

Evaluation of Pregnancy in Kidney Transplant Recipient: A Nationwide Retrospective Study

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Abstract

Background

Kidney transplantation significantly enhances the quality of life and restores fertility for women of childbearing age. Although pregnancy risks in allograft recipients are documented globally, there is a distinct lack of evaluated data regarding outcomes within the Middle Eastern population. This study aimed to evaluate maternal, fetal, and graft outcomes, alongside associated risks, among kidney transplant recipients in state of Qatar.

Methods

We performed a nationwide retrospective observational study at a nationwide kidney transplantation center. The cohort included 91 female recipients of reproductive age (15–49 years) who underwent transplantation between January 2016 and December 2023. Clinical data, including demographics, immunosuppression protocols, and laboratory parameters, were extracted from national electronic medical records.

Results

Within the cohort of 91 females, 12 recipients (13.2%) had a total of 14 pregnancy events, with a mean age of 36 ± 3.7 years at the time of conception. The live birth rate was 57% (8/14), while adverse outcomes included early pregnancy loss (21%), spontaneous abortions between 12 to 20 weeks (14%), and one case of preeclampsia-related intrauterine fetal demise (7%). Notably, 75% of patients (3 out of 4) with a pre-conception serum creatinine $> 120 \mu\text{mol/L}$ experienced adverse outcomes. While allograft function remained stable in the majority of successful deliveries, two patients experienced persistent graft dysfunction postpartum, with one requiring a return to dialysis due to chronic allograft nephropathy. All patients were successfully transitioned from mycophenolate mofetil to azathioprine for pregnancy.

Conclusion

Pregnancy post-kidney transplantation in Qatar is associated with acceptable outcomes for the mother, fetus, and allograft when managed with rigorous multi-specialty involvement. However, pre-conception graft function, specifically a serum creatinine level $< 120 \mu\text{mol/L}$, remains a critical predictor of pregnancy success. These findings emphasize the need for individualized counseling and vigilant monitoring to mitigate risks of rejection and graft loss.

Introduction

Kidney transplantation significantly improves morbidity and mortality especially for women in childbearing age. The positive outcome of transplantation is not only limited to clinical outcomes, it also improve fertility compared to end-stage kidney disease (ESKD) women (1). However, specialized medical attention is needed as pregnancy has been associated with several complications (2, 3).

Guidelines recommend delaying pregnancy for one to two years after kidney allograft transplantation, as this period has the highest risk of rejection and early post-transplant infections (4–6). Several studies have reported

association of low pre-conception graft function and pregnancy complications; therefore the American society of transplantation and European Best Practice Guideline group have recommended a stable kidney function with serum creatinine < 1.5mg/dL or < 120 µmol/L with proteinuria < 500mg/24 hours (7–9). Furthermore, it is recommended to not have any recent episodes of rejection, have a stable immunosuppression regimen and avoid immunosuppression such as mycophenolate mofetil and sirolimus 6 weeks prior to conception.

Despite these guidelines, there has been only a limited number of published data on the outcomes on the fetal and maternal outcomes of pregnancy in kidney transplant recipients in the middle east (10, 11). Hence, we retrospectively evaluated 91 female kidney transplant recipients who were in childbearing age transplanted between 2016 to 2023 in Qatar to determine incidence of pregnancy and evaluate maternal, fetal and graft outcome.

Methods

Patient characteristics:

This is a retrospective observational nationwide study from the State of Qatar. It was done in HMC, the only health care provider for kidney transplantation cases in Qatar. We included all patients with end stage kidney disease who received kidney transplantation between January 2016 to December 2023. Women of childbearing age (15–49 years old) were included. Cases of pregnancy were identified by reviewing patients' files in a national medical record (Cerner-North Kansas City, MO, USA). Data obtained include patients demographics, co-morbidities (presence of hypertension, diabetes mellitus, cardiovascular disease), laboratory tests. We defined early pregnancy loss as fetal demise and miscarriage withing the first trimester (less than 12 weeks), spontaneous abortion as natural termination of pregnancy after 12 weeks but before 20 weeks and intrauterine fetal demise (IUFD) as death of fetus occurring at or after 20 weeks of gestation. The study was approved by the local Medical Research Center (MRC-01-24-207). As per the approval, the study meets the waiver criteria of informed consent, and all data were fully anonymized before we accessed them. Clinical trial number: not applicable

Statistical analysis:

Data was collected in a Microsoft Excel spreadsheet, coded, and anonymized to protect patient identifiers. Categorical variables are presented as frequency distributions and percentages. Continuous variables are summarized as mean ± standard deviation (SD). For statistical analysis, continuous variables were analyzed using mixed-effects models were employed to account for repeated measures and clustering effects where applicable, such as evaluating changes in kidney function parameters over time. A two-sided p-value of < 0.05 was considered statistically significant. Analyses were performed using Graphpad Prism version 10.0.1.

Results

Patients characteristics:

A total of 178 women was registered in the post-transplant registry in Qatar from 2016 to 2023 representing 26% of total registered patient in the same period. 91 patients were in reproductive age during the study time. After kidney transplantation, 12 patients underwent 14 pregnancies, with a mean age of 28 ± 3.1 years at the time of transplantation and 36 ± 3.7 years at conception. Primary kidney disease of recipients was variable including IgA nephropathy, congenital solitary kidney and unknown causes. A prior history of pregnancy was documented in

64% of the cohort, while 28% conceived through in vitro fertilization. Donor types were distributed among living-related donors (50%), living-unrelated donors (42%), and a single case (8%) involving a deceased donor. Regarding racial background, the cohort was composed equally of Middle Eastern (43%) and Asian (43%) women, with a smaller proportion (14%) being Caucasian. None of the patients had a history of diabetes, while 50% had preexisting hypertension. The mean baseline serum creatinine level before conception was 102 ± 36 $\mu\text{mol/L}$ as shown in Table 1.

Table 1 Patient Characteristic:

Variable	Pregnancy (n=14)
Age at transplantation	28 ± 3.1
Age at conception	36 ± 3.7
History of Pregnancy	9 (64%)
In vitro fertilization	4 (28%)
Donor type:	
Living related	6 (50%)
Living unrelated	5 (42%)
Deceased donor	1 (8%)
Ethnicity:	
Middle eastern	6 (43%)
Asian	6 (43%)
Caucasian	2 (14%)
History of Diabetes	0
History of Hypertension	7 (50%)
Baseline creatinine prior to conception ($\mu\text{mol/L}$)	102 ± 36
Immunosuppression prior to conception:	
Tacrolimus	12 (86%)
Cyclosporin	2 (14%)
Mycophenolate Mofetil	8 (57%)
Prednisolone	14 (100%)
Immunosuppression during pregnancy:	
Tacrolimus	12 (86%)
Cyclosporin	2 (14%)
Azathioprine	14 (100%)
Prednisolone	14 (100%)

In terms of immunosuppressive therapy, all patients were receiving prednisolone prior to conception, with 86% on tacrolimus, 14% on cyclosporin, and 57% on mycophenolate mofetil. During pregnancy, mycophenolate was universally discontinued and replaced with azathioprine in all cases. The majority of patients (86%) continued on tacrolimus, while 14% remained on cyclosporin. All women received a combination of azathioprine and prednisolone during pregnancy. Individual patient characteristics are shown in Table 2.

Table 2
Individual recipient characteristics:

Pt	History of pregnancy before Tx	Age (Years)	Time from transplant (Years)	Creatinine prior to conception ($\mu\text{mol/L}$)	Blood pressure prior to pregnancy	Donor source	History of Proteinuria
TxP1	No	35	7	93	117/69	LUR	No
				108	124/85		No
TxP2	Yes	43	8	116	123/85	LUR	No
TxP3	Yes	38	8	105	111/80	LUR	No
TxP4	No	36	7	77	97/71	CAD	No
				78	110/71		No
TxP5	Yes	37	7	68	108/77	LR	No
TxP6	Yes	29	7	64	123/70	LUR	No
TxP7	No	33	8	122	112/71	LR	No
TxP8	Yes	37	7	71	122/79	LR	No
TxP9	Yes	34	5	146	138/97	LR	No
TxP10	No	37	8	75	113/69	LUR	No
TxP11	Yes	30	5	132	127/84	LR	No
TxP12	No	39	12	157	117/83	LR	No
Average:		36	7.4	102	117/78	NA	NA

Pregnancy and Maternal Outcomes

Among the 14 pregnancies in 12 kidney transplant recipients, 8 (57%) resulted in live births, while the remaining 6 (43%) ended in adverse outcomes including 3 early pregnancy loss, 2 spontaneous abortions, and 1 intrauterine fetal demise (IUFD) due to preeclampsia as shown in Table 3. The average maternal age at conception was 36 years, and the mean time from transplantation to conception was 7.4 years. Most deliveries (5 out of 8) were vaginal, with some requiring vacuum assistance, while 3 were cesarean sections performed due to fetal distress or graft protection concerns. One patient conceived and experienced a spontaneous abortion, followed by secondary infertility despite three failed IVF attempts.

Table 3
outcomes of pregnancy, fetal characteristic, and maternal complication:

Pt	Pregnancy event	History of pregnancy post Tx	Prior IVF therapy	Gestational age (w,d)	Sex	Birth weight(g)	Mode of delivery	complication
TxP1	1	-	No	36 w+2d	M	2630	V	None
	2		No	38 w +1d	M	3120	V	None
TxP2	3	Early pregnancy loss	Yes	10 w	-	-	-	-
TxP3	4	-	No	33 w+1d	F	1870	C	None
TxP4	5	Early pregnancy loss	Yes	5 w	-	-	-	-
	6	-		35 w + 5	M	2730	C	None
TxP5	7	-	No	40 w+3d	F	2740	V	None
TxP6	8	Spontaneous abortion	Yes	14 w+2d	-	-	-	-
TxP7	9	-	No	38 w+1d	F	2560	V	None
TxP8	10	-	No	38 w+1d	M	2980	V	None
TxP9	11	Spontaneous abortion	Yes	20 w	-	-	-	-
TxP10	12	-	No	38 w+3d	M	3055	C	
TxP11	13	IUFD	No	22 w	-	-	-	preeclampsia
TxP12	14	Early pregnancy loss	No	12w	-	-	-	-
Average:				27 w+3d		2710		

Fetal Outcomes:

Of the 8 live births, the average gestational age was 37 weeks and 3 days, with a range from 33 weeks and 1 day to 40 weeks and 3 days. Three cases were considered preterm, but all had uneventful neonatal courses. The mean birth weight was 2710 grams, with half of the newborns classified as having low birth weight (< 2500 grams). There were no reported congenital malformations.

Kidney allograft outcomes:

Kidney allograft function remained stable in the majority of pregnancies, with 62.5% of recipients maintaining baseline serum creatinine throughout gestation and postpartum follow-up. However, 5 pregnancies were associated with a creatinine increase of more than 20% compared to baseline, and 2 patients progressed to

persistent graft dysfunction with post-delivery creatinine levels exceeding 200 $\mu\text{mol/L}$ as shown in Fig. 1. One patient required induction of labor due to pre-eclampsia where she developed hypertension, proteinuria, and allograft deterioration. Ultimately she returned to dialysis 6 years post-delivery due to chronic allograft nephropathy. Notably, 3 out of 4 patients with borderline elevated creatinine levels ($> 120 \mu\text{mol/L}$) prior to conception experienced adverse pregnancy outcomes, including early pregnancy loss, spontaneous abortion, and IUFD.

Immunosuppressive management, particularly with tacrolimus, was closely monitored. According to the recorded tacrolimus levels in Fig. 2, trough concentrations were maintained within target therapeutic ranges throughout pregnancy. However, there was a significant drop in tacrolimus trough levels ($P = 0.05$). Prior to pregnancy tacrolimus levels ranged between 5–10 ng/mL and significantly reduced to 4–6 ng/mL in the third trimester while using similar doses. Only 2 patients were on cyclosporin, one patient had significant reduction in cyclosporin level from 90 ng/mL to $< 30\text{ng/mL}$ on two occasions despite dose adjustment. She is the second patient who developed significant allograft dysfunction in third trimester. Despite her uneventful delivery, the patient kidney function continued to worsen. She was unable to attend to her kidney follow up clinic and 3 months after delivery, she underwent kidney allograft biopsy and diagnosed with acute antibody mediated rejection. This recipient progressed to kidney failure despite active treatment of acute rejection with plasma exchange, intravenous immunoglobulin gamma and rituximab.

Discussion

In this study, we share our experience with pregnancy following kidney transplantation, reporting on 14 pregnancies among 12 patients (13% of all included patients). The majority of patients received grafts from living donors, either related or unrelated. Of the 14 pregnancies, 8 resulted in the birth of a living child, most delivered through normal vaginal delivery, while 5 ended in abortion or early pregnancy loss. Our findings align with previously reported abortion rates in post-kidney transplant pregnancies (26–40%) (12, 13), with risk factors potentially linked to maternal characteristics or the use of immunosuppressant medications (14, 15).

Pre-eclampsia was observed in only one case in our cohort (7%). This low incidence is consistent with a recent study reporting pre-eclampsia rates of just 14% in post-kidney transplant pregnancies (10), which is notably lower than the previously reported incidence of 21.5–38% (3, 16, 17). The wide variation in reported pre-eclampsia rates may stem from challenges in diagnosis due to overlapping clinical signs, particularly hypertension—common among kidney transplant recipients—and proteinuria. These diagnostic difficulties can influence clinical judgments, which may vary among physicians (18). Recent studies have suggested that the sFlt-1/PIGF ratio could aid in distinguishing pre-eclampsia from other causes of kidney allograft dysfunction (19, 20), though its widespread use requires validation through large-scale, targeted studies. Furthermore, the use of low-dose aspirin in this high risk population has not been explored in this study, which warrants further evaluation.

In our patient, pre-eclampsia was associated with intrauterine fetal demise (IUFD) and graft function deterioration, persisting even after six months of follow-up following pregnancy termination. While pre-eclampsia is a known risk factor for adverse maternal and fetal outcomes, its long-term impact on graft function remains unconfirmed (16, 21).

In the United States, although recipients of organs from living donors account for only 25% of the general transplant population, 74% of reported post-transplant pregnancies occur among this group (22). This trend may be explained by the higher likelihood of individuals of a reproductive age having family members or relatives

available for organ donation. However, studies indicate there is no significant difference in graft loss between transplants from living related donors and those from living unrelated donors (23).

In addition to baseline kidney function and prior episodes of rejection, deceased donor transplants are considered a risk factor for both short- and long-term graft loss following post-transplant pregnancies (23). Recipients of deceased donor kidneys may experience distinct immune-mediated graft injuries compared to those who receive organs from living donors, potentially due to peri-transplant events such as donor death or prolonged cold ischemia time (24). These differences can influence both pregnancy incidence and graft function outcomes. In our cohort, 11 out of 12 patients received organs from living donors, while one patient received a deceased donor transplant. During follow-up after delivery, we observed no significant differences in graft function between these groups.

In this study, graft function was above baseline in four patients, while it remained stable in all other cases prior to conception. Among patients with successful pregnancies, kidney function stayed stable throughout all trimesters. However, the four patients with abnormal graft function before conception experienced unfavorable pregnancy outcomes, including spontaneous abortion, intrauterine fetal demise (IUFD), early pregnancy loss, and pre-term induced labor due to worsening kidney function.

Deterioration of allograft function during pregnancy has been widely reported in prior studies (25–27). Recently, Kaatz et al. identified the trajectory of eGFR before pregnancy as a predictor of worsening allograft function over time, independent of donor condition, immunosuppressive regimen, time since transplantation, or other comorbidities (28). Additionally, elevated serum creatinine, chronic hypertension, and significant proteinuria at the time of conception were linked to poor allograft outcomes in another study (21).

Notably, no episodes of rejection were observed in our cohort during pregnancy, however, a rejection was observed 3 months post-partum after worsening kidney function. It is believed that low tacrolimus level during pregnancy might be associated with rejection post-delivery. Especially when CNI levels significantly drop during pregnancy. Therefore, the stability of tacrolimus levels and adherence to evidence-based immunosuppressive protocols likely contributed to the preservation of allograft function in most patients. These findings underscore the critical role of individualized immunosuppressive adjustment and vigilant graft surveillance during pregnancy. These findings align with previous studies demonstrating that the incidence of rejection among pregnant kidney transplant recipients is low (23, 29).

In half of our cases, infants were classified as low birth weight, though the overall neonatal outcomes were favorable. Low birth weight is the most reported fetal outcome among kidney transplant recipients, with preterm delivery and intrauterine growth restriction (30, 31). These complications are significant risk factors for neonatal acute kidney injury (AKI) and may contribute to a long-term risk of chronic kidney disease (CKD) (32). These findings emphasize the need for future studies to evaluate the long-term outcomes of offspring born to kidney transplant recipients.

While offspring of kidney transplant recipients are reported to have an increased risk of malformations, particularly cardiovascular defects, even without impacting survival (33), no malformations at birth or postpartum complications were observed in our cohort. Unless associated with genetic disorders, the risk of congenital malformations can be significantly minimized by discontinuing teratogenic medications at least six weeks before conception (13).

There is no consensus on the optimal mode of delivery for kidney transplant recipients. Kidney transplantation is a known risk factor for cesarean delivery, with rates reported as high as 80% in some studies (10). In our cohort, the cesarean section (CS) rate was 37.5%, slightly higher than the overall rate in the Qatari population, which was 29.8% in 2013 (34). Normal vaginal delivery in kidney transplant recipients has been associated with improved neonatal outcomes and does not appear to increase the risk of sepsis, kidney, or cardiovascular complications, as evidenced by a recent study involving 1,435 kidney transplant recipients (35). However, the CS rate remains high in some centers, often due to non-medical factors such as concerns about infection, graft injury, neonatal welfare, and limited confidence in labor trials (36). Further studies are needed to support multidisciplinary decision-making regarding the most appropriate mode of delivery for kidney transplant recipients.

This study has several limitations that warrant consideration. Firstly, its retrospective observational design, which limits the ability to establish causality. Secondly, the relatively small sample size of 12 pregnant recipients undergoing 14 pregnancy events, drawn from a single national center, restricts the statistical power for detecting subtle associations. Furthermore, the study primarily focuses on short-term maternal, fetal, and graft outcomes, and a longer follow-up period would be beneficial to fully assess the long-term impact of pregnancy on graft survival and maternal health. Future prospective, multi-center studies with larger cohorts are needed to validate these findings and provide a more comprehensive understanding of pregnancy in this specific patient population

Conclusion

Despite the mean age during the delivery can be considered as high with average of 34 and an extreme of 42 years, the outcome of pregnancy post kidney transplantation was overall accepted as there is no major complication for the patient, fetus and the kidney function. This may have been achieved by close follow-up from the gynecology and nephrology department even though few patients are not fully complying with appointments and instruction.

Declarations

Conflict of Interest: None.

Funding: No funding was used in the creation of this study

Data availability: The dataset of this study is a property of the Qatar Ministry of Public Health that was provided to the researchers through a restricted-access agreement that prevents sharing the dataset with a third party or publicly. The data are available under restricted access for preservation of confidentiality of patient data. Access can be obtained through a direct application for data access to Her Excellency the Minister of Public Health ([https:// www.moph.gov.qa/english/OurServices/eservices/Pages/Governmental-HealthCommunication-Center.aspx](https://www.moph.gov.qa/english/OurServices/eservices/Pages/Governmental-HealthCommunication-Center.aspx)). The raw data are protected and are not available due to data privacy laws. Aggregate data are available within the paper.

Ethics approval and consent to participate This study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Medical Research Center (MRC) and the Clinical Research Ethics Committee of Hamad Medical Corporation (Protocol ID: MRC-01-24-207). As the study was a retrospective observational analysis of existing medical records and all data were fully anonymized prior to access, the ethics committee granted a waiver of informed consent.

Consent for publication Not applicable. No identifying images or personal clinical details that compromise patient anonymity are presented in this manuscript.

Transplantation Statement The authors declare that no organs or tissues used in this study were obtained from prisoners. All kidney transplantations described in this study were performed at Hamad Medical Corporation (HMC), the sole health care provider for kidney transplantation in the State of Qatar.

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Figures

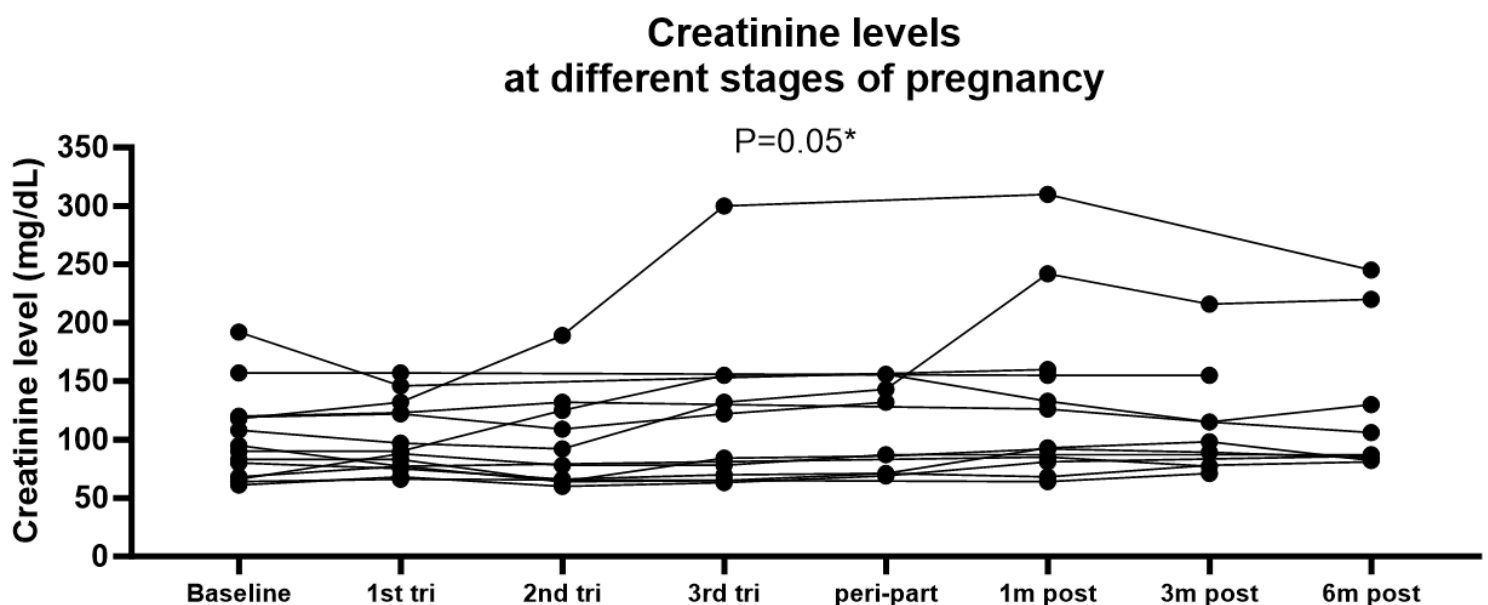


Figure 1

Legend not included with this version

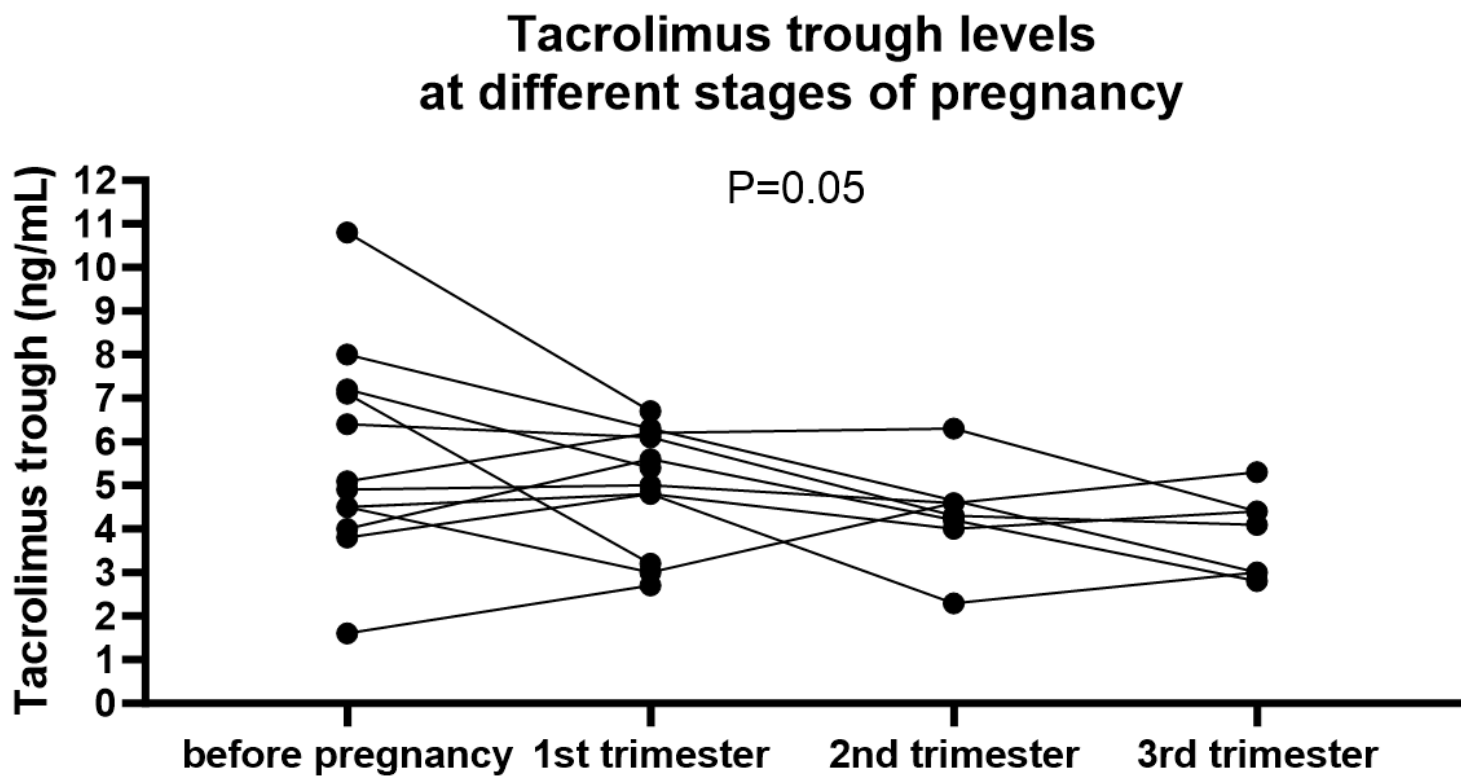


Figure 2

Legend not included with this version