Position Paper

# AISF position paper on liver transplantation and pregnancy

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ABSTRACT

After the first successful pregnancy in a liver transplant recipient in 1978, much evidence has accumulated on the course, outcomes and management strategies of pregnancy following liver transplantation. Generally, liver transplantation restores sexual function and fertility as early as a few months after transplant. Considering that one third of all liver transplant recipients are women, that approximately one-third of them are of reproductive age (18–49 years), and that 15% of female liver transplant recipients are paediatric patients who have a >70% probability of reaching reproductive age, the issue of pregnancy after liver transplantation is rather relevant, and obstetricians, paediatricians, and transplant hepatologists ever more frequently encounter such patients. Pregnancy outcomes for both the mother and infant in liver transplant recipients are generally good, but there is an increased incidence of preterm delivery, hypertension/preeclampsia, foetal growth restriction, and gestational diabetes, which, by definition, render pregnancy in liver transplant recipients a high-risk one. In contrast, the risk of congenital anomalies and the live birth rate are comparable to those of the general population. Currently there are still no robust guidelines on the management of pregnancies after liver transplantation. The aim of this position paper is to review the available evidence on pregnancy in liver transplant recipients and to provide national Italian recommendations for clinicians caring for these patients.

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## 1. Introduction

Most of the information regarding pregnancy in organ transplant recipients derives from kidney transplant recipients, and although several parallelisms can be drawn amongst different organ recipients, patient conditions may differ considerably even in the absence of pregnancy. The first successful pregnancy following liver transplantation (LT) occurred in 1978 and led to excellent maternal and foetal outcomes, despite low birth weight [1]. Although numerous studies have been published reporting single cases [1], case series [2–10], surveys [11,12], population-based studies [13], and registries (e.g. the National Transplantation Pregnancy Registry [14–19] and the UK Transplant Pregnancy Registry

[20]) on pregnancy in liver transplant recipients, no randomized controlled trials have been carried out, and much of the evidence regarding drug safety during pregnancy comes from animal studies. In addition, reporting bias in voluntary registries and selection bias in studies from referral centres limit the strength and quality of scientific evidence. Thus, although efforts have been made towards the development of evidence-based management strategies [21], there are still no robust guidelines on the management of pregnancies after LT [3]. The aim of this position paper is to review the available evidence on pregnancy in LT recipients and to provide national Italian recommendations for clinicians caring for these patients. Following the previous publication [22], the recommendations were drawn using the level of evidence and strength of recommendations graded according to the American College of Cardiology and the American Heart Association Practice Guidelines [23].

## 2. Pregnancy after liver transplantation

In fertile women, successful LT restores menstrual function in 97% of female patients, as well as childbearing potential [23,24]. In general, LT leads to partial or complete normalization of both levels of sex hormones and sexual function within several months, with nearly 48% of women in their fertile age experiencing regular menses, 26% irregular bleeding, and 26% amenorrhea [25,26], while more than 60% of peri-menopausal women

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reportedly experience a higher frequency of menstrual pattern disorders [23,27,28]. Currently, women constitute one-third of all liver transplant recipients, and approximately one-third of them are of reproductive age (18–49 years). In the United States only, approximately 14,000 women of childbearing age are currently liver transplant recipients, and another 500 women will undergo LT every year. Moreover, 15% of female liver transplant recipients are paediatric patients who have a >70% probability of reaching reproductive age [8,29]. Pregnancy outcomes for both the mother and infant in liver transplant recipients are generally good [30,31], but there is an increased incidence of preterm delivery, hypertension/preeclampsia, foetal growth restriction, and gestational diabetes [4,7–10,12,14,16,32,33].

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**Background**

Pregnancy in liver transplant recipients is considered a high-risk pregnancy, with an increased risk of maternal and foetal complications, including pre-eclampsia, gestational diabetes, spontaneous abortion, Caesarean delivery, preterm labour, and intrauterine growth restriction; the risk of congenital anomalies, and live birth rate are comparable to those of the general population.

**Recommendations:**

**2.a.** Pregnant liver transplant recipients must be managed by a team including an obstetrician and a transplant hepatologist. (Grade III)
**2.b.** Medical and obstetrical follow up as well as delivery must be carried out in a tertiary centre and, preferably, in a liver transplant centre. (Grade III)

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## 3. Pre-conception counselling and timing of pregnancy

Together with menstruation, sexual function can return to normal and consequently women who have undergone successful LT may conceive as early as one month following LT [33,34]. In the presence of stable graft function, stable maintenance immunosuppression, and absence of pre-conceptional hypertension, patients are more likely to have successful pregnancy outcomes [19,35]. An inverse association between the interval from liver transplant and abortion rate has been observed [8,36], but not confirmed in all studies [29]. Ideally, preconception counselling should begin during the pre-transplantation evaluation process [21]. Liver transplant recipients should receive counselling regarding contraception and they should be provided with appropriate pre-conception medical advice and education if they wish to become pregnant. Patients should receive counselling regarding the increased risk of potential adverse foetal outcomes, including stillbirth, prematurity and low birth weight, as well as a higher risk of maternal complications such as preeclampsia [11,37].

Although pregnancy does not increase the risk of maternal mortality in liver transplant recipients, these women should be aware of their prognosis for long-term survival and ability to care for a child. In a series of 29 transplant recipients who completed a pregnancy, 5 died between 10 and 54 months postpartum [8]. However, the decision should rely on the patient, and due to the acceptable risks of pregnancy after LT, patients should not be advised against pregnancy [11]. Should the patient manifest her informed intention to become pregnant, her health status regarding the graft (avoidance of recurrence of disease, establishment of minimal required doses of immunosuppression, avoidance of rejection episodes) and general health (renal function, diabetes, hypertension) should be optimized before conception [35].

According to consensus recommendations from the American Society of Transplantation, pregnancy can be considered if there has been (1) no rejection within the year previous to intended conception, (2) there is adequate and stable graft function, (3) no acute infections that may impact foetal growth and well-being, and (4) maintenance immunosuppression is at stable dosing [38].

The optimal timing of conception is still a matter of debate, but waiting 1–2 years after LT is generally recommended [19,21,38,39]. After this interval, the clinical course is usually stable, the risk of rejection is lower, immunosuppression therapy is usually at maintenance levels, and the risk of infections is lower. The recently issued EASL guidelines for liver transplantation also advocate a period of at least 12–24 months between LT and conception [37].

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**Background**

In women of childbearing age, fertility is restored in the first several months after successful liver transplantation, and pregnancy is not only possible, but is generally associated with acceptable maternal and foetal outcomes, and is not associated with increased risk of graft rejection per se.

**Recommendations:**

**3.a.** Counselling must initiate before liver transplantation, and must continue after liver transplantation and before conception. (Grade III)
**3.b.** Stable graft function on maintenance immunosuppression and good maternal health must be ensured before conception. (Grade III)

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## 4. Contraception

Periodic abstinence and *coitus interruptus* are ineffective methods of contraception and cannot be recommended [40]. Barrier methods represent a valid option due to the absence of drug interactions and low cost, although failure rates range between 15% and 32% [41]. Diaphragms might increase the risk of urinary infections, which is already present in transplant recipients [42]. Condoms represent the only form of contraception that prevents most sexually transmitted diseases and should be recommended for all patients without a stable sexual partner [41]. Intrauterine devices, although very effective in the general population, may increase the risk of infections [43] and a potential reduction in their effectiveness has been reported in immunosuppressed patients [44,45]. Drug interactions are obviously only of minor importance, and it has been suggested that intrauterine devices might constitute the best contraceptive option for transplant recipients [41,46]. Regarding oral contraceptives or transdermal contraceptives, the same contraindications as in the general population have to be respected, including personal history of myocardial infarction, stroke or deep vein thrombosis, migraine with focal aura, uncontrolled systemic hypertension, smoking over the age of 35, marked unexplained liver test abnormalities and hepatic adenoma. Being metabolized by the hepatic cytochrome P4503A4 system, drug-to-drug interactions may be a concern, especially with cyclosporine and tacrolimus, which are both metabolized by this enzyme [47]. Oral contraceptives should be used carefully after liver transplantation, with frequent monitoring of liver function tests, and should be used only in recipients with stable graft function for at least 6–8 months and without other contraindications [48,49]. Regarding surgical sterilization, many liver transplant recipients choose this

approach, which avoids drug interactions and is very effective at preventing unwanted conception [23,50].

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**Background**

Although fertility is rapidly restored after transplantation, a shorter interval between transplantation surgery and initiation of pregnancy has been associated with worse outcomes, making contraception paramount.

**Recommendations:**

**4.a.** An interval of at least 12–24 months after successful liver transplantation is recommended before initiation of pregnancy. (Grade III)
**4.b.** Barrier methods are recommended, due to the absence of drug interactions, and condoms should be used in patients without a stable sexual partner to prevent most sexually transmitted diseases. (Grade III)
**4.c.** Special attention is recommended with the use of intrauterine devices, due to a higher risk of infections and reduced effectiveness while on immunosuppression. (Grade III)
**4.d.** Oral contraceptives share common metabolic pathways with immunosuppressive medication and must be used with caution. (Grade III)
**4.e.** Surgical sterilization is recommended in patients who do not desire a future pregnancy. (Grade III)

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## 5. Pre-gestation pregnancy risks associated with post-liver transplantation status

Preconception hypertension (standardized prevalence ratio [SPR] = 3.07, 95% confidence interval [CI], 2.35–3.93), diabetes (SPR = 5.99, 95% CI, 4.15–8.38), and chronic kidney disease ([SPR] = 15.3 ± 4.04) [51] are more frequent in liver transplant recipients, and these constitute major risk factors for obstetric complications including preeclampsia [51–54], macrosomia [55], stillbirth [55], pre-term labour [56], and congenital malformations [55]. The frequency of post-LT hypertension is especially higher in female transplant recipients vs their non-transplanted counterparts in the fertile age range (<45 years) [51]. Moreover, hypertension is statistically more frequent in pregnant patients with a prior LT, with respect to their pregnant non-transplanted counterparts [13].

Diabetes complicates approximately 5.1% of pregnancies after LT [39], and may be present previous to conception, when it is mainly associated to immunosuppressive medication after transplantation, or may develop as gestational diabetes, as a result of the combination of both diabetogenic drugs and pregnancy itself. Because allograft recipients have an increased risk for gestational diabetes, they should undergo a 50-g oral glucose load at 16–18 weeks of gestation. Adequate glycemic control during pregnancy is mandatory to reduce associated adverse maternal and foetal outcomes [55–57].

The presence of pre-conception end-organ damage such as nephropathy in diabetic patients, results in a higher risk for pregnancy-related adverse events including preeclampsia, pregnancy-induced hypertension, preterm delivery, Caesarean section, perinatal death, and stillbirth [58–61].

### 5.1. Risks of pregnancy in liver transplant recipients

Generally, pregnancy does not have a negative impact on graft function, but is associated with significant obstetric risks

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**Background**

Hypertension and diabetes more frequently complicate pregnancies in liver transplant recipients with respect to the general population, and might exist pre-conception or may develop during pregnancy. The presence of pre-conception end-organ damage increases the risk of preeclampsia, preterm delivery, Caesarean section, perinatal death, and stillbirth.

**Recommendations:**

**5.a.** Screening for gestational diabetes with a 50-g oral glucose load should be performed at 16–18 weeks of gestation. (Grade III)
**5.b.** Maintenance of adequate pharmacological control of blood pressure and glycemia during the entire course of pregnancy is mandatory. (Grade III)

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[17,19,39,61,62]. Pregnancy in liver transplant recipients should be considered a high-risk pregnancy because of the increased risk for both maternal and foetal complications [39], and should be managed by a multidisciplinary team including a high-risk obstetrician and a transplant hepatologist [63,64]. Medical and obstetrical follow up as well as delivery should be managed in a tertiary centre and, preferably, in a liver transplant centre.

Maternal deaths and most adverse pregnancy outcomes do not differ significantly between transplant recipients and the general population [13]. However, foetal deaths, antepartum admissions, and maternal and foetal complications overall are 2- to 3-fold greater in liver allograft recipients [13].

### 5.2. Foetal complications

Most foetal complications [13] including spontaneous abortion (5%), preterm birth (27.4%), intrauterine growth restriction (4.8%), and foetal distress (10.3%) are statistically more frequent in transplant recipients compared to the general population [65], but the incidence of congenital anomalies is apparently comparable to that of the non-transplant population (1.4%) [36]. Although some have suggested that the higher risk of preterm birth might be due in part to episodes of graft rejection and early onset preeclampsia, this has not been confirmed [8].

### 5.3. Maternal complications associated to pregnancy

The frequency of maternal complications in liver transplant recipients including death, antepartum haemorrhage, and peripartum infections, is similar to that of the general population, whereas post-partum haemorrhage, blood transfusions, and hypertensive disorders of pregnancy (preeclampsia, but not eclampsia) are more frequent in liver allograft recipients with respect to the general population [13,63]. A meta-analysis on 450 pregnancies in 306 LT recipients showed that although the rates of pre-eclampsia (21.9%), caesarean section delivery (44.6%), and preterm delivery (39.4%) were higher than the rates for the US general population (3.8%, 31.9%, and 12.5%, respectively), the post-LT live birth rate (76.9%) was higher than the live birth rate for the US general population (66.7%), and the post-LT miscarriage rate (15.6%) was lower than the miscarriage rate for the general population (17.1%) [53].

Hypertension (present in as many as 39% of pregnancies after LT) and preeclampsia (present in as many as 18% of pregnancies after LT) probably constitute major factors contributing to the increased prevalence of preterm delivery and foetal growth restriction in transplant recipients [19]. Pregnancy-induced hypertension and

preeclampsia may be related to immunosuppressive therapy and an increased incidence of baseline renal dysfunction in liver transplant recipients. The incidence of hypertension according to the type of immunosuppression is between 22% and 29% with corticosteroids [14], 68% and 73% with cyclosporine, and 47% and 54% with tacrolimus [17]. It is unclear if the steroid component of immunosuppression is the determinant of the greater frequency of pregnancy-induced hypertension in these patients [8]. Tacrolimus-based immunosuppressive regimens have been associated with lower rates of hypertension [6,8,66]. Overall, the small number of patients evaluated and the suboptimal quality of evidence do not allow for univocal conclusions.

### 5.4. Maternal complications regarding transplant recipient status

The reported incidence of rejection (with a mean age at conception of $26.8 \pm 3.4$ years) is highly variable (from 0% to 20%) [4,6–10,14,30,67–69], whereas rejection rates in the non-pregnant population after liver transplantation are approximately 2–3% [69,70]. Voluntary suspension of immunosuppression by the mother has been reported as the cause of a higher rate of rejection, and episodes are generally reversible with steroid boluses and re-establishment of adequate immunosuppressive therapy [71]. In a recently published study on King's College's experience analyzing 117 conceptions in 79 patients, acute cellular rejection was significantly more common in women who conceived within 12 months of LT ($P = 0.001$) [63].

Although there have been reports of worsening renal function during pregnancy after LT [3], many other series have not reported such finding, and pregnancy does not seem to trigger humoral rejection involving anti-HLA class I and II antibodies [72]. At present, there is not sufficient evidence to consider renal function deterioration a frequent finding in this group of patients.

### 5.5. General obstetric outcomes

Regarding obstetric outcomes in liver transplant recipients, the following frequencies have been reported: spontaneous abortion 11–19% [3,7,8,20,35], Caesarean delivery 20–63% [3–5,7–10,20,36], preterm labour (<37 weeks gestation) 14–53% [3–5,8–10,20,36], graft rejection 5–17% [4,7–10,20,36,37], and hypertensive disorders of pregnancy (preeclampsia/eclampsia) 5–33% [3–5,7–10,36].

A review of 285 pregnancies after LT found a non-significant higher frequency of abortions in patients transplanted for autoimmune hepatitis [36]. At present, there is not enough evidence that the risk of rejection is dependent upon the indication for LT.

Caesarean sections are statistically more frequent in liver transplant recipients vs their counterparts with no previous transplantation [13], whereas the frequency of premature rupture of membranes, *placenta previa*, and placental abruption are similar in transplanted pregnant patients compared to the general population [13].

### 5.6. Management of pregnancy in a liver transplant recipient

#### 5.6.1. Metabolic complications

Gestational diabetes is likely provoked by chronic prednisone administration, thus these patients may benefit from diabetes screening between 16 and 18 weeks of gestation.

Hypertension must be adequately controlled, avoiding angiotensin receptor blockers and angiotensin-converting enzyme inhibitors, which are contraindicated during pregnancy; according to the American College of Obstetricians and Gynaecologists (ACOG), methyldopa constitutes an appropriate first-line agent [73,74].

#### 5.6.2. Infectious complications

Infections frequently affect transplant recipients [75], and although urinary infections and pyelonephritis are more frequent and severe in renal transplant recipients [76], surveillance, prompt diagnosis and therapy of possible infections is warranted in LT as well [21].

The transplanted graft is a source of cytomegalovirus (CMV), and patients typically receive prophylaxis against CMV for 1–3 months postoperatively, when the risk of infection is highest. The greatest risk of congenital infection in the foetus is represented by primary CMV infection during pregnancy, but recurrent CMV infection in the immunosuppressed female patient has also been reported to cause congenital CMV in the infant [77]. Monitoring for de novo CMV infection, or, more frequently, reactivation induced by immunosuppression, is paramount, as it can cause serious foetal malformations if left untreated [78,79].

CMV infection, transmitted to the foetus through the transplacental route as well as during delivery or breastfeeding, can cause serious complications in the foetus, including hydrops fetalis, stillbirth, mental retardation, visual, and hearing loss, and preterm birth with neonatal deaths in offspring of liver transplant recipients [80,81]. The presence of maternal immunity does not absolutely protect the foetus, although it does reduce the likelihood of transmission [82,83]. However, antiviral prophylaxis has not generally been recommended during pregnancy [84].

Other infections that may pose additional risks in the immunosuppressed mother include toxoplasmosis, primary herpes simplex infection, primary varicella infection, HIV infection, and infection with either hepatitis B or C virus [85,86]. Prenatal screening can detect each of these infections, although in many cases the mother presents just before prenatal screening when maternal prophylaxis can no longer be considered.

#### 5.6.3. General management

The following constitute general management guidelines for pregnancy after LT [87].

- As in case of all high risk pregnancies, monthly evaluation including clinical examination, assessment of graft function and maternal health by monitoring blood pressure, routine laboratory tests including urinary culture is warranted [21].
- Moreover, viral serology for hepatitis B and C, Toxoplasma, routine blood tests for hepatic and renal functions, and CMV as well as microbiological cultures of vaginal smears for B-hemolytic *Streptococcus*, *Chlamydia trachomatis*, *Mycoplasma* spp., *Ureaplasma urealyticum*, *Candida* spp., and *Escherichia coli* should be repeated monthly.
- A first trimester ultrasonography should be performed to determine gestational age, and this exam should be repeated at 20 weeks for assessment of foetal morphology. Thereafter, beginning at 24 to 26 weeks of gestation, serial ultrasonography should be performed every 4 weeks to evaluate foetal growth [21].
- Foetal heart rate should be assessed weekly from week 28 until delivery [36].
- If intra-uterine growth retardation is documented, foetal health should be strictly monitored by serial ultrasound biometry, Doppler assessment, and electronic foetal heart rate monitoring [88].
- Supported by recent evidence, the mode of delivery is independent from the transplant recipient status; the frequency of Caesarean sections is at present not different between transplant recipients and their non-transplanted counterparts [13]. Caesarean section should be reserved for obstetrical complications,

**Table 1**
Pregnancy category of immunosuppressive drugs commonly used after liver transplantation.

| Drug | Pregnancy category | Risks/observed associations |
|---|---|---|
| Corticosteroids (prednisone, prednisolone, and methylprednisolone) | B | Intrauterine growth retardation, maternal hypertension, gestational diabetes, foetal adrenal insufficiency |
| Calcineurin inhibitors | C | Intrauterine growth retardation, maternal hypertension, gestational diabetes, renal dysfunction, foetal perinatal hyperkalemia |
| Mycophenolate mofetil | D | Spontaneous abortion, malformations including microtia, hypoplastic nails and shortened fifth fingers, cleft lip and palate, absence of auditory canals, neonatal death with multiple malformations |
| mTOR inhibitors | C | Animal studies have shown decreased foetal weight, delayed ossification of skeletal structures, but no teratogenicity. The risk in humans cannot be ruled out. |
| Azathioprine | D | Intrauterine growth retardation, foetal anaemia, thrombocytopenia, leucopenia, decreased foetal immunoglobulin levels, neonatal infection and sepsis, preterm delivery, low birth weight |

mTOR (mammalian target of rapamycin). According to the Food and Drug Administration of the United States, the following are the drug safety categories during pregnancy. Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the foetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). Category B: Animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women. Category C: Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Category D: There is positive evidence of human foetal 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. Category X: Studies in animals or humans have demonstrated foetal abnormalities and/or there is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits FDA immunosuppressive drugs recommended during pregnancy and lactation.

and there is no particular contraindication to vaginal delivery in relation to the transplant status [66].

## 6. Immunosuppression during pregnancy

The benefits of immunosuppressive therapy in transplant recipients generally outweigh the slightly increased risk of adverse pregnancy outcome and most women taking these drugs will have normal, healthy babies [18], without evidence of increased risk of neurological impairment when followed into childhood years [89]. The lowest possible dose needed to prevent rejection should be used, in order to avoid potential adverse effects on mother and foetus [18,19,21]. Maintenance of pre-conception immunosuppression is recommended, with the exception of mycophenolic acid products and azathioprine, which should be discontinued before conception and replaced with an alternative medication [21] (Table 1).

Although studies have shown relatively stable plasmatic values of immunosuppressants during pregnancy [36], other studies have demonstrated a variable demand for tacrolimus, with highest tacrolimus demand coinciding with the lowest values of hematocrit physiologically observed during pregnancy [71]. Plasma levels of immunosuppressive drugs should be monitored, and dosing adjusted in relation to the physiological changes of pregnancy and graft function [21] to avoid under or over dosing related to physiological changes of pregnancy.

### 6.1. Calcineurin inhibitors

Calcineurin inhibitors (including cyclosporine and tacrolimus) have not been definitively associated with teratogenicity; rates of major foetal malformation in exposed infants are similar to those of the non-exposed population, and no specific pattern of malformation has been reported [5]. Initial reports of calcineurin inhibitor-induced intrauterine growth restriction, spontaneous abortions, and premature births were associated with elevated levels (tacrolimus levels 8.5–9.9 ng/mL) [90,91], and have not been confirmed by subsequent studies [5,6,90].

For patients taking either cyclosporine or tacrolimus, frequent monitoring of renal function and drug levels is warranted, especially since during pregnancy the hepatic cytochrome P450

enzymes may be inhibited, which can lead to increased serum level of tacrolimus. The dose may therefore have to be significantly reduced to prevent toxicity (sometimes by as much as 60%) [38,39,78]. Increased monitoring of blood levels of cyclosporine is also warranted, due to increased hepatic clearance during pregnancy [92,93].

### 6.2. Steroids

The shorter-acting agents prednisone, prednisolone, and methylprednisolone, which are metabolized by placental 11-hydroxygenase, can cross the placenta, but maternal – to cord – blood ratios are approximately 10:1 and result in foetal exposure that corresponds to approximately 10% of the maternal dose [94]. Aside from their use as immunosuppressants after transplantation, these are also employed routinely for the treatment of maternal disorders and also for inducing foetal pulmonary maturation when pre-term birth is foreseen [95].

Although an association between corticosteroid use during pregnancy and cleft lip and/or palate in animal models [96,97] as well as in humans [98–100] was initially reported, this data was based on old studies in which high doses of steroids (mean dose $27 \pm 29$ mg/day) were used, and teratogenicity deriving from maternal underlying disease and/or the concomitant use of established teratogens such as carbamazepine cannot not be ruled out. Newer and larger studies have demonstrated no such association, and have established the safety of corticosteroid use in pregnancy [101–103]. Therefore, according to the United States Food and Drug Administration, at present there is no evidence that either prednisone or methylprednisolone is teratogenic in humans (Food and Drug Administration [FDA] risk category B).

Aside from steroid-associated complications that can be observed in all non-pregnant patients such as immunosuppression, avascular necrosis of bone, osteopenia, hypertension, hyperglycemia, cataracts, and striae, maternal pregnancy-specific complications such as development or worsening of gestational diabetes and hypertension may complicate the course of pregnancy [104,105].

The routine use of oral calcium and vitamin D supplements is warranted to prevent osteoporosis, especially in patients treated with steroids [105,106].

Patients who have been treated with corticosteroids during pregnancy should be given "stress doses" of hydrocortisone for any emergency surgery, Caesarean section, or prolonged labour and delivery. Neonates should be monitored for evidence of adrenal insufficiency and infection. Women who choose to breastfeed while taking high doses of glucocorticoids could wait 4 h after ingesting a dose to resume breastfeeding, a strategy that will decrease the amount of glucocorticoid in milk [107,108].

### 6.3. Azathioprine

Azathioprine is apparently not teratogenic in humans [109], although its oncogenic risk raises concerns about its use in pregnancy and breastfeeding [6,8]. Azathioprine crosses the placenta, but the lack of foetal enzymatic activity capable of converting azathioprine to its active metabolites seemingly protects the foetus from any teratogenic effects of azathioprine early in pregnancy [105]. Although this drug has been associated with an increased risk of growth retardation [110,111], the underlying condition (e.g. hypertension in renal transplant recipients) may have actually been the major contributor in reported cases. On the other hand, there have been reports of normal pregnancies and neonates in patients treated with azathioprine and prednisone [86,112,113].

Infants exposed to azathioprine in early pregnancy (including pregnancies in organ transplant recipients) may be at a moderately increased risk of congenital malformations, specifically ventricular/atrial septal defects. There is also an increased risk of growth restriction and preterm delivery, but it is not clear is these complications could be partly due to the severity of maternal illness [114]. Azathioprine has been associated with a dose-related myelosuppression in the foetus, but leukopenia is not usually a problem in the neonate if the maternal white blood count is maintained at values higher than $7500\,\text{mm}^{-3}$ [115]. Because of the potential for carcinogenesis and the unknown long-term effects of foetal immunosuppression, use of azathioprine should be withheld if possible; reduction of the azathioprine dose at 32 weeks' gestation may prevent serious neonatal leukopenia and thrombocytopenia, while close prenatal foetal growth monitoring and long-term post-natal evaluation of the offspring are warranted [115].

### 6.4. Mycophenolate mofetil

Mycophenolate mofetil (MMF), which blocks de novo purine synthesis in T and B lymphocytes, has been associated with teratogenic risks including developmental toxicity, intrauterine death, and malformations at doses which appeared to be within recommended clinical doses based on body surface area [116]. Exposure to mycophenolate mofetil during early pregnancy has been associated with a higher incidence of structural malformations. In the study by Sifontis and collaborators [117], amongst 33 pregnancies with early exposure to MMF (with TAC) in different organ transplant recipients (including pregnancies in 26 kidney, 1 kidney/pancreas, 3 liver, and 3 heart transplant recipients), 15 resulted in spontaneous abortion, and malformations including hypoplastic nails and shortened fifth fingers, microtia with cleft lip and palate, isolated microtia, and neonatal death with multiple malformations were reported in 4/15 live births from kidney transplant recipients. As a result of this significant teratogenic risk, the United States Food and Drug Administration has issued a boxed warning concerning the risk of first trimester foetal loss and congenital malformations [118]; this drug is now classified as US FDA category D medication and should not be used during pregnancy [21,38].

### 6.5. Mammalian target of rapamycin (mTOR) inhibitors

Evidence is still scarce regarding the use of sirolimus and everolimus during pregnancy after LT and they are contraindicated in pregnancy. They should also be discontinued at least 12 weeks prior to attempted conception [119], switching to a calcineurin inhibitor for the duration of pregnancy. When weighing the risks for the foetus, there is still a great deal of ambiguity about whether sirolimus is intrinsically teratogenic, and it is therefore contraindicated for pregnancy (FDA Category C). Actual evidence of adverse effects is lacking, and there have been numerous reports of successful maternal and foetal outcomes during pregnancies in which sirolimus or everolimus were used [19,118,120–123].

Although revision according to stricter evidence is ongoing [123], and considering that in transplant recipients many factors other than a direct teratogenic effect are present, such as vascular issues, direct effects of maternal conditions and also the interaction with other potential pharmacological agents [124], currently, the following is the official Pregnancy Category of immunosuppressive drugs. (Data from [125])

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**Background**

The benefits of immunosuppression in maintaining adequate graft function outweigh the possible risks associated with foetal exposure, and the goal is to use the minimal dose required to avoid rejection while minimizing foetal exposure. Pregnancy may alter pharmacokinetics and pharmacodynamics of immunosuppressive drugs, and may determine the need for dose adjustments.

**Recommendations:**

**6.a.** Maintenance immunosuppression with corticosteroids and/or calcineurin inhibitors must be continued. (Grade II-2)
**6.b.** Mycophenolate mofetil and azathioprine are contraindicated during pregnancy and must be suspended at least 12 weeks before planned conception, substituting them with Pregnancy category B or C immunosuppressive agents. (Grade II-2)
**6.c.** Frequent monitoring of plasmatic levels of immunosuppressive medications is recommended. (Grade III)
**6.d.** mTOR inhibitors should be withheld until stronger and unequivocal evidence of safety is available. (Grade III)

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## 7. Post-partum and breastfeeding

Maternal drug toxicity is more likely postpartum, as physiological changes of pregnancy regarding hematocrit, total body water content and distribution return to the pre-gestational stage and foetal hepatic metabolism is no longer a contributor to pharmacodynamics and pharmacokinetics. Careful attention to immunosuppressive drug levels, cyclosporine and tacrolimus in particular, is warranted as maternal intravascular volume and glomerular hyperfiltration return to normal [19,38].

Breastfeeding is generally discouraged because of the passage of immunosuppressive drugs, particularly cyclosporine and tacrolimus, to the baby; however, the consensus opinion of the American Society of Transplantation (AST) is that breastfeeding need not be viewed as absolutely contraindicated [38], and evidence is accumulating supporting safety of this practice [17], provided monitoring of drug levels is performed in the infant. A report on a kidney transplant recipient on cyclosporine immunosuppression demonstrated a breast milk cyclosporine 2-hour

post-dose concentration of 49 µg/L and blood concentration in the infant shortly after breastfeeding which was undetectable (<10 µg/L) [126]. Another study of kidney and kidney/pancreas recipients treated with cyclosporine showed breast milk concentrations ranging from 50 to 227 ng/mL and was below the detection limit of 30 ng/mL in all breastfed infants, with no adverse events observed [127]. In contrast, measurable levels in the infant may be a substantial reason to discontinue breastfeeding [128]. The documented benefits of breastfeeding may outweigh the potential risks of infant immunosuppressive exposure [17,78].

Small amounts of glucocorticoids can be present in the breast milk of women on steroid therapy; however, no adverse effects have been reported, and the American Academy of Paediatrics has declared prednisone and prednisolone safe and compatible with breast-feeding [107]. Special attention should be devoted to diagnosing and treating postpartum depression, which may be exaggerated by chronic steroid use [129,130].

Low concentrations of azathioprine are found in breast milk, and nursing is not recommended due to the long-term potential of immunosuppression and carcinogenesis [107]. There are no data on the safety of MMF and mTOR inhibitors regarding their use during breastfeeding.

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**Background**

Although breastfeeding is generally discouraged due to the passage of immunosuppressive drugs to the neonate, this practice may be considered in mothers receiving corticosteroids and/or calcineurin inhibitors, upon demonstration of negligible amounts of the drug in breast milk.

**Recommendations:**

**7.a.** Breastfeeding is not recommended. (Grade III)
**7.b.** Breastfeeding during therapy with mTOR inhibitors, azathioprine, or mycophenolate mofetil is contraindicated. (GIII)

**Final recommendation:**

The creation of an Italian National Transplantation Pregnancy Registry, which fosters active, complete, and continuous centre reporting on course of pregnancies, use of immunosuppressive therapies, and outcomes in liver transplant recipients is highly encouraged. (Grade III)

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## Conflict of interest

None declared.

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