



RABIN MEDICAL CENTER
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Pregnancy & Delivery in Liver Recipients

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Maternal-Fetal Medicine

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When did it all start ?

1978




American Journal of Obstetrics and Gynecology

Volume 132, Issue 3, 1 October 1978, Pages 340–341



Communication in brief

Successful pregnancy in a liver transplant patient

William O. Walcott, M.D.  ^{a, b}, Dale E. Derick, M.D. ^{a, b}, John J. Jolley, M.D. ^{a, b}, Donald L. Snyder, M.D. ^{a, b} Rudi Schmid, M.D.

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Is it indeed an issue ?

- **Liver transplant restores sexual function and fertility within few months**
- **Age & fertility are appropriate and relevant:**
 - 1/3 are women
 - 1/3 are at reproductive age (18-40 years)
 - 1/6 are children
 - 2/3 probability for reaching reproductive age
- **In the USA (2013)**
 - 14K women of childbearing age are liver recipients

YES

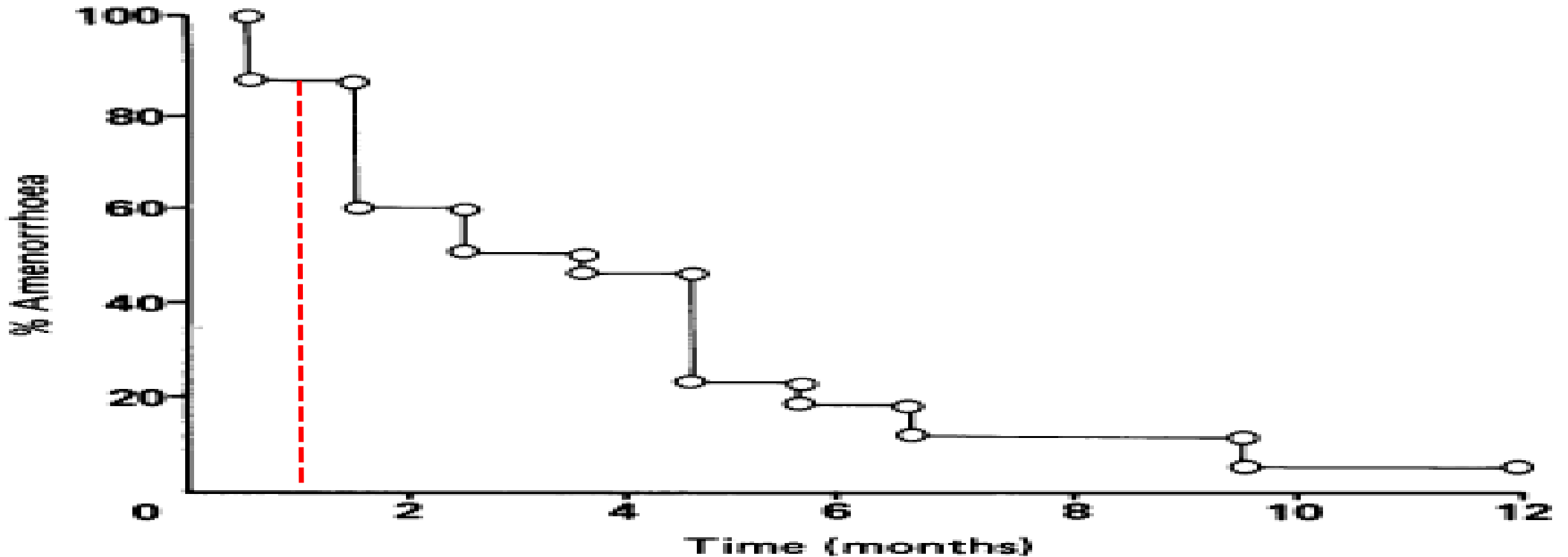
Evidence base....

No RCT

Pre-Conception Counselling

Is there a Time Factor₁₁₁ ?

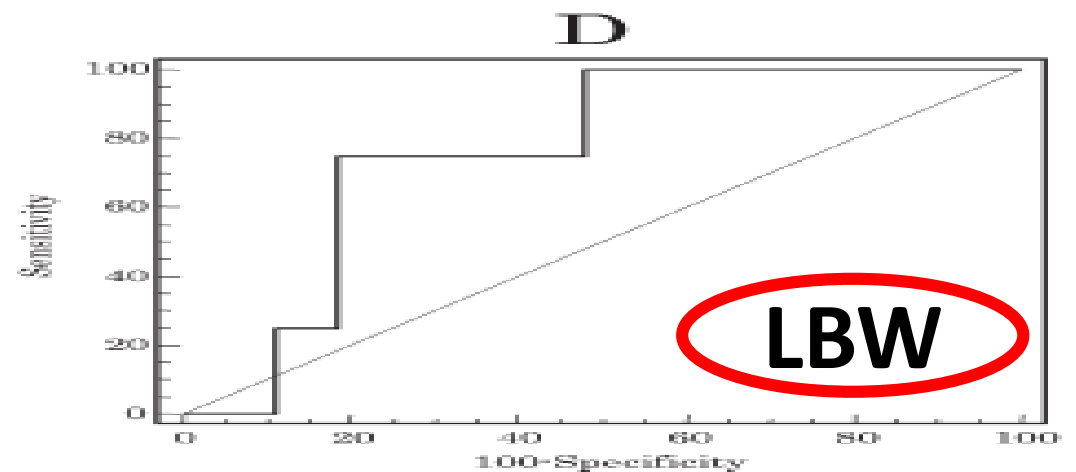
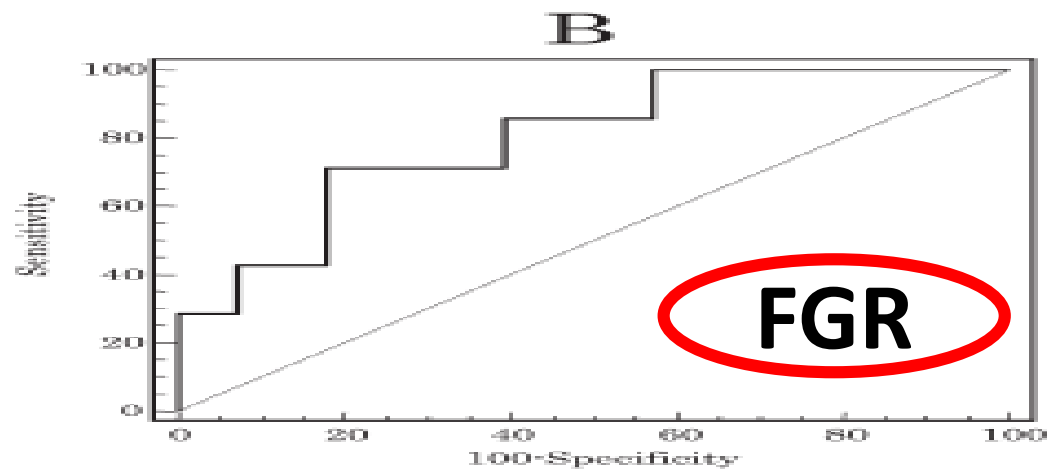
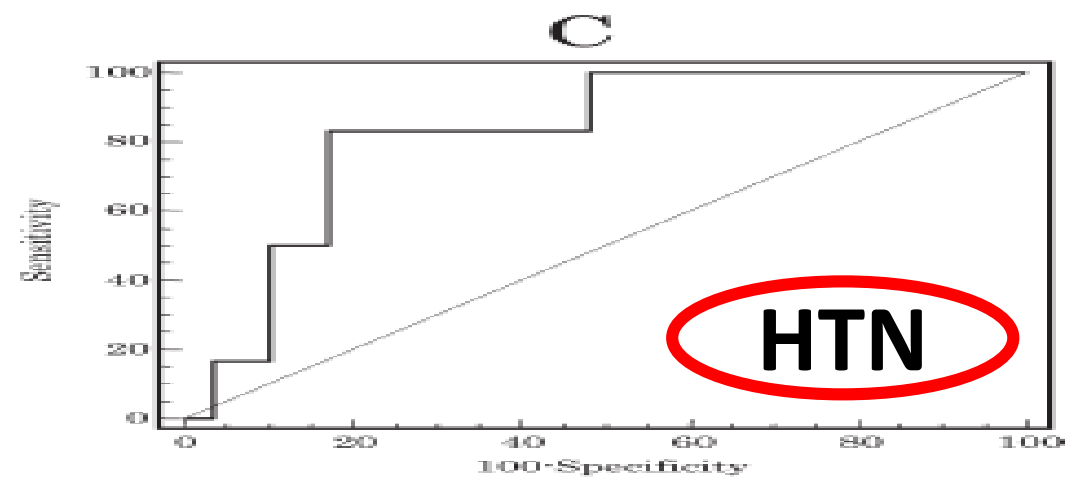
- Preconception counselling should start prior to liver transplant



Cundy et al. Recovery of menstruation and pregnancy after liver transplantation. Gut. 1990

Is there a Time Factor₂₂₂ ?

Inverse association between interval from transplant and adverse outcome



What Should you say in counselling ?

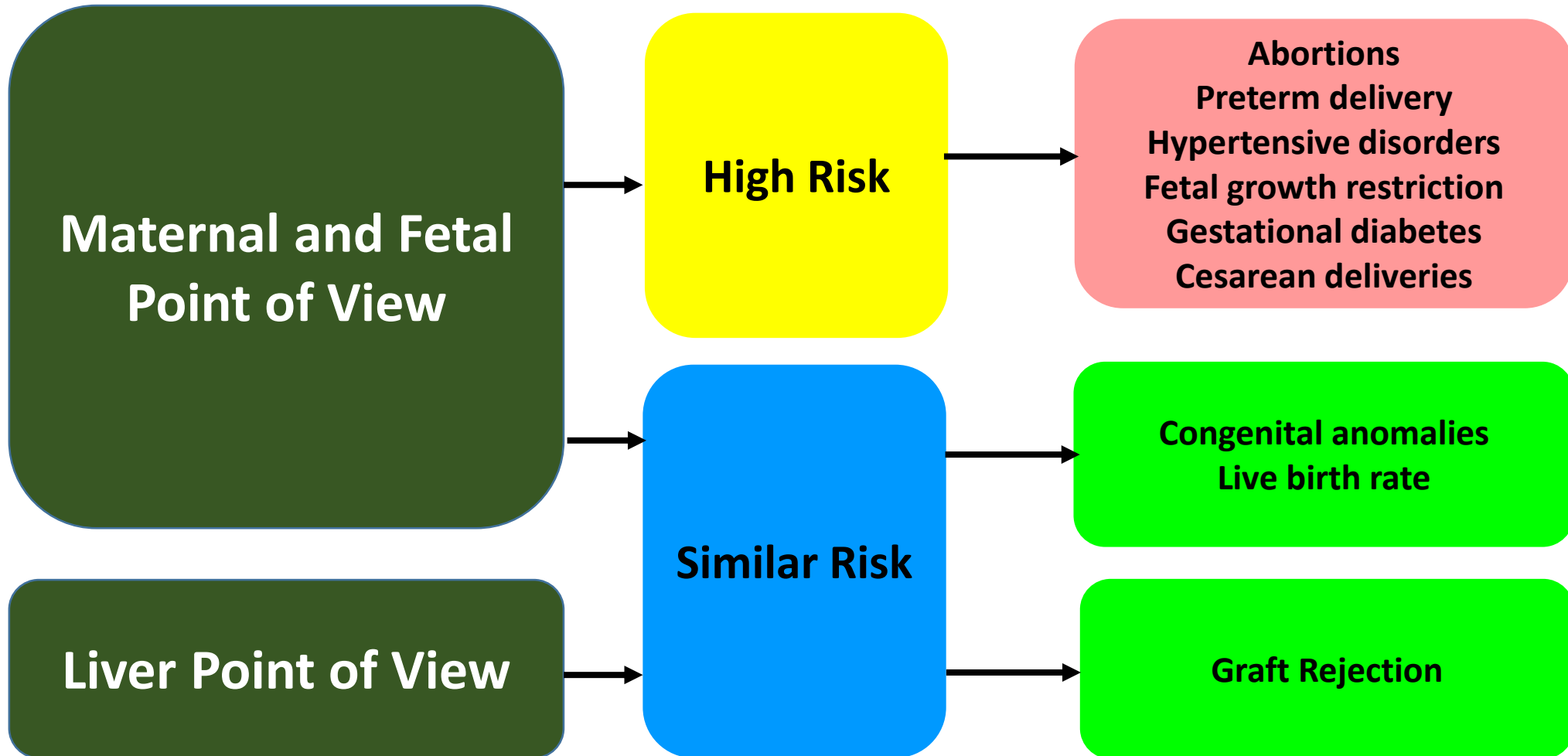
- **Pregnancy in liver recipients → High risk**
- **Maternal, fetal and graft outcomes are acceptable → Pregnancy is not C/I**

- **Good prognostic factors:**
 - Stable graft function
 - Stable immunosuppression
 - Normo-tension

- **Components of counselling:**
 - Maternal Health: Renal function, Diabetes and Hypertension
 - Graft Function: Avoid rejection, Infection and Disease recurrence

Pre-Conception Care: Outcomes

Maternal, fetal and graft outcomes are acceptable → Pregnancy is not C/I



Pre-Conception Care: Maternal Health

- **Higher preconceptional co-morbidities:**

- **Standardized prevalence ratio:**

- Hypertension → 3.07 (95% CI 2.35-3.93)
- Diabetes → 5.99 (95% CI 4.15-8.38)
- Chronic kidney disease → 15.3 (95% CI 10.9-19.34)

- **Major risk factors for obstetric complications**

(Preeclampsia, Macrosomia, Stillbirth, PTL, Congenital malformations)

Pre-Conception Care: Graft Function

Consensus recommendations of the American Society of Transplantation

- **Pregnancy can be considered if:**
 - (1) No rejection within the previous year
 - (2) Adequate and stable graft function
 - (3) No acute infections
 - (4) Stable immunosuppression

- **Optimal timing of conception** → 12-24 months post transplant

Pre-Conception Care: Contraception

Diaphragms	Might increase the risk of UTI and Vaginal Infections
Condoms	Prevents STDs
Oral Transdermal Transvaginal	Same contraindications as in the general populations Drug interactions: Cyclosporine, Tacrolimus Should be used carefully: <ul style="list-style-type: none">• Frequent monitoring of liver function tests• Stable graft function for at least 6 months
IUDs	May increase the risk of infections Reputs of reduced effectiveness in immunosuppressed patients No drug interactions Probably the best contraceptive option

Adverse Pregnancy Outcome

**Maternal
Fetal
Graft**

Adverse Outcome: Graft

Pregnancy does not have a negative impact on graft function

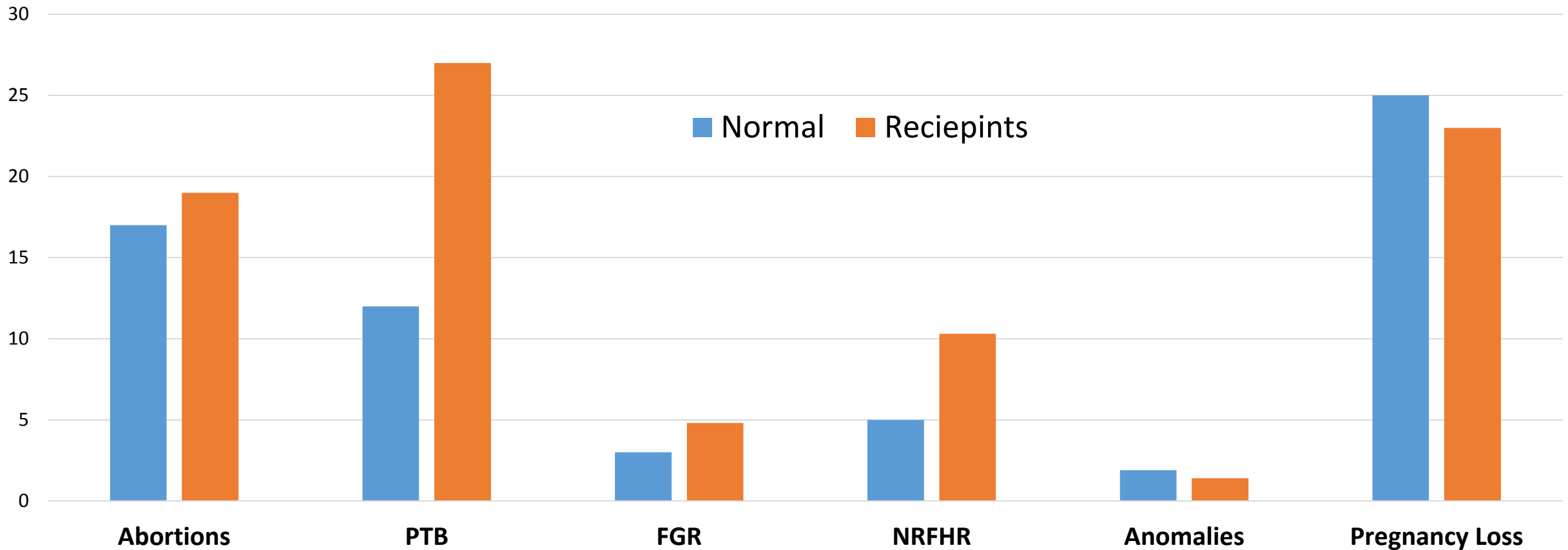
- **Graft Rejection in during pregnancy:**
 - Variable incidence → 0-4%
 - Non pregnant → 2-3%
- **Why rejection may occur?**
 - Voluntary suspension of immunosuppression
 - Early conception (within 12 months of transplant)

Miniero et al. Outcome of pregnancy after organ transplantation: a retrospective survey in Italy. *Transplant International* 2005

Jabiry-Zieniewicz et al. Outcome of four high-risk pregnancies in female liver transplant recipients on tacrolimus immunosuppression. *Transplantation Proceedings* 2007

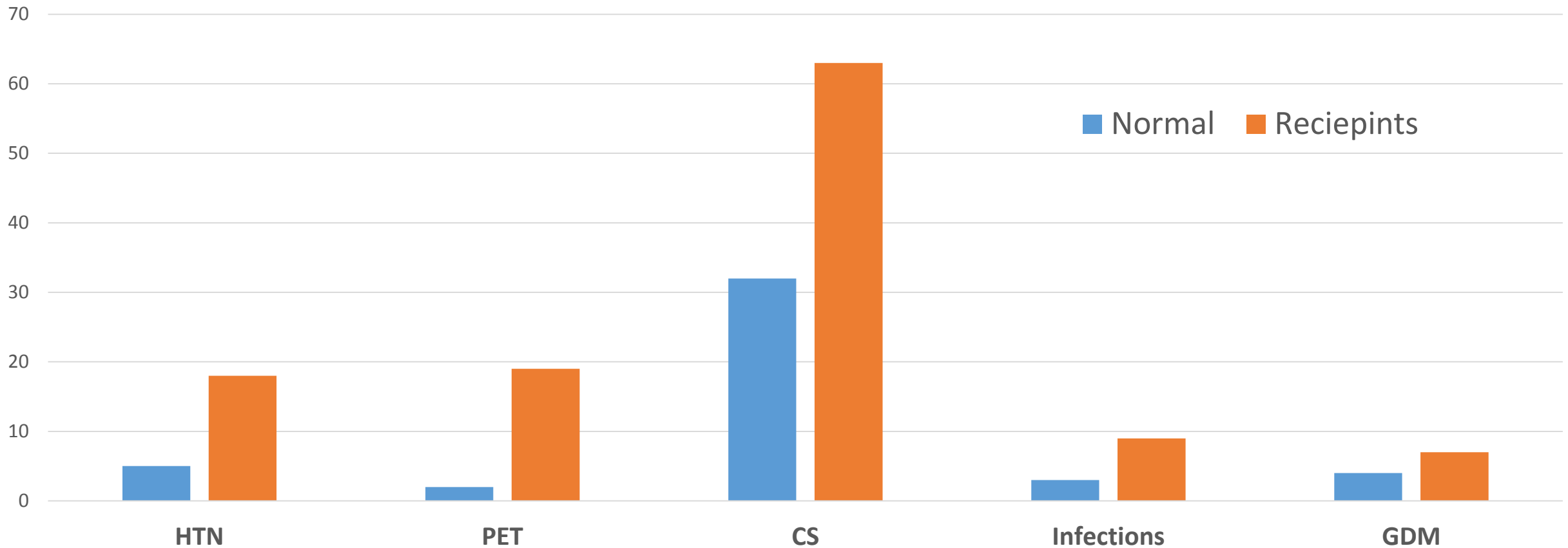
Adverse Outcome: Fetal

Pregnancy is associated with a higher risk of fetal complications



Adverse Outcome: Maternal

Pregnancy is associated with a higher risk of maternal complications



Adverse Outcome: Preeclampsia

- **Preeclampsia may be related to immunosuppressive therapy:**
 - Steroids → 22-29%
 - Tacrolimus → 47-54%
 - Cyclosporine → 68-73%

- **Abnormal baseline renal dysfunction in liver transplant recipients**

Armenti et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clinical Transplantation* 2004

Radomski et al. National Transplantation Pregnancy Registry: analysis of pregnancy outcomes in female liver transplant recipients. *Liver Transplantation and Surgery* 1995

Cyganek et al. Intrauterine growth restriction in pregnant renal and liver transplant recipients: risk factors assessment. *Transplantation Proceedings* 2014

Adverse Outcome: Infections

- **Infections frequently affect transplant recipients**
 - Primary and Secondary CMV
 - Toxoplasmosis
 - HSV
 - Varicella
 - HIV
 - HBV
 - HCV

Immunosuppression

Immunosuppression

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

Immunosuppression

- **The benefits of immunosuppression outweigh the risk**
 - Most women have normal pregnancy outcome with reassuring long term follow up
- **Lowest possible dose**
- **Plasma levels should be monitored**

Coscia et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clinical Transplantation* 2009

Coscia et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clinical Transplantation* 2010

Sibanda et al. Pregnancy after organ transplantation: a report from the UK Transplant pregnancy registry. *Transplantation* 2007

Deshpande et al. Pregnancy after solid organ transplantation: a guide for obstetric management. *Reviews in Obstetrics & Gynecology* 2013

Armenti et al. Report from the National Trans-plantation Pregnancy Registry: outcomes of pregnancy after transplantation. *Clinical Transplantation* 2006

Rabkin et al. Late mortality after orthotopic liver transplantation. *American Journal of Surgery* 2001

Immunosuppression: Cyclosporine and Tacrolimus

- **Calcineurin inhibitor:** Cyclosporine
Tacrolimus (Prograf)
- **Not associated with teratogenicity**
- **Initial reports of FGR, PTB, SA** (Only when elevated levels)
- **Frequent monitoring of renal function and drug levels:**
 - Hepatic cytochrome P450 is inhibited → Increased serum levels
 - Hepatic clearance may be reduced → Dose reductions of 60%

Immunosuppression: Steroids

- **Prednisone:**
 - Metabolized by placental 11-hydroxygenase → Cross the placenta in 10:1 ratio
- **Possible association with cleft lip and/or palate:**
 - High doses of steroids
 - Category B, without evidence of human teratogenicity
- **Side effects** → AVN, Osteopenia, HTN, GDM, Cataracts, Ulcers
- **Adrenal insufficiency** → Stress dose & Neonatal monitoring

Immunosuppression: Azathioprine

- **Category D, although apparently not teratogenic in humans:**
 - Initial reports of malformations (???)
 - Crosses the placenta
 - No fetal enzymatic activity capable of converting azathioprine to its active metabolites
- **May be associated with FGR & PTB**
- **Neonatal cytopenia** → post partum surveillance

Immunosuppression: Mycophenolate mofetil

- **Mycophenolate mofetil (Cellcept, Myfortic):**
 - Blocks de novo purine synthesis in T and B lymphocytes
- **Teratogenic risks** → IUFD, Abortions, Malformations
- **Contraindicated in pregnancy:**
 - Category D

Guidelines

What about Guidelines ?

- **Almost no guidelines on the management of pregnancies after liver transplantation:**
 - **Guide for obstetric management:** Deshpande et al. Reviews in Obstetrics & Gynecology 2013
 - **EASL:** Clinical practice guidelines: liver transplantation. Journal of Hepatology 2015
 - **AISF:** Italian position paper on liver transplantation and pregnancy: DALD 2016

Deshpande et al. Pregnancy after solid organ transplantation: guide for obstetric management. Reviews 2013

EASL clinical practice guidelines: liver transplantation. Journal of Hepatology 2015

AISF position paper on liver transplantation and pregnancy. DALD 2016

Guidelines: AISF

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)**

Guidelines: AISF

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)

Guidelines: AISF

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)

Guidelines: AISF

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 still-birth.

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)

Guidelines: AISF

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)

Guidelines: AISF

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)

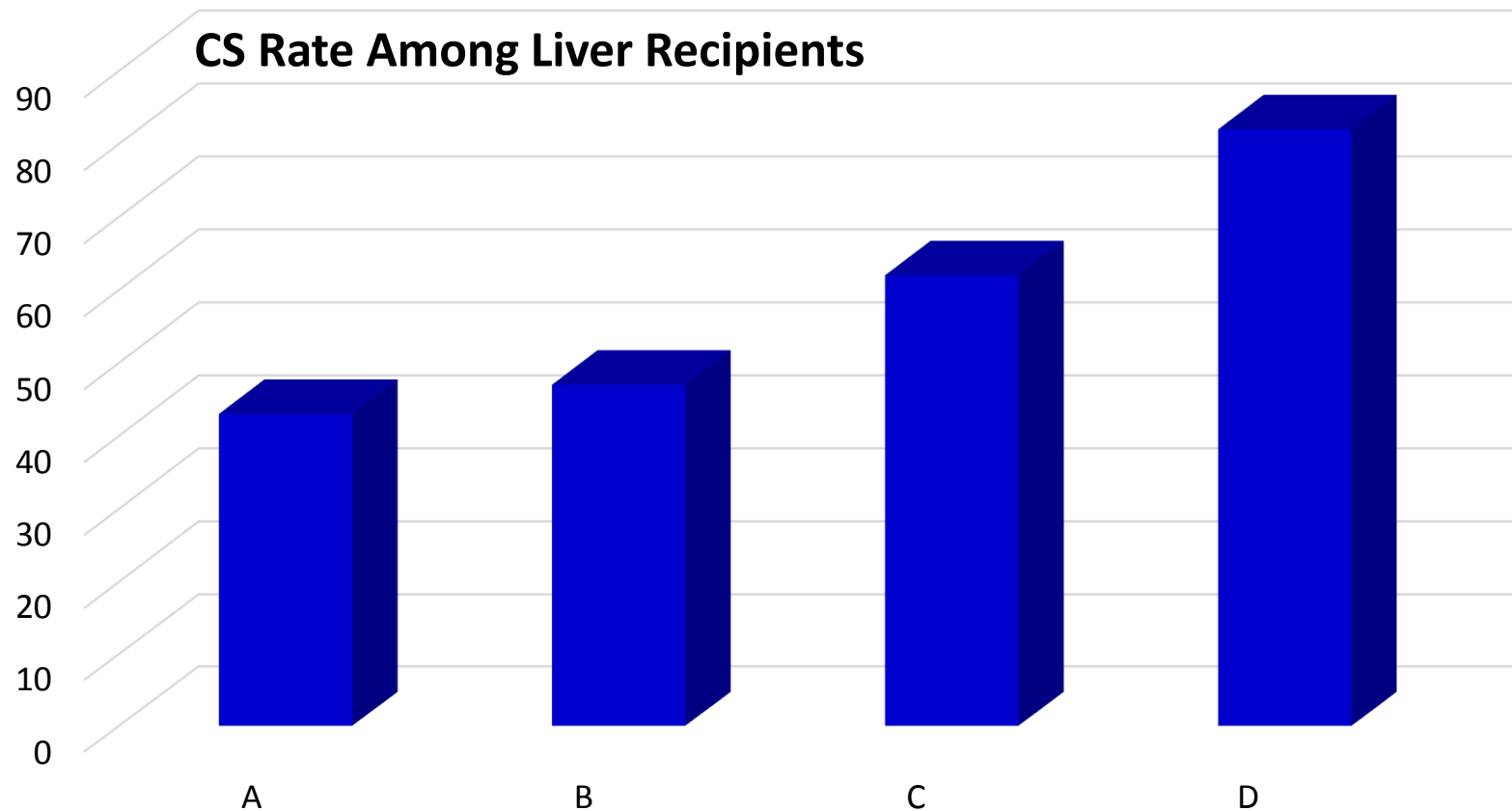
Final recommendation:

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)

Mode of Delivery

Mode of Delivery

Overall CS Rate: X2



Mode of Delivery

Vaginal Delivery is not Contraindicated

Table 6. Indications for Cesarean Delivery

Previous cesarean delivery	3
Preeclampsia	3
Fetal distress	2
Breech presentation	1
Failed VBAC	1
Failed induction	1
Total	11

VBAC = vaginal birth after cesarean.

Safe, Feasible & Good Outcome
Immunosuppression Adjustment
High Risk Close Surveillance
Multidisciplinary Team Effort