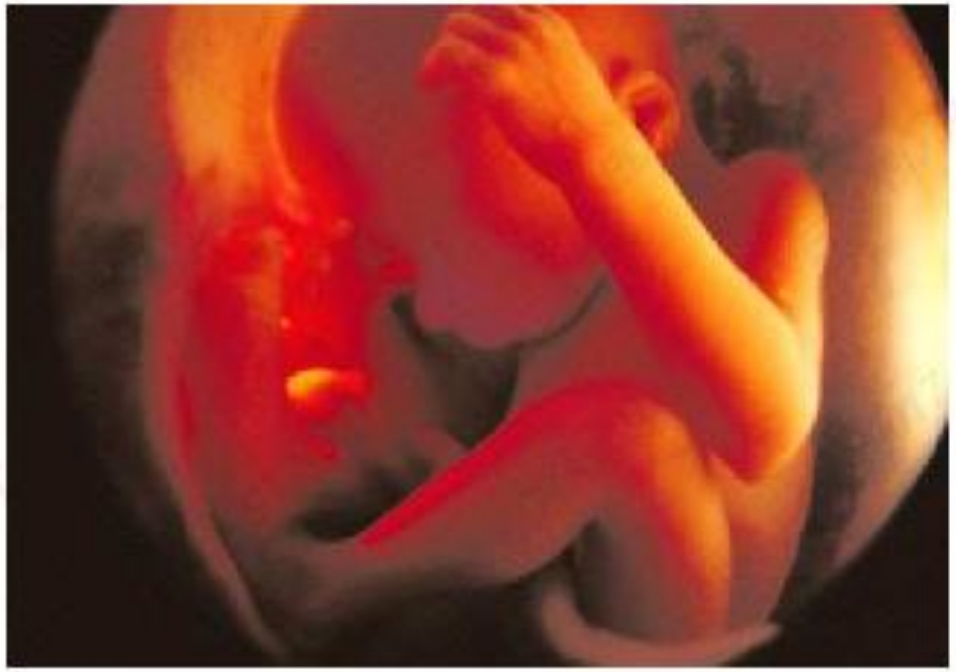
بسم الله الرحمن الرحيم

Pregnancy in kidney transplantation



Dr F Pourrezagholi

SBMU

Shahid Labbafinejad Hospital

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".

The donor and recipient have a total of five babies, all of them in good health, at the time NEJM paper was published .

Murray JE, Reid DE, Harrison JH, Merrill JP (1963) Successful pregnancies after human renal transplantation. N Engl J Med 269:341–343

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

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

Journal of Nephrology (2018)

PREGNANCY COUNSELLING

Pregnancy counselling should begin when a patient chooses renal replacement therapy.

Although many recipients believe that they can become pregnant with a transplant, there is a possibility of infertility after transplantation.

These facts need to be communicated before the transplant.

(2020) Pregnancy Counseling for Kidney Transplant Recipients.

PREGNANCY COUNSELLING

Pregnancy can cause kidney function to deteriorate, and poor renal function before pregnancy leads to allograft loss during pregnancy.

Pregnancy should be attempted after renal function has stabilized after transplantation.

Menstrual recovery after transplantation and contraception methods should be explained to recipients to prevent unexpected pregnancy

(2020) Pregnancy Counseling for Kidney Transplant Recipients.

Preconception counseling

Preconception counseling should be initiated during the pretransplant evaluation.

The following issues should be discussed with the patient prior to, as well as soon after, transplantation:

- Pregnancy outcomes (both maternal and fetal) after transplant
- Maternal risks, including both potential obstetric complications and risks to the allograft
- Contraceptive methods
- Recommended timing of conception after transplant
- Management of maintenance immunosuppression before, during, and after pregnancy

Clin J Am Soc Nephrol. 2013;8(2):290.

CONTRACEPTION

The optimal form of contraception for transplant recipients is not known and is individualized based upon the side-effect profile.

We prefer to delay the start of estrogen-containing contraceptives (pills, ring, or patch) until six weeks posttransplant because of the increased risk of thromboembolic events with estrogen use.

Transplantation. 2013 May;95(10):1183-6.

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

More effective

Less than 1 pregnancy per 100 women in 1 year

TIER 1

Reversible

Implant

Intrauterine device (IUD)

Permanent

Male sterilization (vasectomy)

Female sterilization (abdominal, laparoscopic, hysteroscopic)

How to make your method most effective

After procedure, little or nothing to do or remember

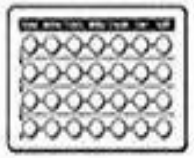
Vasectomy: Use another method for first 3 months

4 to 7 pregnancies per 100 women in 1 year

TIER 2

Injectable

Pill



Patch

Ring

Injectable: Get repeat injections on time

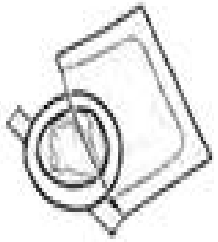
Pills: Take a pill each day

Patch, ring: Keep in place, change on time

More than 13 pregnancies per 100 women in 1 year

TIER 3

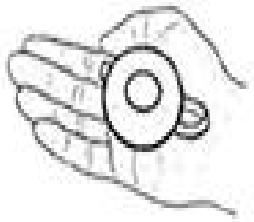
Male condom



Female condom

Withdrawal

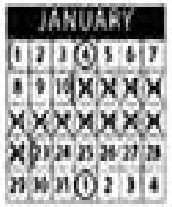
Sponge



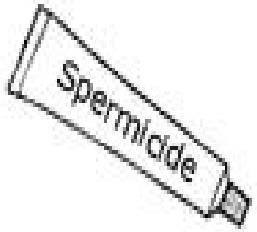
Parous women

Nulliparous women

Fertility awareness-based methods



Spermicide



Diaphragm

Less effective

Condoms, sponge, withdrawal, spermicides, and diaphragms: Use correctly every time you have sex

Fertility awareness-based methods: Abstain or use condoms on fertile days. Newest methods (Standard Days, Natural Cycles, and Symptothermal) may be easier to use and consequently more effective.

A 25-year-old woman with ESKD from FSGS on maintenance hemodialysis for 6 months received a living donor kidney transplant.
Her creatinine stabilized at 1.0 mg/dl, proteinuria at 0.2 g/g, and BP at 110/70 mm Hg. Her medications included tacrolimus,MMF, prednisone,trimethoprim-sulfamethoxazole, and atorvastatin.
At 6 months post-transplant, she indicated the desire to have children.

Can I Become Pregnant?

Timing of conception

The optimal time for conception after kidney transplantation is uncertain.

Based on the 2005 AST, provided that the following conditions are met :

- It has been more than one year since kidney transplantation.
- Graft function is optimal, defined as a serum creatinine of <1.5 mg/dL), with no or minimal proteinuria.
- There have been no episodes of rejection in the previous year.
- The patient is not on known teratogenic or fetotoxic medications.
- The immunosuppressive regimen is stable at maintenance levels.

Am J Transplant. 2005;

- There are no concurrent fetotoxic infections, such as CMV.
- 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.

Am J Transplant. 2005;

Transplantation patients appear to have a lower **pregnancy rate** than the general public

Pregnancy rate

- The best data come from a longitudinal cohort of 30,078 female transplant recipients aged 15 to 45 years .
- During the first three post transplant years, the pregnancy rate was 33 per 1000 women compared with more than 100 per 1000 women in the general population.

Am J Transplant 2009; 9:1541.

Fertility and Contraceptive Issues After Kidney Transplantation in Women

M. Lessan-Pezeshki, S. Ghazizadeh, M.R. Khatami, M. Mahdavi, E. Razeghi, S. Seifi, F. Ahmadi, and S. Maziar

ABSTRACT

Purpose: Our purpose was to investigate reproductive performance among kidney transplant recipients.

Materials and Methods. We studied 126 kidney transplanted women 15 to 68 years of

PREGNANCY RATES AND FERTILITY IN RENAL TRANSPLANT RECIPIENTS

- There is limited understanding of fertility in women with renal transplants,
- Infertility problems in13out of 126(10.4%)women with renal transplants,5 which is comparable with general population rates.

Many factors drive this low rate:

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

Will My Baby Be OK?

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 IUGR remains high.

Predictors of good maternal and fetal outcomes Include:

a younger maternal age, stable graft function with no recent episodes of graft rejection, serum creatinine level of ,1.5 mg/dl, proteinuria of ,500 mg a day, and normal or well controlled hypertension

BMC Nephrol 20: 24, 2019

Shah *et al. BMC Nephrology* (2019) 20:24
https://doi.org/10.1186/s12882-019-1213-5

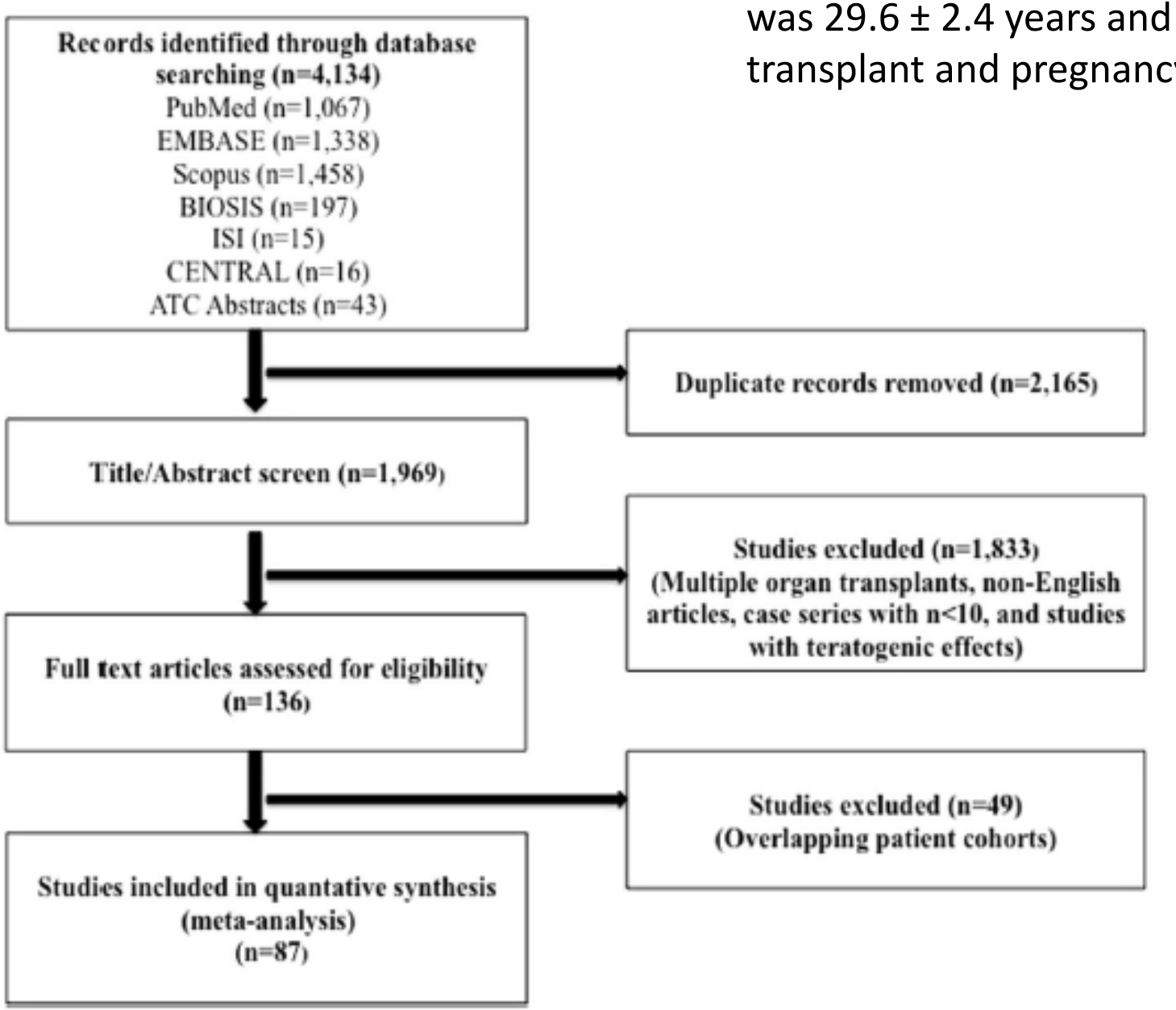
BMC Nephrology

RESEARCH ARTICLE Open Access

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

Silvi Shah[1*], Renganathan Lalgudi Venkatesan[2], Ayank Gupta[2], Maitrik K. Sanghavi[2], Jeffrey Welge[3], Richard Johansen[2], Emily B. Kean[2], Taranpreet Kaur[1], Anu Gupta[4], Tiffany J. Grant[2] and Prasoon Verma[5]

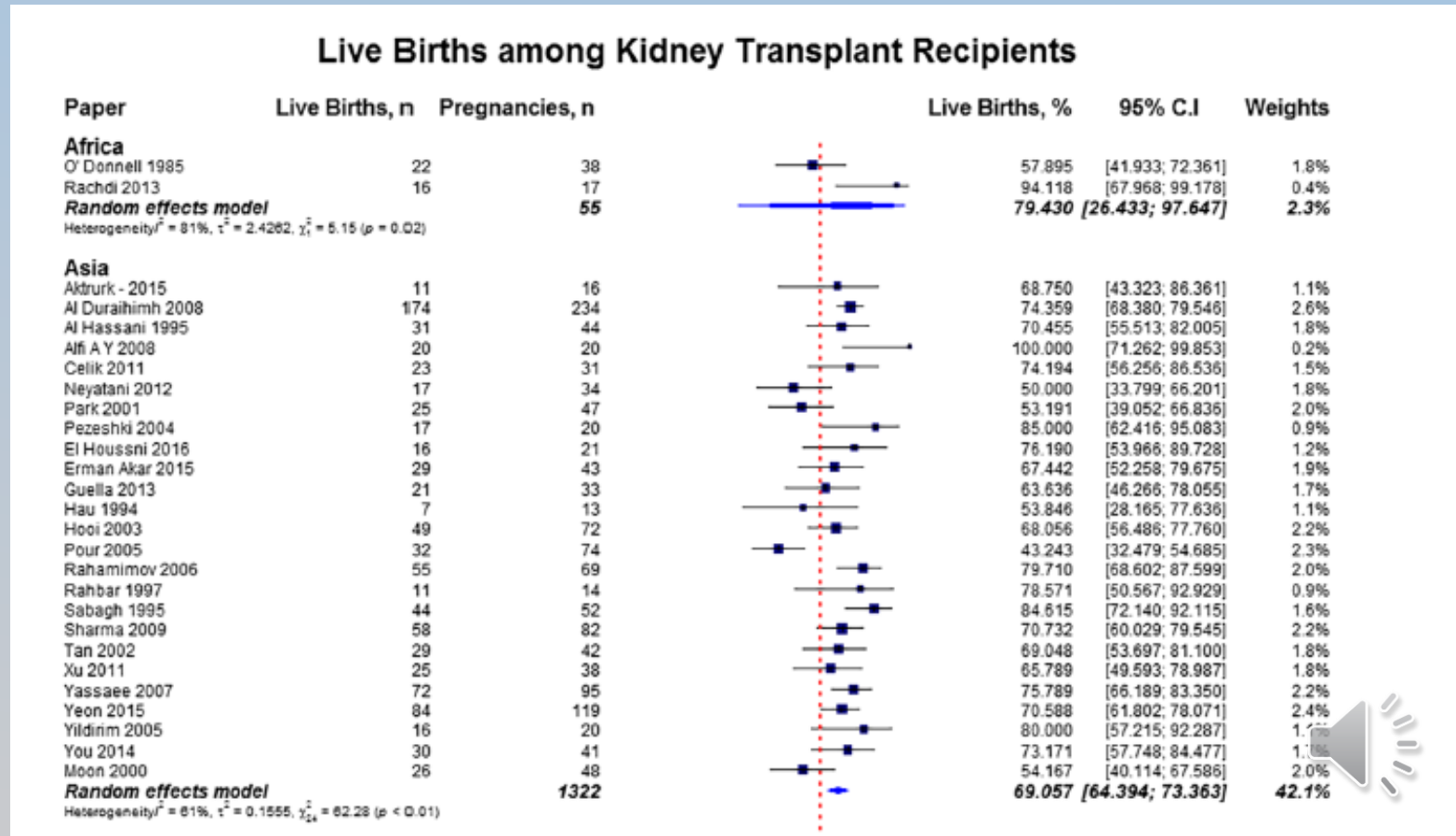
In 4174 kidney transplant recipients ,mean maternal age was 29.6 ± 2.4 years and mean interval between kidney transplant and pregnancy was 3.7 years.



The results of this meta-analysis show :

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.



Risk of Fetal Complications

The rate of live births in allograft recipients is comparable to general population and ranges from 71 to 79%.
The incidence of preterm delivery has be as high as 40 to 60% versus 5 to 15% in general population.

They have high incidence of preterm birth (52 to 53%), low birth weight (42 to 46%), and IUGR (30 to 50%) .

Can I Take My Usual Medications?

Dosing of immunosuppressant medications …..

- There are no guidelines about dosing of immunosuppressant medications during pregnancy, but several studies have provided recommendations
- Tacrolimus trough blood levels decreased during the second trimester (from 5.8 2.8 to 4.2 1.8 ng/ml).
- cyclosporine levels decreased during the second trimester from 125.1 65.1 to 75.4 35 ng/ml.

- MMF is a teratogen and is substituted with azathioprine at least 6 weeks before attempting pregnancy.
- Belatacept and mTORinhibitors and shouid be avoid.
- Prednisone is considered safe in pregnancy .
- To maintain whole blood drug levels of CNIs a 20%–25% increase in total dose.

Am J Transplant 9[Suppl 3]: S1–S155, 2009

kidney INTERNATIONAL
May 2017 Volume 91, Issue 5, Pages 1047–1056

Table 3 | Drug safety in pregnancy

Safe	Not safe	Safety not determined
Immunosuppressants		
Tacrolimus	Cyclophosphamide	Sirolimus
Cyclosporin	Mycophenolate products	Everolimus
Azathioprine	Rituximab	
Corticosteroids		
Hydroxychloroquine		
Antihypertensives		
Labetalol	Angiotensin-converting enzyme inhibitors	
Calcium channel antagonists	Angiotensin receptor blockers	
Methyldopa	Minoxidil	
Hydralazine		
Furosemide		
Antibiotics commonly used in immunosuppressed patients		
Aciclovir	Ganciclovir	
Valaciclovir	Valganciclovir	
	Co-Trimoxazole	
Lamivudine	Quinolones	
Tenofovir		
Isoniazid		
Nystatin (topical)		

Kidney International (2017) **91,** 1047–1056

Will I and My Kidney Be OK?

MATERNAL COMPLICATIONS

Preeclampsia: Preeclampsia might be difficult to diagnose in women with renal transplants because many of them have preexisting hypertension, and several develop gestational proteinuria without preeclampsia.

Gestational Diabetes

Women with renal transplants are at higher risk of developing gestational diabetes than the general population. Screening with oral glucose tolerance testing should be offered to all women with renal transplants earlier in gestation.

MATERNAL COMPLICATIONS

Graft Injury During Delivery

This complication is extremely rare and is restricted only to those with surgical deliveries.

Vaginal delivery is not affected by the anatomic location of the graft.

Infections

UTI is the most common infection encountered by women with renal transplants during pregnancy, with incidence rates ranging from 14.6%to 42%. If pregnancy is delayed until at least 1 year after transplantation, the risk for opportunistic infections is likely to be lower.

American Journal of Transplantation 2011

Pregnancy in Renal Transplant Recipients and Donors

Kate Bramham, PhD

Seminars in Nephrology, Vol 37, No 4, July 2017, pp 370–377

Data from the US National Transplant Pregnancy Registry (NTPR) indicated that women with graft loss during or after pregnancy were more likely to have higher pre pregnancy creatinine than those with stable graft function (1.5 - 0.6 mg/dLversus1.3 0.4 mg/dL) and African-American women have an increased risk for graft loss within 2 years of delivery(13%) in comparison with whites(5%).

The graft failure rate did not differ in pregnant women as compared to non pregnant allograft recipients at follow-up of 10 years (19% versus 21%)

Risk factors associated with graft loss
include history of drug treated hypertension,
prepregnancy creatinine ≥ 1.4mg/dL, and proteinuria.

Shah *et al. BMC Nephrology* (2019) 20:24
https://doi.org/10.1186/s12882-019-1213-5

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RESEARCH ARTICLE Open Access

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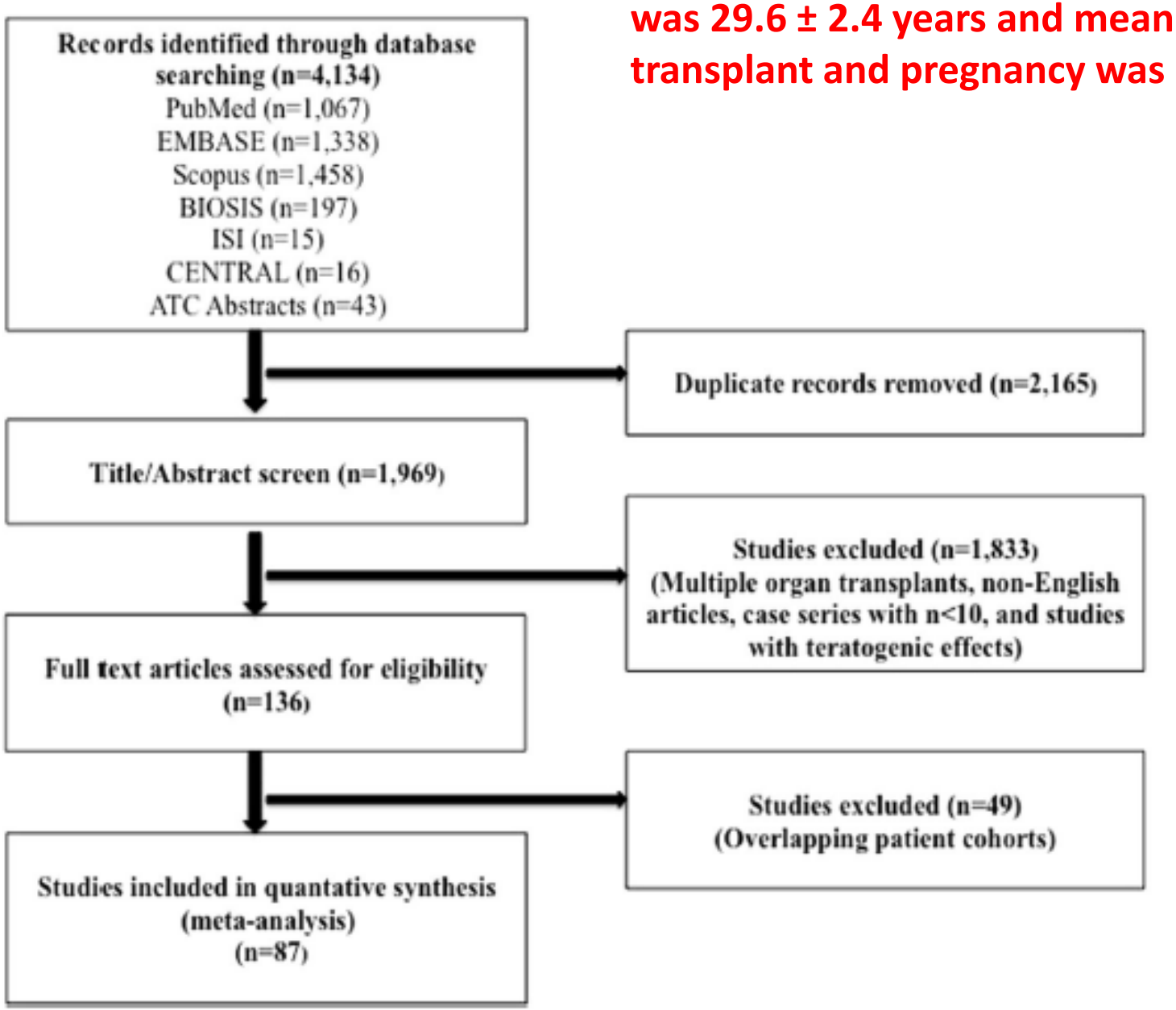

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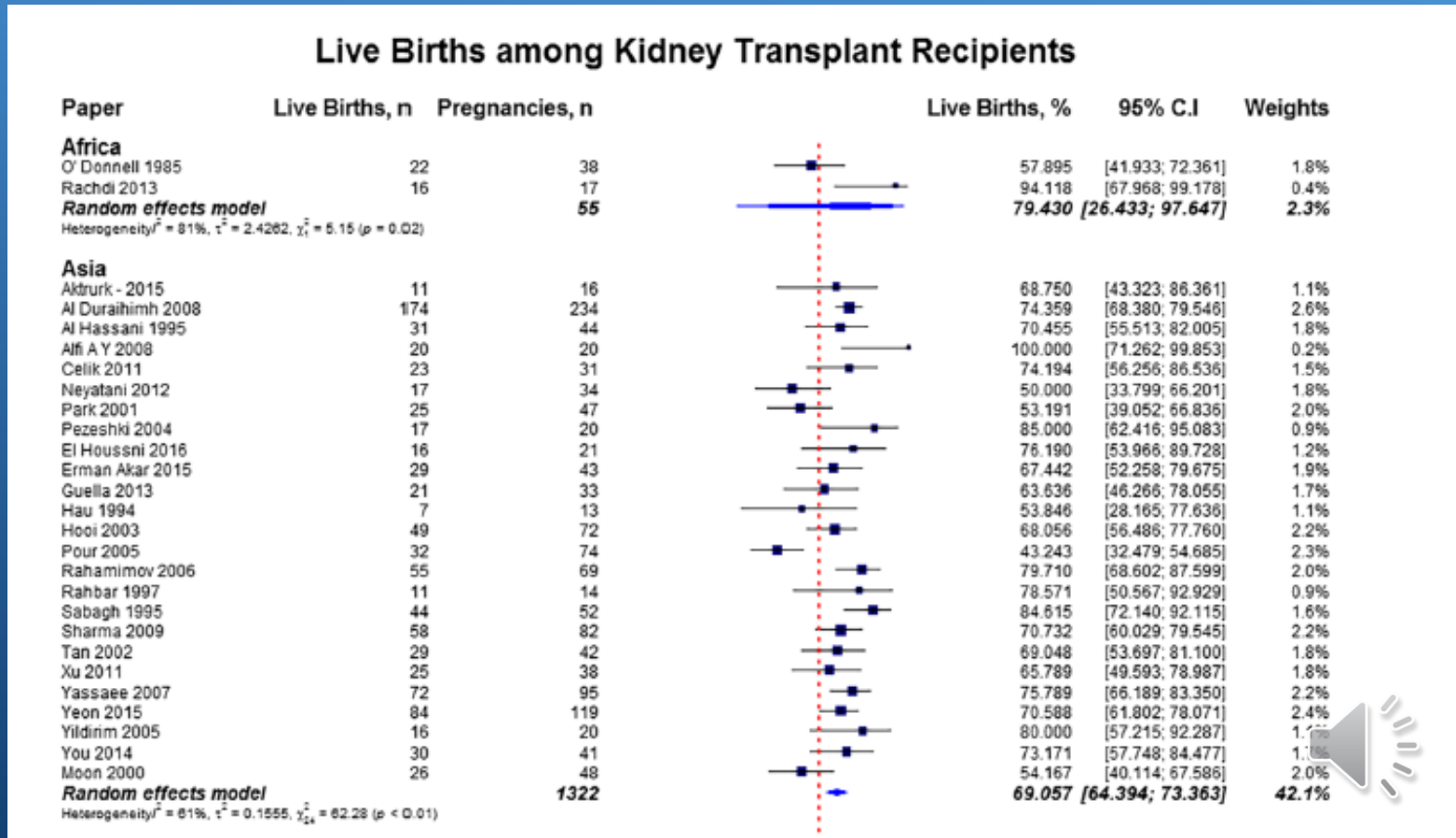


Most studies have shown that maternal death (defined as death of a pregnant woman or within 42 days of termination of pregnancy) and long-term survival of pregnant transplant recipients appears to be comparable with that of nonpregnant recipients .

Journal of Nephrology (2018) 31:665–681

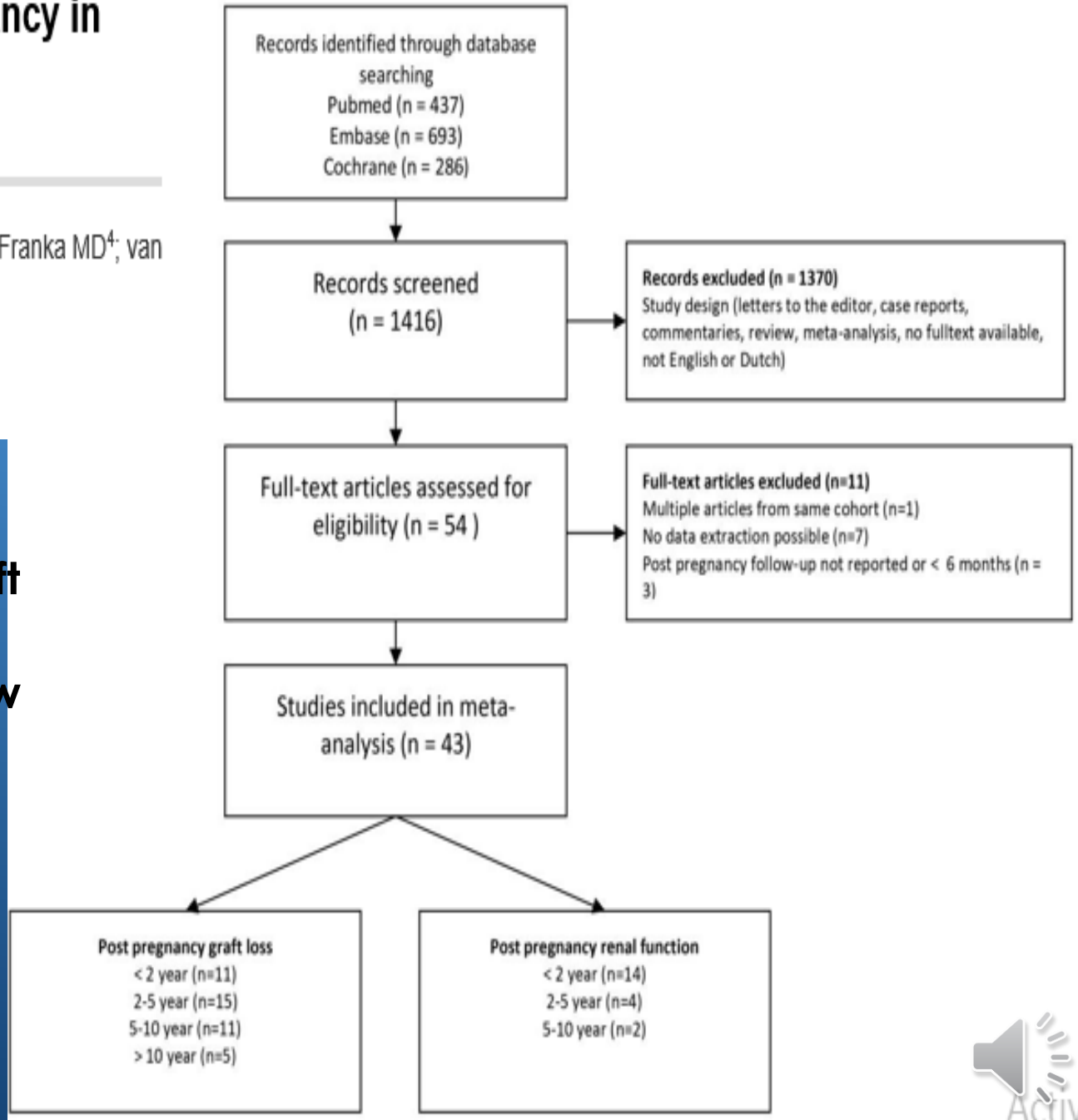
Long term graft survival and graft function following pregnancy in kidney transplant recipients

a systematic review and meta-analysis

van Buren, Marleen C. MSc[1,*]; Schellekens, Anouk MD[2,*]; Groenhof, T. Katrien J. MD[3]; van Reekum, Franka MD[4]; van de Wetering, Jacqueline MD PhD[2]; Paauw, Nina D. MD PhD[1]; Lely, A. Titia MD PhD[1]

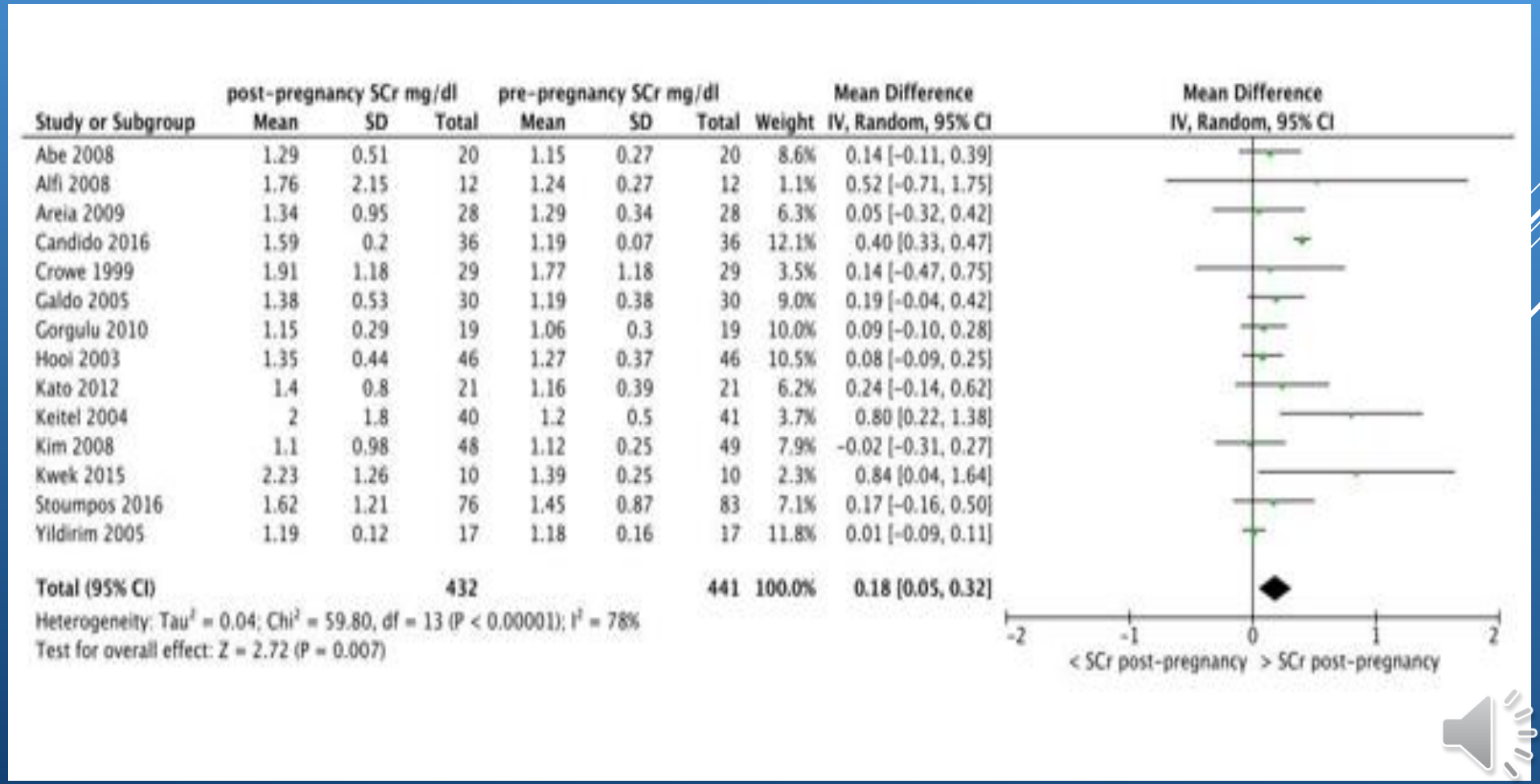
Transplantation: October 21, 2019 - Volume Online First - Issue - p
doi: 10.1097/TP.0000000000003026

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.



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.



Study or Subgroup	post-pregnancy SCr mg/dl Mean	SD	Total	pre-pregnancy SCr mg/dl Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abe 2008	1.29	0.51	20	1.15	0.27	20	8.6%	0.14 [-0.11, 0.39]
Alfi 2008	1.76	2.15	12	1.24	0.27	12	1.1%	0.52 [-0.71, 1.75]
Areia 2009	1.34	0.95	28	1.29	0.34	28	6.3%	0.05 [-0.32, 0.42]
Candido 2016	1.59	0.2	36	1.19	0.07	36	12.1%	0.40 [0.33, 0.47]
Crowe 1999	1.91	1.18	29	1.77	1.18	29	3.5%	0.14 [-0.47, 0.75]
Galdo 2005	1.38	0.53	30	1.19	0.38	30	9.0%	0.19 [-0.04, 0.42]
Gorgulu 2010	1.15	0.29	19	1.06	0.3	19	10.0%	0.09 [-0.10, 0.28]
Hooi 2003	1.35	0.44	46	1.27	0.37	46	10.5%	0.08 [-0.09, 0.25]
Kato 2012	1.4	0.8	21	1.16	0.39	21	6.2%	0.24 [-0.14, 0.62]
Keitel 2004	2	1.8	40	1.2	0.5	41	3.7%	0.80 [0.22, 1.38]
Kim 2008	1.1	0.98	48	1.12	0.25	49	7.9%	-0.02 [-0.31, 0.27]
Kwek 2015	2.23	1.26	10	1.39	0.25	10	2.3%	0.84 [0.04, 1.64]
Stoumpos 2016	1.62	1.21	76	1.45	0.87	83	7.1%	0.17 [-0.16, 0.50]
Yildirim 2005	1.19	0.12	17	1.18	0.16	17	11.8%	0.01 [-0.09, 0.11]
Total (95% CI)			**432**			**441**	**100.0%**	**0.18 [0.05, 0.32]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 59.80$, $df = 13$ ($P < 0.00001$); $I^2 = 78\%$

Test for overall effect: $Z = 2.72$ ($P = 0.007$)

Will I Need a Cesarean Section, and Can I Breastfeed?

- Vaginal delivery is well tolerated and recommended in uncomplicated pregnancies.
- Cesarean section should be done for obstetric indications
- In the event of surgery, care should be taken to avoid injury to the ureter of the kidney allograft.

J Nephrol 31: 665–681, 2018

Breast-Feeding

Transplant recipients taking prednisone, azathioprine, cyclosporine, and tacrolimus **should not be discouraged** from breast-feeding.

It is well established now that the infants who are breast-fed by mothers on prednisone, azathioprine, and cyclosporine/tacrolimus have a lesser exposure via breast milk than in utero and they do not have adverse effects.

Breast feeding is recommended by the American Association of Pediatrics for the first 6 months of life and this practice is not opposed by the American Society of Transplantation.

Although low levels of drug and drug metabolites can be detected in breast milk, a regimen of **tacrolimus, azathioprine and prednisone** is felt to be safe .

BMC Nephrol 20: 24, 2019

Follow-Up of This Patient

This patient did not wish to delay pregnancy.

MMF was switched to azathioprine.

Aspirin 81 mg daily was started.

Trimethoprim- sulfamethoxazole and atorvastatin were stopped.

She became pregnant at about 10 months post-transplant.

Her BP remained well controlled without medications.

Although there was a small increase in proteinuria to 0.5 g/g, her serum creatinine improved from 1.0 to 0.8 mg/dl.

- She was induced at 36 weeks of gestation because of an abrupt rise in serum creatinine, and had a cesarean section delivery for a nonreassuring fetal heart rate.
- Her baby was healthy but of low birth weight.
- She elected not to breast feed.
- Her creatinine returned to baseline post delivery and has
- remained stable 2 years post-transplant.

THANK YOU