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PEER-REVIEW REPORT

Name of journal: *World Journal of Meta-Analysis*

Manuscript NO: 82949

Title: Infertility, Pregnancy and Breastfeeding in Kidney Transplantation Recipients: Key Issues

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03547306
Position: Peer Reviewer
Academic degree: PhD
Professional title: Chief Doctor
Reviewer's Country/Territory: Serbia
Author's Country/Territory: Saudi Arabia

Manuscript submission date: 2022-12-31

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-12-31 14:26

Reviewer performed review: 2022-12-31 14:27

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty

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Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation
Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

very nice

Author reply

Thank you for your positive comment. I am glad that you find the article interesting.

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Title: Infertility, Pregnancy and Breastfeeding in Kidney Transplantation Recipients: Key Issues

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03622345
Position: Peer Reviewer
Academic degree: Doctor, MD, PhD
Professional title: Professor
Reviewer's Country/Territory: Reviewer_Country
Author's Country/Territory: Saudi Arabia

Manuscript submission date: 2022-12-31
Reviewer chosen by: AI Technique
Reviewer accepted review: 2022-12-31 10:26
Reviewer performed review: 2023-01-04 09:25
Review time: 3 Days and 22 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [Y] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [Y] Grade D: No novelty

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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [Y] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In this review there is no definite conclusion, un related details to different topics, no conclusion.

Author reply:

Thank you for your comment. I made many changes to my manuscript, and references increased from 74 to 102, additional information was added based on reviewers' comments. I amended my conclusion so that, interested in transplantation can have a take home message by reading the conclusion only.

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Title: Infertility, Pregnancy and Breastfeeding in Kidney Transplantation Recipients: Key Issues

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03546647
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Assistant Professor, Surgeon
Reviewer's Country/Territory: Italy
Author's Country/Territory: Saudi Arabia

Manuscript submission date: 2022-12-31

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2023-01-11 10:10

Reviewer performed review: 2023-01-11 12:18

Review time: 2 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The present narrative review focuses on a relevant topic, but it mostly fails to provide in depth discussion regarding most relevant issues related to conception and pregnancy after kidney transplantation. Major comments 1) In the section "Impact of pregnancy on graft survival", the authors should discuss the possibility of selection bias (relative contraindication to pregnancy in case of suboptimal allograft function) affecting the interpretation of results. 2) In the section "Management of immunosuppression", both male- and female-related issues should be considered. 3) In the section "Management of immunosuppression", common drug-related side effects and interactions that may have an impact on pregnancy as well as follow up strategies aiming to reduce the risk of rejection after switching medications should be discussed. 4) In the section

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"Management of immunosuppression", the opportunity to switch from tacrolimus to cyclosporine in case of impaired fasting glucose, abnormal OGTT, or gestational diabetes should be discussed. 5) In the section "Manage non-immunosuppression drugs", a brief discussion about commonly used antibiotics during pregnancy would be appreciated. 6) The present review fails to discuss any frequent infectious complication potentially affecting pregnancy, including TORCH. Minor comments 1) Please, provide higher quality images. 2) There are several typos scattered throughout the manuscript.

Author reply:

Thank you for your valuable comments and I tried to address all your concerns in the revised article.

Answers to major comments:

Answer to comment 1 (In the section "Impact of pregnancy on graft survival", the authors should discuss the possibility of selection bias (relative contraindication to pregnancy in case of suboptimal allograft function) affecting the interpretation of results.): To evaluate possible bias in patients' selection that may affect outcomes and interpretation of results, M. Pappias and colleagues evaluated pregnancy outcomes after living kidney donation in a systematic review. In this study, 2 authors used the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) method to evaluate participant selection, exposure, and results. Robvis online software plotted risk-of-bias evaluations. GRADE (Grading of recommendations, assessment, development, and evaluations) method graded study certainty. As a result, authors concluded that after

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donation, the absolute chance of pregnancy related and associated complications remain minimal, which is comparable to other studies[27].

Answer to comment 2 (In the section "Management of immunosuppression", both male- and female-related issues should be considered): In addition to female recipient preparation for pregnancy, male recipients who desires paternity should be also properly counseled about the impact of immunosuppression on fertility. Few studies have reported the negative effect of immunosuppressive drugs, particularly sirolimus, on male fertility. Sirolimus was shown to be linked to reduced fertility following kidney transplantation, due to its toxic effect on the sperm[33,34]. That's why, unrecovered fertility in male recipients maintained on mammalian target of rapamycin inhibitors (mTORi) following renal transplant surgery, should raise the suspicion of possible drug toxicity.

Answer to comment 4 (In the section "Management of immunosuppression", the opportunity to switch from tacrolimus to cyclosporine in case of impaired fasting glucose, abnormal OGTT, or gestational diabetes should be discussed) :CNIs, in particular tacrolimus, are associated with increased risk of Post-transplant Diabetes Mellitus. It is well established that tacrolimus is more diabetogenic than cyclosporine[43,44]. Increased tacrolimus levels have been strongly linked to altered glucose tolerance, toxic effect on islet cells with subsequent development of diabetes mellitus. In pregnant recipients treated with tacrolimus with new onset hyperglycemia, shifting to safer drug such as cyclosporine could be an option. However, a recent systematic review and meta-analysis compared the impact of cyclosporine and tacrolimus on pregnancy outcomes in liver/kidney transplant recipients, found no significant differences in the incidence of gestational diabetes between them[45].

Answer to comment 5 (In the section "Manage non-immunosuppression drugs", a

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brief discussion about commonly used antibiotics during pregnancy would be appreciated): In the other hand, antibiotics during pregnancy are used more frequently, as the incidence of infections is higher in transplanted patients, owing to the use of potent immunosuppression. Urinary tract infections are prevalent in female transplant patients, and the risk rises by up to 40% during pregnancy, presumably due to physiologic anatomic changes occurring in the urinary tract[58]. The prescription of antibiotics in kidney transplant recipients should always be considered for a potential interaction and possible adverse effects. Antibiotics such as Nitrofurantoin, Amoxicillin, Cephalexin, Cefpodoxime and Fosfomycin are considered safe in pregnancy in kidney transplant recipients with no drug-drug interaction[59]. Ciprofloxacin and Trimethoprim/Sulfamethoxazole are generally not recommended in pregnancy with and without transplantation. Antibiotics that are generally used for the management of upper and lower tract infections include macrolides, quinolones, penicillins and cephalosporins. Clarithromycin, but not azithromycin should be avoided in kidney transplant recipients irrespective of pregnancy, because of its effect on the hepatic/intestinal enzyme CYP3A4 metabolism and subsequent increase in tacrolimus level and possible toxicity. Azithromycin is safe to use during pregnancy in renal transplant recipients, but attention should be paid to the risk of arrythmia as both drugs increase QTc interval. The use of quinolones in pregnancy is still controversial in literature because of concerns on their adverse effects on the fetus formation. However, animal studies did not show an increase in major birth defects, abortion or maternal complications[60]. Hence, quinolones can be prescribed in complicated and life threating infections.

Penicillins and cephalosporins are generally acceptable in kidney transplant recipients in the context of pregnancy.

Answer to comment 6 (The present review fails to discuss any frequent infectious

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complication potentially affecting pregnancy, including TORCH):

IMPACT OF KIDNEY TRANSPLANTATION AND PREGNANCY ON THE INCIDENCE OF INFECTION AND OUTCOMES

After kidney transplantation, infection is the second major cause of mortality among transplant patients, behind cardiovascular disease. Up to seventy percent of kidney transplant recipients will encounter an infection episode during the first three years following transplantation, according to estimates[61]. As mentioned earlier, bacterial urinary tract infections are more prevalent during pregnancy in a kidney transplant recipient because of potent immunosuppression used.

Other than urinary tract infection, pregnant transplant recipients are at risk of TORCH infections. TORCH infections are a category of infectious disorders that can be transmitted to a newborn during pregnancy, delivery, or shortly after birth. Toxoplasmosis, rubella, cytomegalovirus, herpes, and others are termed as TORCH. In transplant recipients, the risk of cytomegalovirus infection during pregnancy is minimal, as conception is often planned 1–2 years following transplantation. Congenital cytomegalovirus (CMV) is the leading nongenetic cause of congenital sensorineural hearing loss and neurological impairment[62,63]. Therefore, it is essential that CMV infections be monitored.

Another TORCH virus, Herpes simplex virus can occur during pregnancy in immunocompromised patients as primary infection or activation of latent infection. In case of herpetic infection valacyclovir or acyclovir can be used safely during pregnancy. Caesarean delivery in infected mothers reduces the incidence of newborn herpes 1 or 2. Therefore, caesarean section should be performed if cervical cultures show herpes. To prevent primary varicella-zoster virus (VZV) infection after transplantation, pretransplant screening for past VZV infection should be conducted, and naive patients

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should be immunized with live attenuated varicella vaccine if possible[58].

Toxoplasmosis in pregnant transplant recipients can be caused by either reactivation of a latent infection or primary infection. In a fitting clinical setting, toxoplasmosis should be evaluated in the differential diagnosis of pneumonia, culture-negative sepsis, and encephalitis. Toxoplasmosis should be screened quarterly in pregnant kidney transplant patients. Sulfadiazine, pyrimethamine and spiramycin should be given to immunosuppressed individuals with growing antibody titers to prevent congenital toxoplasmosis infection[64].

As a conclusion, many illnesses can be avoided or ameliorated by pre- and post-transplant care, pretransplant screening of infections and updated immunization remain the major standard of treatment. Protocol polymerase chain reaction screening of CMV, BK virus and others, in the post-operative period has been also shown to reduce the incidence of infectious complications. Finally, most opportunistic infections occurring in pregnant transplanted patients can be preventable, therefore, transplant nephrologists carry a major responsibility in the delivery of best available medical care for all patients.

Answers to minor comments:

I changed onefigure which was not well organized. I modified the content of the table because of reference problems. I also added the number of references in the table.
I also corrected some typos.

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Title: Infertility, Pregnancy and Breastfeeding in Kidney Transplantation Recipients: Key Issues

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06126039
Position: Peer Reviewer
Academic degree: Doctor, PhD
Professional title: Academic Research, Associate Professor, Consultant Physician-Scientist, Surgeon, Surgical Oncologist
Reviewer's Country/Territory: Tunisia
Author's Country/Territory: Saudi Arabia

Manuscript submission date: 2022-12-31

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2023-01-08 11:22

Reviewer performed review: 2023-01-16 11:16

Review time: 7 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

findings of this manuscript: a transplant recipient planning pregnancy should discontinue sirolimus 12 weeks before pregnancy, and MMF 8 weeks before. The combination of calcineurin inhibitors, azathioprine and steroids are safe in pregnant recipients

Author reply:

Thank you for your comment