B, Fontes PA, et al. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. Transplantation 2003;76:827-832.
44) Kainz A, Harabacz I, Cowlrick IS, Gadgil S, Hagiwara D. Analysis of 100 pregnancy outcomes in women treated systemically with tacrolimus. Transpl Int 2000;13:S299-S300.
45) Patapis P, Irani S, Mirza DF, Gunson BK, Lupo L, Mayer AD, et al. Outcome of graft function and pregnancy following liver transplantation. Transpl Proc 1997;29:1565-1566.
46) Coscia LA, Constantinescu S, Moritz MJ, Frank AM, Ramirez CB, Doria C, McGrory CH AV. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2008:89-105.
47) Coscia LA, Constantinescu S, Moritz MJ, Frank AM, Ramirez CB, Maley WR, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transplant 2010;65-85.
48) Kamarajah SK, Arntdz K, Bundred J, Gunson B, Haydon G, Thompson F. Outcomes of pregnancy in recipients of liver transplants. Clin Gastroenterol Hepatol 2019;17:1398-1404.
49) Sifontis NM, Coscia LA, Constantinescu S, Lavelanet AF, Moritz MJ, Armenti VT. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation 2006;82:1698-1702.
50) Kim M, Rostas S, Gabardi S. Mycophenolate fetal toxicity and risk evaluation and mitigation strategies. Am J Transplant 2013;13:1383-1389.
51) Veroux M, Corona D, Veroux P. Pregnancy under everolimus-based immunosuppression. Transpl Int 2011;24:e115-e117.
52) Coffin CS, Shaheen AAM, Burak KW, Myers RP. Pregnancy outcomes among liver transplant recipients in the United States: a nationwide case-control analysis. Liver Transplant 2010;16:56-63.
53) Songin T, Pietrzak B, Brawura-Biskupski-Samaha R, Kociszewska-Najman B, Jabiry-Zieniewicz Z, Cyganek A, et al. Pregnancy after kidney and liver transplantation: its outcome and effect on the graft, mother, and neonate. Ann Transplant 2014;19:660-666.
54) Ghazali S, Czuzoj-Shulman N, Spence AR, Mishkin DS, Abenhaim HA. Pregnancy outcomes in liver transplant patients, a population-based study. J Matern Neonatal Med 2017;30:261-266.
55) Álvaro E, Jimenez LC, Palomo I, Manrique A, Alegre C, Garcia M, et al. Pregnancy and orthotopic liver transplantation. Transpl Proc 2013;45:1966-1968.
56) Westbrook RH, Yeoman AD, Agarwal K, Aluvihare V, O'Grady J, Heaton N, et al. Outcomes of pregnancy following liver transplantation: the King's College Hospital experience. Liver Transplant 2015;21:1153-1159.
57) Lim TY, Gonsalkorala E, Cannon MD, Gabeta S, Penna L, Heaton ND, et al. Successful pregnancy outcomes following liver transplantation is predicted by renal function. Liver Transplant 2018;24:606-615.
58) Deshpande NA, James NT, Kucirka LM, Boyarsky BJ, Garonzik-Wang JM, Cameron AM, et al. Pregnancy outcomes of liver transplant recipients: a systematic review and meta-analysis. Liver Transplant 2012;18:621-629.
59) Baskiran A, Karakas S, Ince V, Kement M, Ozdemir F, Ozsay O, et al. Pregnancy after liver transplantation: risks and outcomes. Transplant Proc 2017;49:1875-1878.
60) Kubo S, Uemoto S, Furukawa H, Umeshita K, Tachibana D. Pregnancy outcomes after living donor liver transplantation: results from a Japanese survey. Liver Transplant 2014;20:576-583.
61) Jabiry-Zieniewicz Z, Szpotanska-Sikorska M, Pietrzak B, Kociszewska-Najman B, Foroncewicz B, Mucha K, et al.

Pregnancy outcomes among female recipients after liver transplantation: further experience. Transpl Proc 2011;43:3043-3047.
62) Radomski JS, Moritz MJ, Muñoz SJ, Cater JR, Jarrell BE, Armenti VT. National transplantation pregnancy registry: analysis of pregnancy outcomes in female liver transplant recipients. Liver Transplant Surg 1995;1:281-284.
63) Cyganek A, Pietrzak B, Kociszewska-Najman B, Grzechocińska B, Songin T, Foroncewicz B, et al. Intrauterine growth restriction in pregnant renal and liver transplant recipients: risk factors assessment. Transplant Proc 2014;46:2794-2797.
64) American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol 2013;122:1122-1131.
65) Kanzaki Y, Kondoh E, Kawasaki K, Mogami H, Chigusa Y, Konishi I. Pregnancy outcomes in liver transplant recipients: a 15-year single-center experience. J Obstet Gynaecol Res 2016;42:1476-1482.
66) Blume C, Sensoy A, Gross MM, Guenter HH, Haller H, Manns MP, et al. A comparison of the outcome of pregnancies after liver and kidney transplantation. Transplantation 2013;95:222-227.
67) Hyppönen E, Cavadino A, Williams D, Fraser A, Vereczkey A, Fraser WD, et al. Vitamin D and pre-eclampsia: original data, systematic review and meta-analysis. Ann Nutr Metab 2014;63:331-340.
68) Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol 2018;38:181.
69) Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm pre-eclampsia. Obstet Med 2018;377:613-622.
70) Caron N, Rivard GÉ, Michon N, Morin F, Pilon D, Moutquin JM, et al. Low-dose ASA response using the PFA-100 in women with high-risk pregnancy. J Obstet Gynaecol Canada 2009;31:1022-1027.
71) Rouas-Freiss N, Naji A, Durrbach A, Carosella ED. Tolerogenic functions of human leukocyte antigen G: from pregnancy to organ and cell transplantation. Transplantation 2007;84:S21-S25.
72) Samuels P, Cohen AW. Pregnancies complicated by liver disease and liver dysfunction. Obstet Gynecol Clin North Am 1992;19:745-763.
73) Rodin A, Duncan A, Quartero HWP, Pistofidis G, Mashiter G, Whitaker K, et al. Serum concentrations of alkaline phosphatase isoenzymes and osteocalcin in normal pregnancy. J Clin Endocrinol Metab 1989;68:1123-1127.
74) Bacq Y, Zarka O, Brechot J, Mariotte N, Vol S, Tichet J, et al. Liver function tests in normal pregnancy: a prospective study of 103 pregnant women and 103 matched controls. Hepatology 1996;23:1030-1034.
75) Wu A, Nashan B, Messner U, Schmidt HH, Guenther HH, Niesert S, et al. Outcome of 22 successful pregnancies after liver transplantation. Clin Transplant 1998;12:454-464.
76) Raakow R, Neuhaus R, Büscher U, Schmidt S, Rayes N, Glanemann M, et al. Parenthood following liver transplantation. Transpl Proc 2001;33:1450-1452.
77) Ville Y, Fernandez H, Samuel D, Bismuth H, Frydman R. Pregnancy in liver transplant recipients: course and outcome in 19 cases. Am J Obstet Gynecol 1993;168:896-902.
78) Armenti VT, Daller JA, Constantinescu S, Silva P, Radomski JS, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry: outcomes of pregnancy after transplantation. Clin Transplant 2006:57-70.
79) Rodríguez-Perálvarez M, Rico-Juri JM, Tsochatzis E, Burra P, De la Mata M, Lerut J. Biopsy-proven acute cellular rejection as an efficacy endpoint of randomized trials in liver transplantation: a systematic review and critical appraisal. Transpl Int 2016;29:961-973.
80) Constantinescu S, Axelrod P, Coscia LA, Moritz MJ, Armenti VT. Risk factors for graft loss within 5 years post pregnancy in female kidney recipients. Am J Transplant 2011;11:205.
81) Sibanda N, Briggs JD, Davison JM, Johnson RJ, Rudge CJ. Pregnancy after organ transplantation: a report from the U.K. Transplant Pregnancy Registry. Transplantation 2007;83:1301-1307.
82) Moon DB, Lee SG, Hwang S, Kim KH, Ahn CS, Ha TY, et al. Characteristics and management of splenic artery aneurysms in adult living donor liver transplant recipients. Liver Transplant 2009;15:1535-1541.
83) Mattila M, Kemppainen H, Isoniemi H, Polo-Kantola P. Pregnancy outcomes after liver transplantation in Finland. Acta Obstet Gynecol Scand 2017;96:1106-1111.
84) Pruvot FR, Declerck N, Valat-Rigot AS, Gambiez L, Canva V, Labalette M, et al. Pregnancy after liver transplantation: focusing on risks to the mother. Transpl Proc 1997;29:2470-2471.
85) Morton A. Liver transplantation and pregnancy. Aust New Zeal J Obstet Gynaecol 2003;43:236-238.
86) Wijarnpreecha K, Thongprayoon C, Sanguankeo A, Upala S, Ungprasert P, Cheungpasitporn W. Hepatitis C infection and intrahepatic cholestasis of pregnancy: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2017;41:39-45.
87) Ovadia C, Seed PT, Sklavounos A, Geenes V, Di Illio C, Chambers J, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet 2019;393:899-909.
88) Prodromidou A, Kostakis ID, Machairas N, Garoufalia Z, Stamopoulos P, Paspala A, et al. Pregnancy outcomes after liver transplantation: a systematic review. Transplant Proc 2019;51:446-449.
89) Moritz M, Coscia L, Constantinescu S, Armenti D. National transplantation pregnancy registry: cholestasis of pregnancy in liver transplant recipients. Am J Transplant 2015;15(suppl 3):110.
90) Jabiry-Zieniewicz Z, Dabrowski FA, Pietrzak B, Wielgos M. Pregnancy complications after liver transplantation. Int J Gynecol Obstet 2015;128:27-29.
91) Concepcion BP, Schaefer HM. Caring for the pregnant kidney transplant recipient. Clin Transplant 2011;25:821-829.
92) Ross DS, Dollard SC, Victor M, Sumartojo E, Cannon MJ. The epidemiology and prevention of congenital cytomegalovirus infection and disease: activities of the centers for disease control and prevention workgroup. J Women's Heal 2006;15:224-229.
93) Schreiber-Zamora J, Kociszewska-Najman B, Borek-Dzięcioł B, Drozdowska-Szymczak A, Czaplińska N, Pawlik O, et al. Neurological development of children born to liver transplant recipients. Transpl Proc 2014;46:2798-2801.
94) Kimmich N, Dutkowski P, Krähenmann F, Müllhaupt B, Zimmermann R, Ochsenbein-Kölble N. Liver transplantation during pregnancy for acute liver failure due to HBV infection: a case report. Case Rep Obstet Gynecol 2013;2013:1-5.
95) Toti L, Manzia TM, Romano P, Lenci I, Baiocchi L, Anselmo A, et al. Successful management of a same-day emergency delivery and liver transplant in a 27 weeks pregnant woman with fulminant hepatic failure. Transpl Int 2010;23:114-115.
96) Sato H, Tomita K, Yasue C, Umeda R, Ebinuma H, Ogata S, et al. Pregnant woman with non-comatose autoimmune acute liver failure in the second trimester rescued using medical therapy: a case report. Hepatol Res 2015;45:349-355.
97) Catnach SM, McCarthy M, Jauniaux E, Fitt S, Tan KC, Nicolaides K, et al. Liver transplantation during pregnancy complicated by cytomegalovirus infection. Transplantation 1995;60:510-511.

98) American Academy of Pediatrics. Breastfeeding and the use of human milk. Pediatrics 2012;129:e827-e841.
99) Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. Am J Obstet Gynecol. 2015
100) Bartsch E, Medcalf KE, Park AL, Ray JG, Al-Rubaie ZTA, Askie LM, et al. Clinical risk factors for pre-eclampsia determined in early pregnancy: Systematic review and meta-analysis of large cohort studies. BMJ. 2016;
101) Ward RM, Bates BA, Benitz WE, Burchfield DJ, Ring JC, Walls RP, et al. The transfer of drugs and other chemicals into human milk. Pediatrics 2001;108:776-789.
102) Constantinescu S, Pai A, Coscia LA, Davison JM, Moritz MJ, Armenti VT. Breast-feeding after transplantation. Best Pract Res Clin Obstet Gynaecol 2014;28:1163-1173.
103) Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatol (United Kingdom) 2016;55:1693-1697.
104) Osadchy A, Koren G. Cyclosporine and lactation: when the mother is willing to breastfeed. Ther Drug Monit 2011;33:147-148.
105) Bramham K, Chusney G, Lee J, Lightstone L, Nelson-Piercy C. Breastfeeding and tacrolimus: serial monitoring in breastfed and bottle-fed infants. Clin J Am Soc Nephrol 2013;8:563-567.
106) Zheng S, Easterling TR, Hays K, Umans JG, Miodovnik M, Clark S, et al. Tacrolimus placental transfer at delivery and neonatal exposure through breast milk. Br J Clin Pharmacol 2013;76:988-996.