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International Society of Nephrology



Iranian Society of Nephrology

PREGNANCY IN KIDNEY TRANSPLANTATION



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The history of pregnancy after kidney transplantation

Starts with young twin sisters: “In May, 1956, one of a pair of 21-year-old identical twin females from Oklahoma as a recipient from her twin sister”.

Later, The twin had successful full term pregnancy. The donor and recipient have a total of five babies, all of them in good health, at the time this paper was published .



Murray JE N Engl J Med (1963)

After that ,many other successful pregnancies have been reported among the kidney transplant population.

With the excellent results of the first pregnancies after KT ,the era of pregnancy after kidney transplantation had begun.

Journal of Nephrology (2018)

TOPICS

- **Fertility after renal transplantation**
- **Obstetric outcomes**
 - Maternal and Fetal outcomes**
 - Predictors of pregnancy outcomes**
- **Effect of pregnancy on graft function and outcomes**
- **Optimal Time to Conception**
- **Immunosuppressant drugs**
- **Mode of delivery**
- **Contraception**
- **Breastfeeding**

FERTILITY

Women with ESRD have impaired fertility.
Pregnancy in women on dialysis is rare and about 0.9 to 7%.

Kidney transplantation offers the best hope to women with ESRD who wish to become pregnant .

BMC Nephro. 2019

Ovulatory cycles can begin within 4 weeks after transplantation and menstruation becomes regular by 6-9 months.

Normal levels of circulating sex steroids are typically restored within 6 months.

Transplantation April 2017

Factors contribute to low pregnancy rate :

- the fear of graft loss
- inadequate renal function
- advanced age at the time of transplantation
- better education regarding the use of contraceptive methods

[J Am Soc Nephrol](#). 2009 Nov

Obstetric outcomes

Maternal and Fetal outcomes:

The most of the data on outcomes of pregnancy comes from the retrospective studies, case reports, single-center studies, and four voluntary registries including TPR; NTPR and ERA-EDTA .


Limitations of these studies include retrospective design, small patient numbers, and reporting bias.

RESEARCH ARTICLE

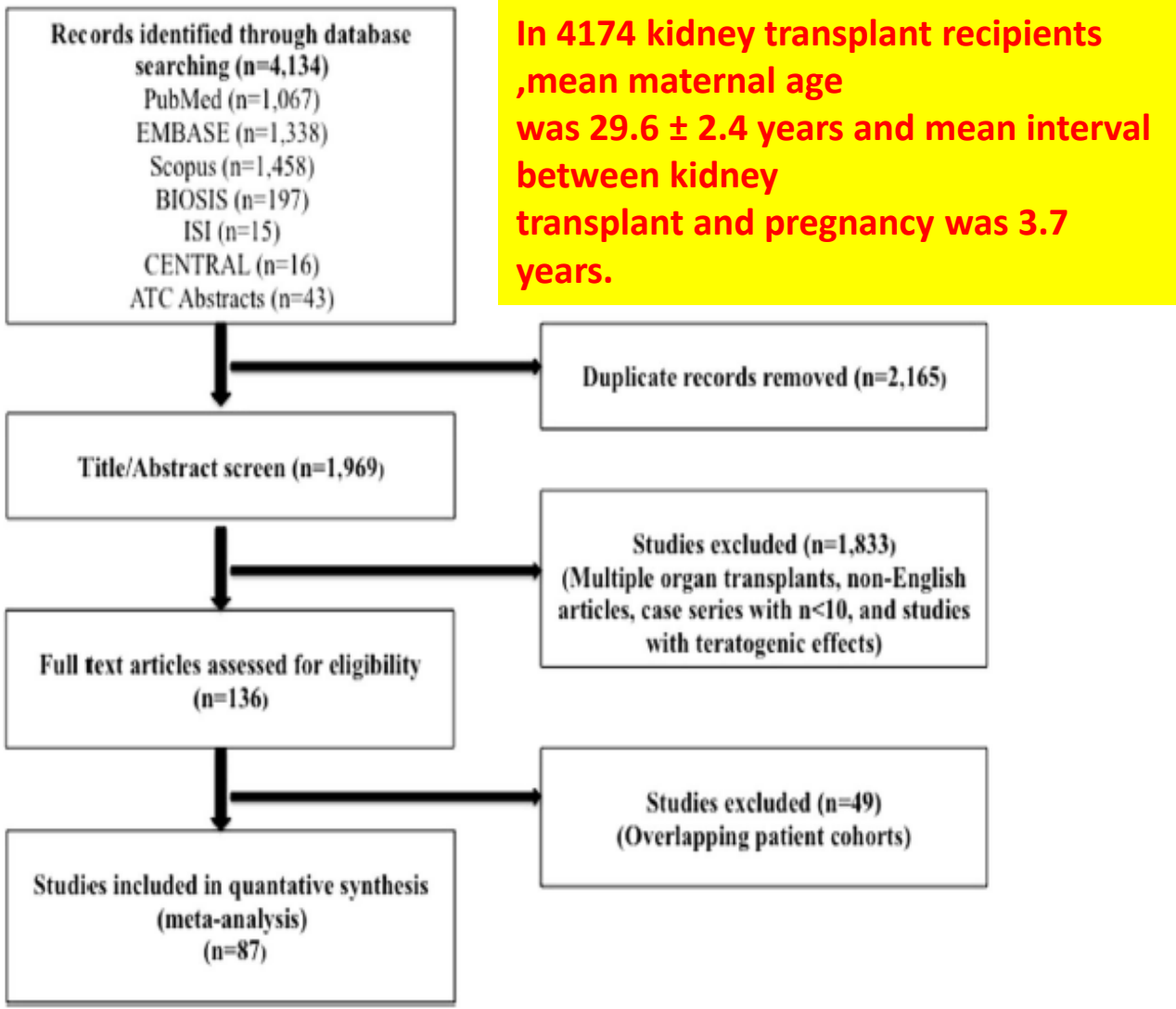
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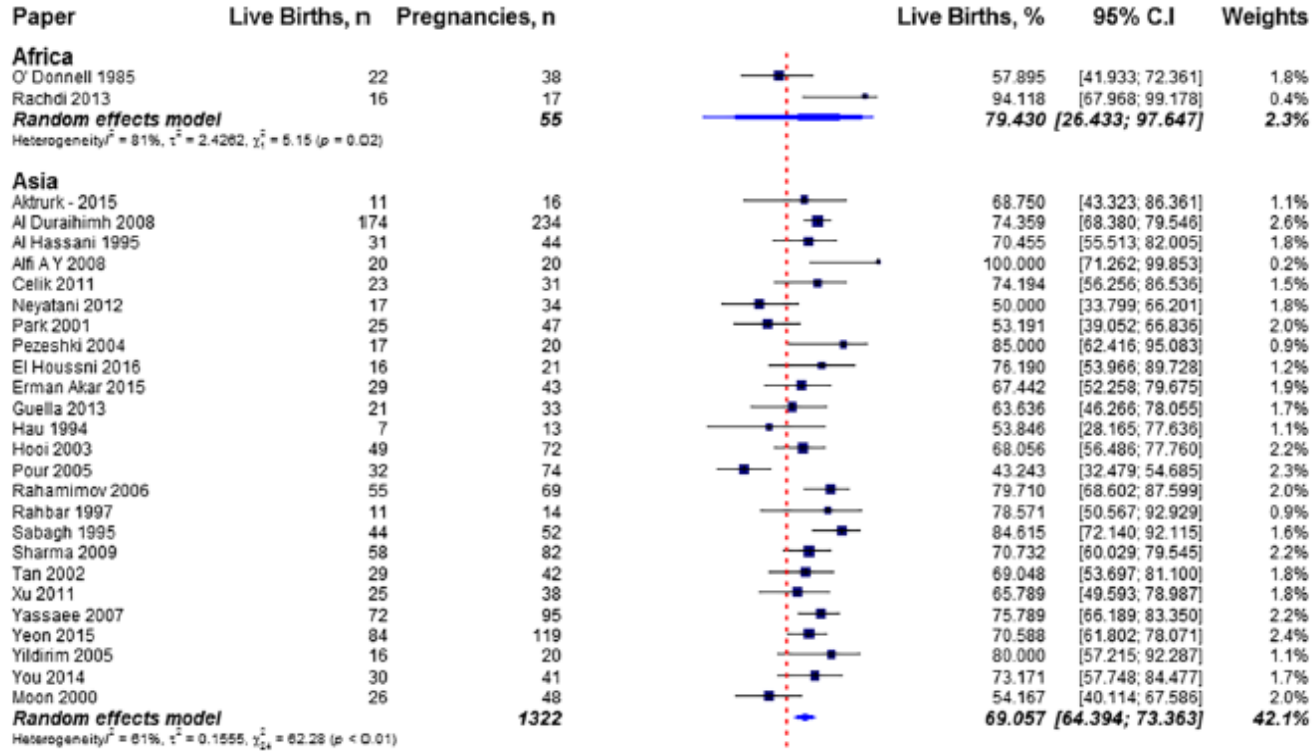
Pregnancy outcomes in women with kidney transplant: Metaanalysis and systematic review

Silvi Shah^{1*} , Renganathan Lalgudi Venkatesan², Ayank Gupta², Maitrik K. Sanghavi², Jeffrey Welge³, Richard Johansen², Emily B. Kean², Taranpreet Kaur¹, Anu Gupta⁴, Tiffany J. Grant² and Prasoon Verma⁵

Meta-analysis to ***all studies*** of pregnancy-related outcomes in kidney transplant recipients from ***all around the world***, and estimate pooled incidences of ***pregnancy outcomes, maternal complications, and fetal complications***.

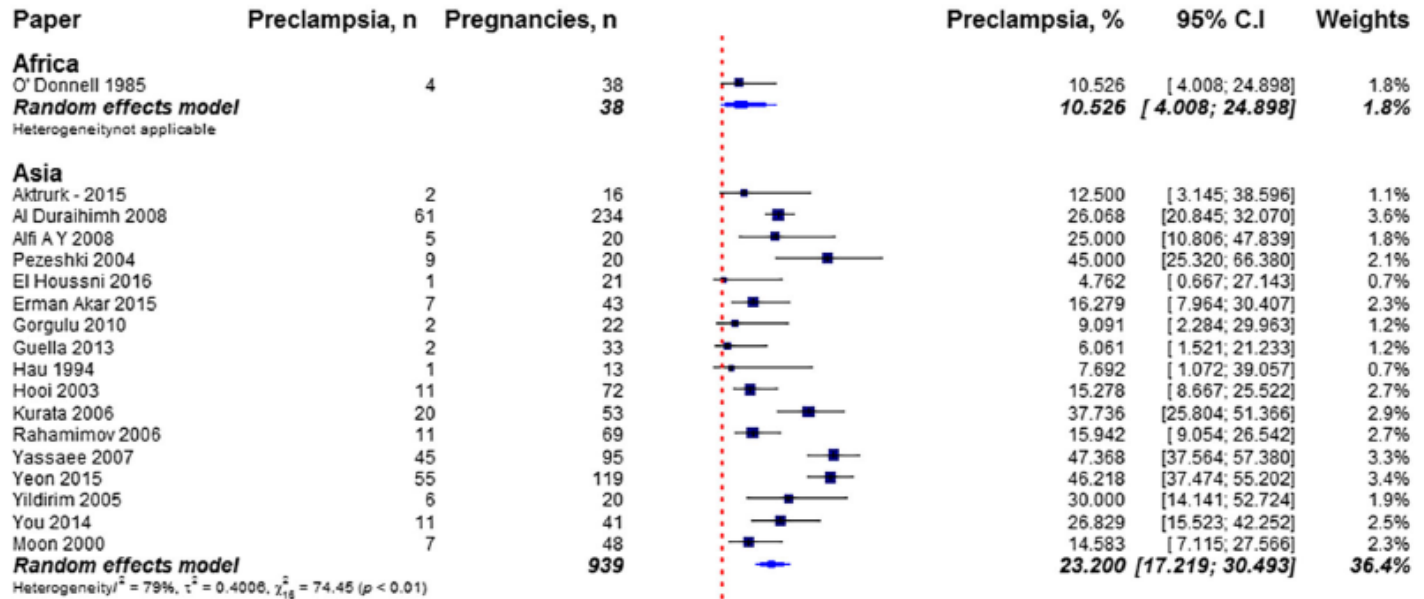


Live Births among Kidney Transplant Recipients



Majority of pregnancies in women after kidney transplant result in **live birth**, but maternal and fetal adverse events are common.
Rates of **preeclampsia**, **still birth**, and **cesarean section** were significantly higher than in the general population.

Preclampsia among Kidney Transplant Recipients



CONCLUSION

The rates of **preeclampsia** were almost six fold higher .
 The rate of **cesarean section** was higher than two folds.
 The rate of *gestational diabetes* and *prematurity* were increased in kidney transplant patients

Pregnancy is not a “zero-risk” situation:

In the general population, hypertensive disorders in more than 10% , PE in 3–5% and also gestational diabetes are seen.

All these events are more common in KT patients.

Journal of Nephrology (2018)

Although the majority of pregnancies after KT result in a **live birth**, the risk of fetal complications, such as preterm birth, low birth weight, and fetal growth restriction remains high.

Most studies have shown that **maternal death** (defined as death of a pregnant woman or within 42 days of termination of pregnancy) and **long-term survival** of pregnant transplant recipients appears to be comparable with that of nonpregnant recipients .

Journal of Nephrology (2018) 31:665–681

Pregnancy Outcomes in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis

Predictors of pregnancy outcomes

A number of factors have been associated with **poor pregnancy outcomes** in kidney transplant recipients.

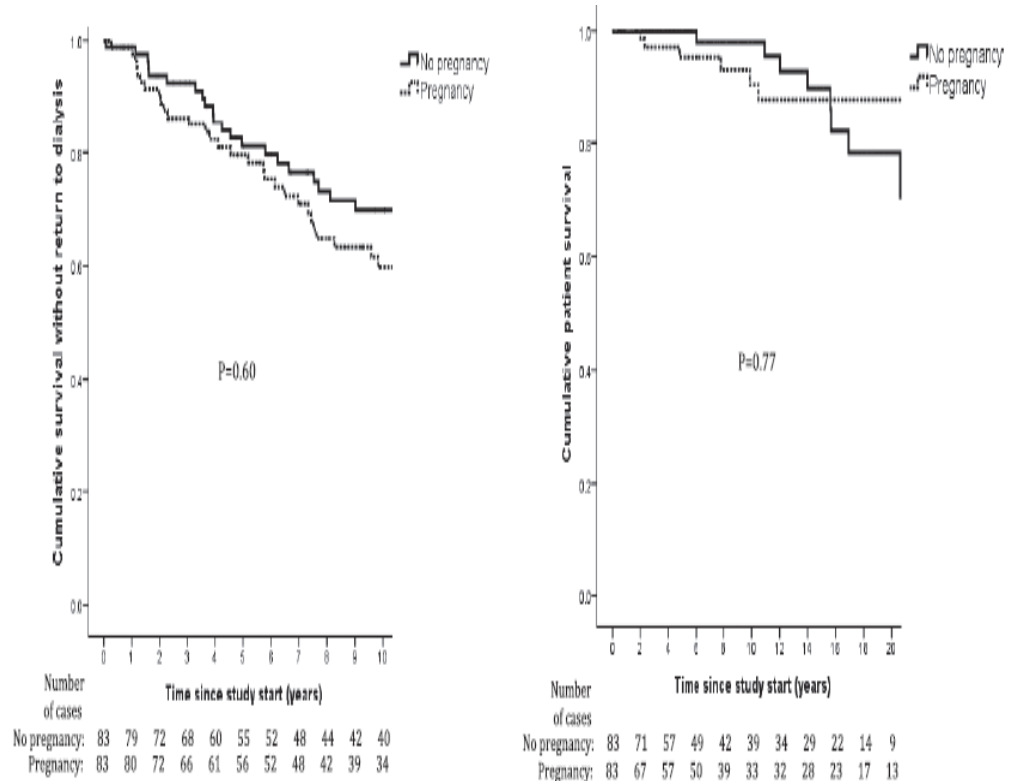
In a systematic review and meta-analysis of 50 studies (4706 pregnancies in 3570 recipients), hypertension, a **serum creatinine >1.5 mg/dL** and **proteinuria** were predictors of adverse pregnancy outcomes.

Table 2: Maternal¹ demographics, pregnancy outcomes, obstetric complications and delivery outcomes among kidney transplant recipients

Maternal demographics	Mean	USA, 2006 ²
Age at pregnancy	29.0 years (28.9–29.1)	NA
Transplant-pregnancy interval	3.2 years (3.1–3.3)	NA
Pregnancy outcome	Pooled incidence	USA, 2006
Live birth	73.5% (72.1–74.9)	66.7% ³
Miscarriage ⁴	14.0% (12.9–15.1)	17.1% ³
Abortion ⁵	9.5% (8.6–10.4)	NA
Stillbirth	2.5% (2.0–3.0)	NA
Ectopic pregnancy	0.6% (0.4–0.9)	NA
Obstetric complication	Pooled incidence	USA, 2006
Hypertension ⁶	54.2% (52.0–56.4)	NA
Preeclampsia	27.0% (25.2–28.9)	3.8%
Gestational diabetes	8.0% (6.7–9.4)	3.9%
Delivery outcome	Mean/Pooled incidence	USA, 2006
Cesarean section	56.9% (54.9–58.9)	31.9%
Preterm delivery ⁷	45.6% (43.7–47.5)	12.5%
Gestational age	35.6 weeks (35.5–35.7)	38.7 weeks
Birth weight	2420 grams (2395–2445)	3298 grams

Obstetric and long-term kidney outcomes in renal transplant recipients: a 40-yr single-center study

In this large single-center study over 40 yr, the majority of pregnancies in KT recipients to have good outcomes. There were no significant differences in long-term transplant and patient survival in KT mothers.



Which patients are the “best candidates” for pregnancy after KT

- (a) Normal or good kidney function ($>$ above 60 ml/min)
- (b) No rejection for 1 year before pregnancy
- (c) No proteinuria or little proteinuria (300–500 mg/day)
- (d) No hypertension or well-controlled hypertension
- (e) Low-dose immunosuppression with “allowed” drugs
- (f) At least 6 months but the best 2 years after KT
- (g) Discontinuation of potentially teratogen drugs for at least 6 weeks before coception

Journal of Nephrology (2018)

Effect of pregnancy on graft function and outcomes

During normal pregnancy, GFR increases by approximately 50 percent.

In pregnant KT, an increase in GFR of approximately 30% in the first trimester which is sustained with a small decrease in the second trimester and returns to prepregnancy level during the third trimester.

[Am J Transplant.](#) 2011 Nov;11

Pregnancy After Renal Transplantation

Dominik Chittka, MD¹ and James A. Hutchinson, MD, PhD

Transplantation April 2017

Three prepregnancy factors are highly associated with graft loss or decline in kidney function during pregnancy: **a history of drug-treated HTN, elevated serum creatinine and proteinuria.**

Pregnancy itself has no impact on graft function in absence of these risk factors.

Risk of Rejection

Pregnancy is a state of immunological tolerance associated with immunodepressant activity of lymphocytes which creates tolerance to fetus and may benefit the renal allograft.

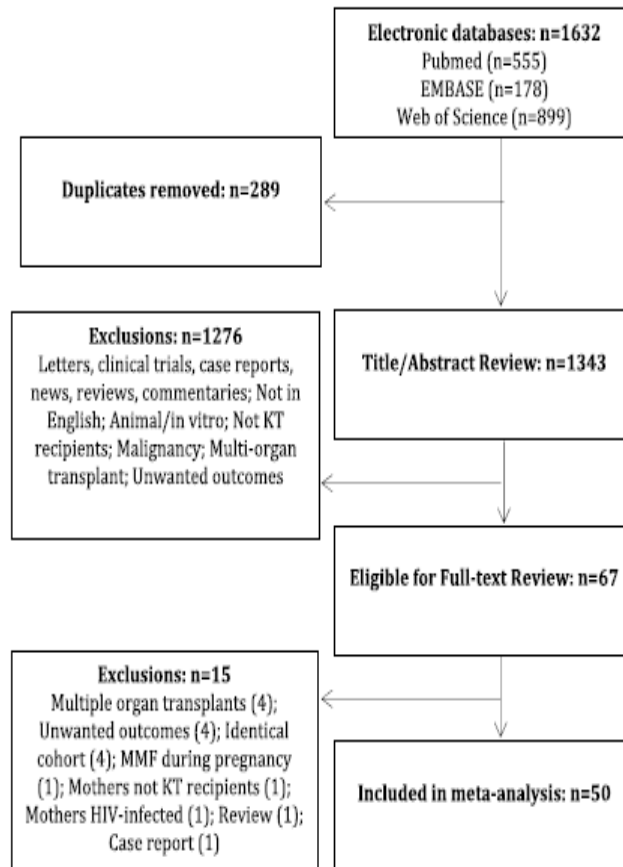
There is a possibility that the antigenic stimulus provided by the fetus may trigger graft rejection as well.

Risk factors : high serum creatinine, recent rejection before pregnancy, and changing levels of IS drugs but not the different regimen .

Diagnosis :Ultrasound guided allograft biopsy.

International Journal of Nephrology 2016

Pregnancy Outcomes in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis



Among 2412 pregnant recipients , 102 (4.2%) experienced an episode of acute rejection and 1-year postpregnancy graft loss was 5.8% , 2 years graft loss was 8.1% ,5 years graft loss was 6.9%.

These studies suggested that pregnancy did not have a deleterious effect upon the allograft.

Long term graft survival and graft function following pregnancy in kidney transplant recipients

a systematic review and meta-analysis

van Buren, Marleen C. MSc¹; Schellekens, Anouk MD²; Groenhof, T. Katrien J. MD³; van Reekum, Franka MD⁴; van de Wetering, Jacqueline MD PhD²; Paauw, Nina D. MD PhD¹; Lely, A. Titia MD PhD¹

Transplantation: October 21, 2019 - Volume Online First - Issue - p
doi: 10.1097/TP.0000000000003026

This study is an updated meta-analysis on graft survival with comparison with nonpregnant KT recipients and for the first time long-term follow up (up to 10 year) of graft function after pregnancy.

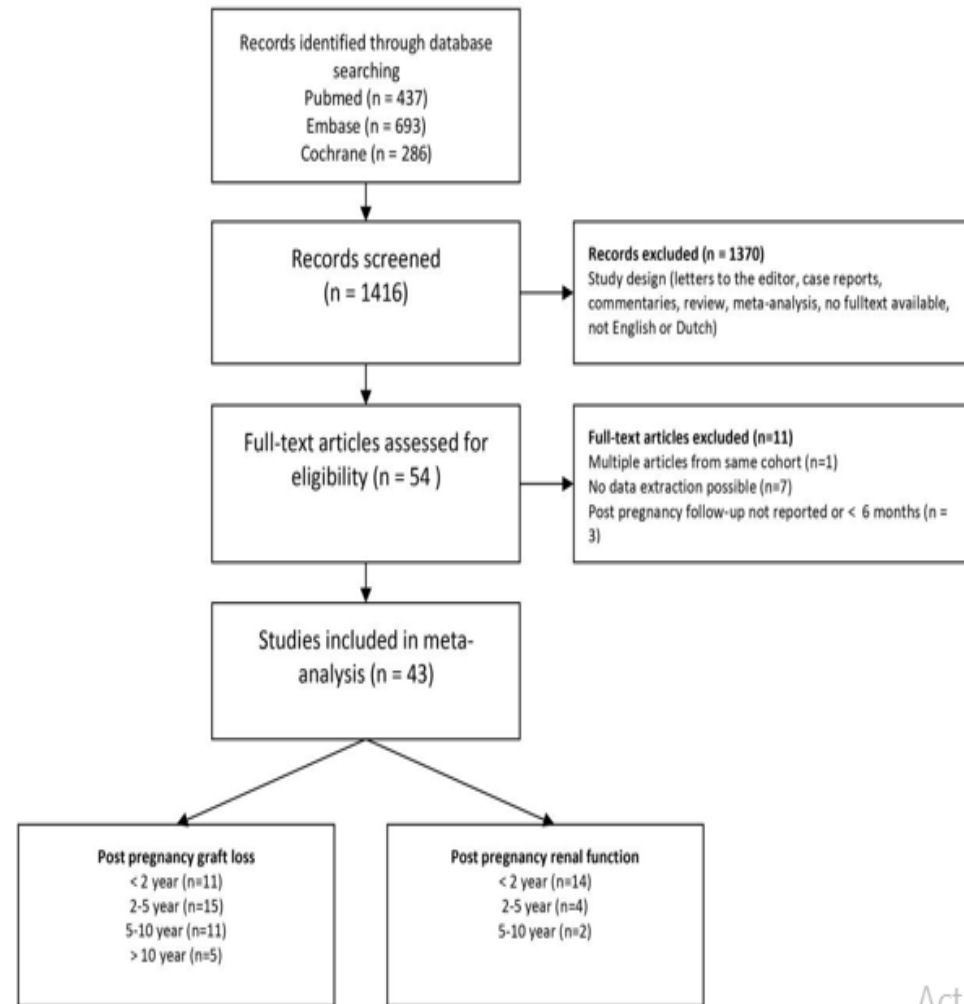
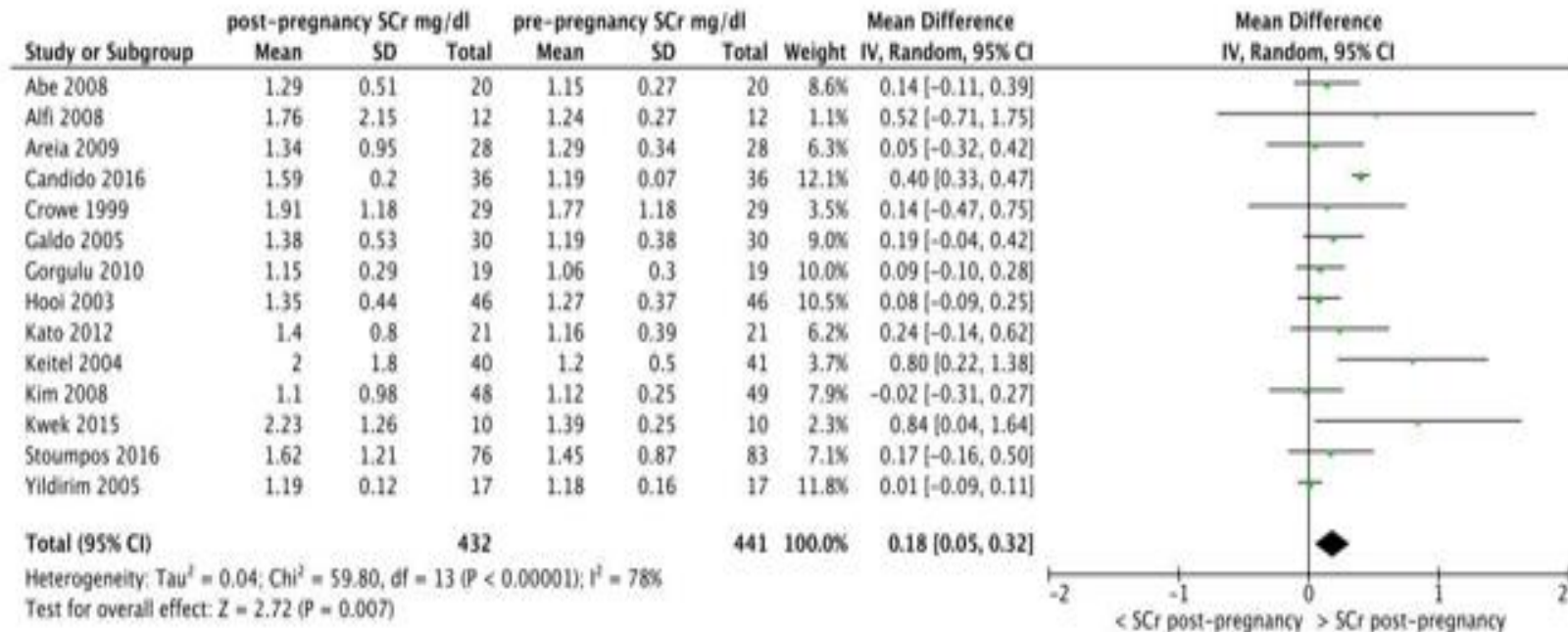


Table 3 Predictors of graft loss or renal function deterioration after pregnancy

Risk factors	Negative association		No association	
	Unit	Author	Unit	Author
Hypertension Before or at the beginning of pregnancy	>140/90 mmHg Drug treated hypertension	Queipo Zaragoza (2003) Sibanda (2007), Abe (2008), Kato (2012)	Preexisting hypertension Chronic hypertension Chronic hypertension	Stoumpos (2016) Svetitsky (2018) Vannevel (2018)
Proteinuria	> 1 gram/day	Queipo Zaragoza (2003)	> 0.3 gram/day > 0.5 gram/day	Thompson (2003) Rocha (2013)
Preeclampsia	Borderline effect (OR, 1.09; 95% CI [0.92-1.34] P =0.09).	Svetitsky (2018)	-2.69 (-14.54 to 9.15) P = 0.65	Vannevel (2018)
Pre pregnancy SCr	> 1.47 – 1.50 mg/dl > 1.69 – 1.75 mg/dl > 2.10 mg/dl Worse graft function (OR 1.71; 95% CI [CI 1.15-3.45] P = 0.04)	O'Reilly (2001), Alfi (2008) Thompson (2003), Keitel (2004) Kim (2008), Crowe (1999), Queipo Zaragoza (2003) Aivazoglou (2010) Svetitsky (2018)	< 2.26 mg/dl < 1.3 mg/dl Worse graft function (OR - 0.11 95% CI [-0.44 to 0.23] P = 0.52)	Hooi (2003) Rocha (2013) Vannevel (2018)
Age at transplantation	Older age (OR 1.13; 95% CI [1.03-1.21] P = 0.03)	Svetitsky (2018)		
Transplant to conception interval	< 1 year	Alfi et al. (2008)	General < 1 year < 2 year > 5 year Months (OR 0.05 95% CI [-0.07 to 0.18] P = 0.42)	Stoumpos (2016) Pour-Reza-Gholi (2005) Fischer (2005) Gaughan (1996) Vannevel (2018)



GL and **SCr** after pregnancy in KT recipients when compared to nulliparous KT recipients are **stable** up to 10 years postpartum.

Systematic review of the literature showed that mainly **pre pregnancy proteinuria**, **hypertension** and **high SCr** are risk factors for GL.

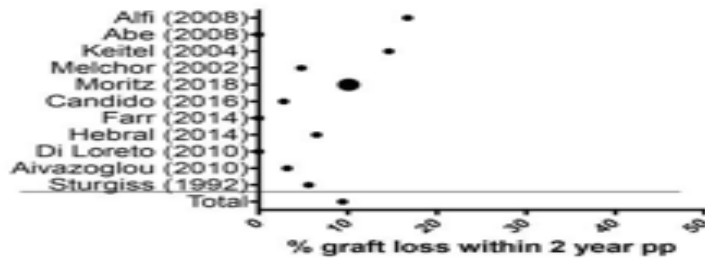


Figure 2a

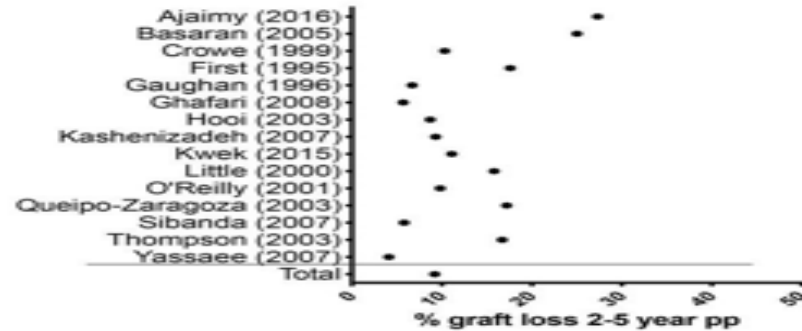


Figure 2b

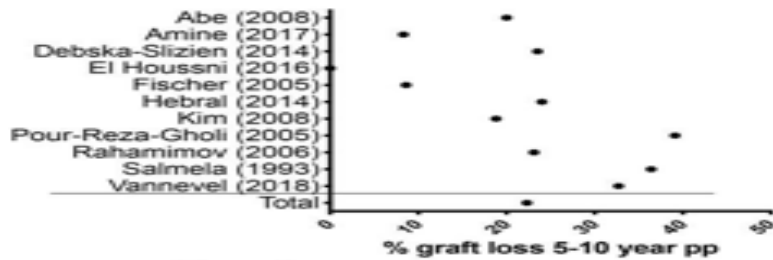


Figure 2c

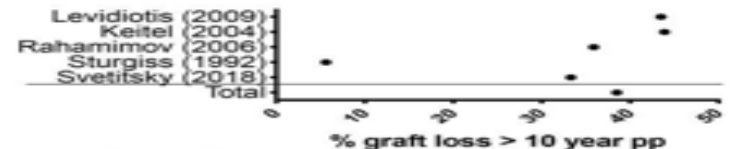


Figure 2d

Figure 2a-d: Pooled incidence of post-pregnancy graft loss

- 2A. Graft loss within two year post-pregnancy: 9.4%, n=1347 (range 10-1100), total graft loss n=126 (range 0-111)
- 2B. Graft loss two to five years post-pregnancy: 9.2%, n=600 (range 8-139), total graft loss n=55 (range 1-8)
- 2C. Graft loss five to ten years post-pregnancy: 22.3%, n=395 (range 12-81), total graft loss n=88 (range 0-18)
- 2D. Graft loss more than ten year post-pregnancy: 38.5%, n=234 (range 18-118), total graft loss n=90 (range 1-51)

The most important predictors for worse graft outcomes in pregnancy after KT is related to GFR changes.

Overall, if prepregnancy KT function is good it remains good after pregnancy.

Optimal Time to Conception

The optimal timing of pregnancy after kidney transplantation remains uncertain.

The ideal time is between 1 and 2 years according to guidelines by American Society of Transplantation.

European best practice guidelines recommend delaying pregnancy for a period of 2 years after transplantation.

International Journal of Nephrology Volume 2016

Baseline evaluation prior to conception :

- Identify any important clinical events (episodes of rejection, CMV infections) in the preceding year
- History for potential teratogenic medications
- Change the patient's maintenance IS regimen
- PCR testing for CMV and BK virus

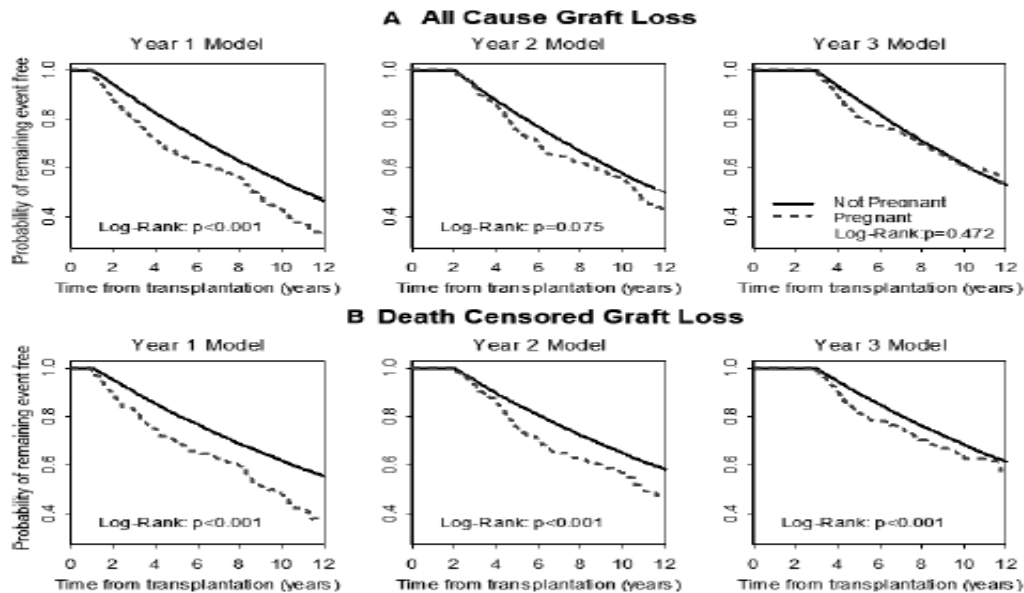
Patients who have a history of recent (but not currently active) CMV disease should be advised to wait **at least six months and preferably one year** from the resolution of disease before trying to conceive.

[Reproduction and transplantation: report on the AST Consensus Conference on Am J Transplant 2005; 5:1592.](#)

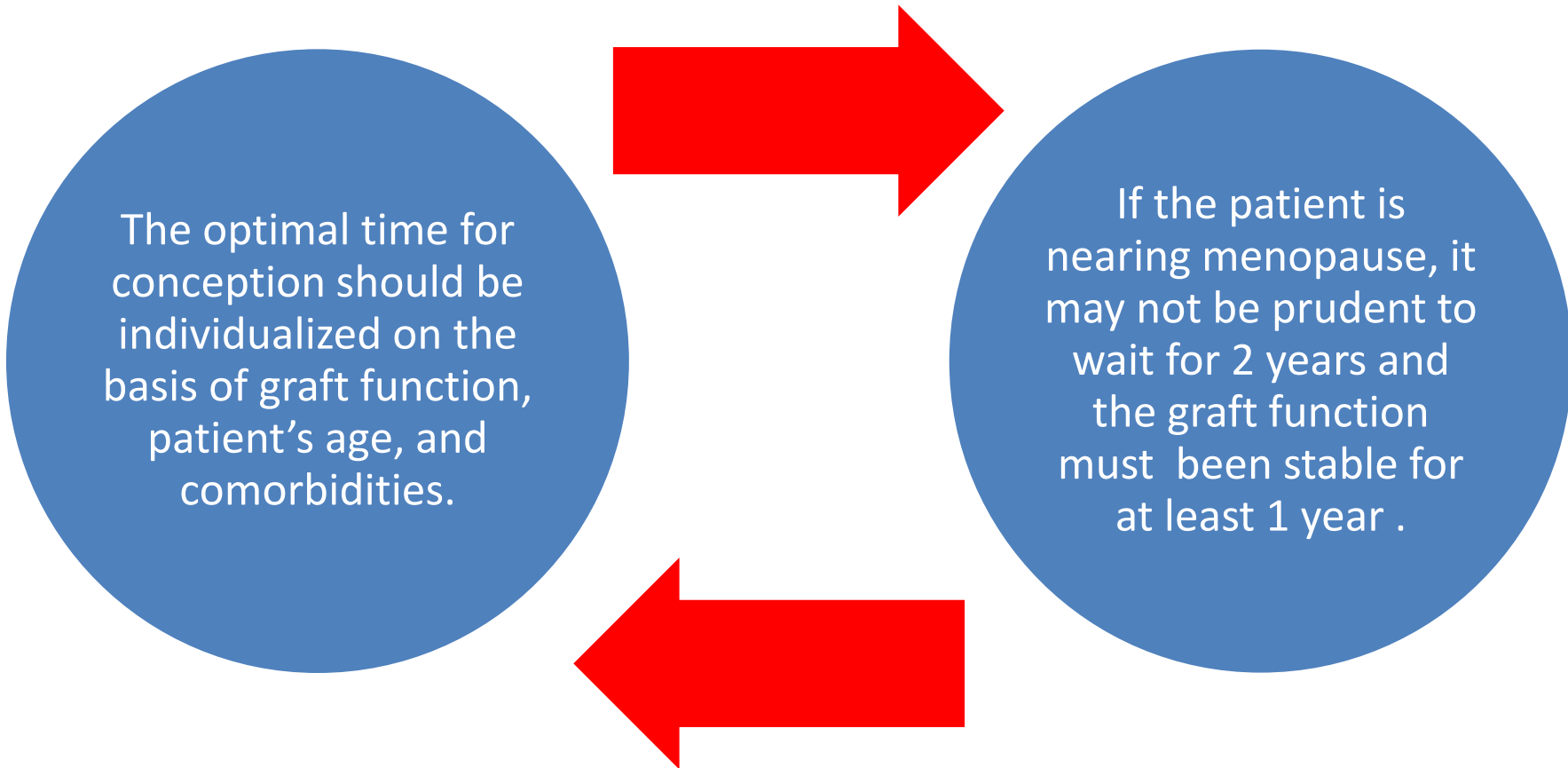
Timing of Pregnancy After Kidney Transplantation and Risk of Allograft Failure

The 44 246 women aged 15–45 years who received a first kidney transplant between January 1, 1990 and December 31, 2010 and were captured in USRDS.

Among the study population ,729 women (3.3%) who became pregnant during the first 3 posttransplant years.



The key findings of this study were that pregnancy in the **first year** after transplantation is associated with an increased risk of both ACGL and DCGL, while pregnancy in the second year was associated with an increased risk of DCGL.



The optimal time for conception should be individualized on the basis of graft function, patient's age, and comorbidities.

If the patient is nearing menopause, it may not be prudent to wait for 2 years and the graft function must be stable for at least 1 year .

Am J Transplant 2016; 16:2360–2367.

Immunosuppression:

- Modification of the maintenance IS drugs is necessary prior to conception.
- The recommended regimen is :a CNI, [azathioprine](#), and [prednisone](#).
- MMF should be discontinued **at least six weeks** prior to conception.
- mTOR inhibitors should be discontinued **at least 8 to 12 weeks**

Drug	Main features	FDA rating
Usually considered as safe		
Azathioprine	This is the most widely used immunosuppressive drug. It is teratogen in animal models, but not in humans, possibly because the foetal liver is not able to activate the drug. KDIGO and European Best Practice Guidelines suggest switching from mycophenolate to azathioprine before pregnancy	D
Cyclosporine A	This calcineurin inhibitor has not been associated with increased teratogenicity; however, small for gestational age babies and preterm delivery have been reported, possibly due to the maternal disease and not specifically to the drug. Levels may vary in pregnancy and the hypertensive, hyperglycaemic and nephrotoxic effects should be mentioned	C
Tacrolimus	The drug has similar effects and side effects to cyclosporine A; experience is more limited than with the previous drug	C
Steroids	Together with azathioprine these are the most often employed and best known drugs. The most frequently used short-acting corticosteroids include prednisone, methylprednisolone and prednisolone, while betamethasone and dexamethasone are among the long-acting drugs. No major malformations have been reported, and the issue of labiopalatoschisis is debated. A higher risk of premature rupture of membranes has been reported. Other relevant side effects include infectious risk, and the increased risk of gestational diabetes	C
To be avoided		
Mycophenolate	Severe foetal malformations are reported, mainly involving cardiovascular and cranial malformations. Discontinuation for at least 6 weeks, to stabilize kidney function, is usually indicated after kidney transplantation	D
m-Tor inhibitors	Very few studies have considered their use in pregnancy. They are teratogenic in animals and discontinuation in humans is a matter of debate. KDIGO guidelines suggest discontinuation in anticipation of pregnancy	C
Rituximab, simulect	Too few studies to allow safe use in pregnancy. Need for further evidence, but trials are unlikely to be undertaken	C, D

Activate Windows
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- ❑ There are no guidelines about dosing of immunosuppressant medications during pregnancy.
- ❑ An increase in the CNI dose by approximately 20% to 25% during gestation to maintain optimal drug levels.
- ❑ MMF is associated with an increased risk of spontaneous abortion, and congenital limb and facial defects that known as **MMF foetal syndrome** .

Kidney International (2017) 91, 1047–1056

When a patient has an unplanned pregnancy resulting in MPA exposure during organogenesis.

Although not all pregnancies exposed to MPA have resulted in adverse outcomes, thus leaving space for individual choice.

If pregnancy continued

Repeat fetal sonography is advisable to attempt prenatal diagnosis of any MPA embryopathy.

Echocardiography at 23 weeks to rule out cardiac defects.

[J Pediatr Genet](#), 2015 Jun; 4(2): 42–55.

Pregnancy Outcomes Related to Mycophenolate Exposure in Female Kidney Transplant Recipients



Jun-2016

A cohort study using retrospective and prospective de-identified data collected by the NTPR

A total of 382 cases where KTRs were managed on MPA and became pregnant were used.

Birth Defects

Birth defects were experienced in 23 total pregnancy cases out of 256 total applicable cases .

Discontinuing MPA during 2 trimester or beyond increased the risk of birth defects 6.06 times when compared to those who discontinued >6 weeks prior to pregnancy.

Miscarriages :
A total of 115 miscarriages were reported for 382 pregnancies.

CONCLUSION

There was **no trend of increasing incidence of miscarriages** the later a KTR discontinued MPA up to the second trimester, while discontinuation at the second trimester and beyond increased the risk of miscarriage 9.35 times when compared to those who discontinued >6 weeks prior to pregnancy .

Mode of delivery

Vaginal delivery is the preferred route of delivery and cesarean section is indicated only for obstetric indications.

Damage to the transplant is rare at vaginal delivery and more likely during caesarean section.

EBPG Expert Group on Renal Transplantation, vol. 17, supplement 4, pp. 50–55, 2002.

In uncomplicated pregnancies that who are taking prednisone doses of 5 mg/day or less, the use of stress-dose glucocorticoids is not recommended.

In patients who are experiencing **a complicated pregnancy**(acutely ill, hemodynamically unstable, likely to undergo surgery) stress-dose glucocorticoids is recommended .

Maternal-FetalMedicine:Principles and Practice, Saunders, Philadelphia, Pa, USA, 2004.

Breast-Feeding

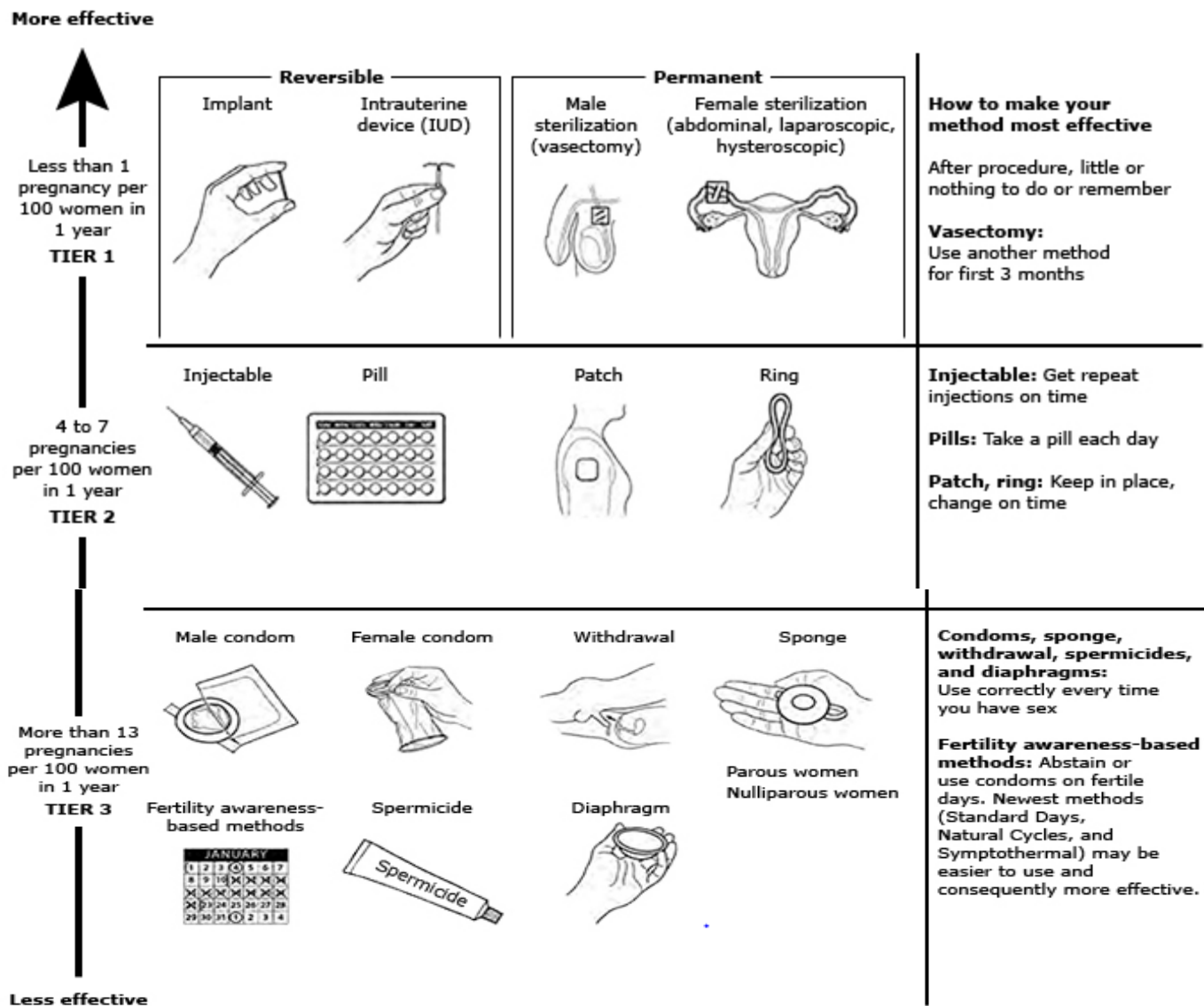
- ❑ Transplant recipients taking prednisone, azathioprine, cyclosporine, and tacrolimus should not be discouraged from breast-feeding .
- ❑ Exposure to these agents via breast milk is less than in utero and has not been associated with any adverse effects.
- ❑ The estimated absorption of tacrolimus from breast milk is equivalent to 0.23% of the maternal dose, which is negligible.
- ❑ Infants breast-fed by women on cyclosporine receive less than 300 mcg per day ,absorb undetectable amounts .
- ❑ Exposure of breast milk to corticosteroids is at most 0.1% of total maternal dose .
- ❑ The amount of azathioprine in breast milk and infant serum is also negligible .

Clinical Journal of the American Society of Nephrology, vol. 8, 2013.

Contraception

- ❖ All transplanted women in childbearing age should receive contraceptive counseling before transplantation and contraception should be started immediately after transplantation.
- ❖ The optimal form of contraception for transplant recipients is not known and is individualized .

Condoms should always be used to reduce the risk of sexually transmitted infections



CDC Recommendations:

Uncomplicated transplant – Women with uncomplicated KT can use any method IUDs, the progestin-only methods (implant, injection, or pills), or estrogen-containing methods (pill, patch, or ring).

Delay the start of estrogen-containing contraceptives (pills, ring, or patch) until six weeks posttransplant because of the increased risk of thromboembolic events.

Complicated transplant – Women with complicated KT (acute or chronic allograft nephropathy).

These women can use any of the progestin-only methods.

TAKE HOME MESSAGE

- ❑ Sexual function typically improves in both women and men within a few weeks posttransplant.
- ❑ Women of childbearing age and men should receive counseling regarding contraception before transplantation and at posttransplant.
- ❑ Male and female transplant recipients to start contraception before they become sexually active.
- ❑ Pregnancy in women with KT should be planned, considered high risk, and ideally managed by an expert multidisciplinary team.

The following summarizes the criteria for KT recipients contemplating pregnancy:

- ✓ At least 1 year after transplantation
- ✓ Stable allograft function and creatinine < 1.4mg/dL
- ✓ No recent episodes of acute rejection
- ✓ Blood pressure \leq 140/90mmHg
- ✓ No or minimal proteinuria \leq 500mg/24 hours
- ✓ Prednisone \leq 15mg/day
- ✓ Azathioprine \leq 2mg/kg/day
- ✓ Stopping MMF and mTors 6 weeks prior to conception



**MANY THANKS TO
ALL**