Ultra-high-risk pregnancies in women after renal transplantation

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A B S T R A C T
Objectives: This study evaluates pregnancy outcomes in renal transplant recipients who have additional obstetrical, surgical, or urological risk factors.

Study design: Data from our transplantation and obstetrical databases were retrospectively analyzed to identify all women of reproductive age who had undergone renal transplantation between 1999 and 2013 at our tertiary referral center and had subsequently become pregnant. Characteristics of pregnancy and perinatal outcome parameters; obstetrical, urological, and surgical risk factors; and graft function were assessed. Descriptive data analysis, Fisher’s exact test, unpaired Student’s t-test and one-way analysis of the variance were performed.

Results: The overall pregnancy rate after renal transplantation was 5% (n = 13). 77% of the patients (n = 10) had ultra-high-risk pregnancies due to additional risk factors. These included twin pregnancy, placenta previa/percreta, hypertension; previous heart transplantation, previous myocardial infarction; postoperative lymphocele, urinary leakage, hydronephrosis, or vesico-ureteral reflux. Two patients had two consecutive pregnancies. A total of 12 deliveries with 13 newborns were achieved. Cesarean section and preterm delivery rates were 67% and 50%, respectively. Mean gestational week at delivery was 36 ± 3. Mean creatinine levels were higher in women with preterm deliveries and in those of advanced age. Mean time between transplantation and delivery was 79 ± 36 months. All patients had adequate graft function after a mean follow-up of 128 ± 50 months after renal transplantation.

Conclusions: Pregnant women after renal transplantation commonly present with additional risk factors. In these ultra-high-risk pregnancies successful outcomes can be achieved in a multidisciplinary setting. Adequate graft function and urinary tract evaluation is necessary.

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Introduction

Although only 2% of women of child-bearing age become pregnant after renal transplantation, the pregnancy rate in transplant recipients has increased during the last years [1]. Pregnancies after renal transplantation are high-risk pregnancies that can cause obstetrical dilemmas, due to side effects of immunosuppressive agents and associated comorbidities. Female renal transplant recipients show higher rates of preeclampsia, small-for-gestational-age (SGA) fetuses, preterm deliveries, and cesarean sections [2,3]. If additional obstetrical risk factors or previous surgical and urological complications exist, the effect on the individual patient is even more serious. Consequently, the potentiated risk for both the mother and the fetus leads to ultra-high-risk pregnancies. Urological complications include ureteral leakage, vesicoureteral reflux (VUR), and hydronephrosis due to ureteral obstruction [4,5]. On voiding cystourethrogramy, VUR rates of up to 86% have been reported in asymptomatic transplant recipients, causing urinary tract infections (UTIs), graft dysfunction, or even graft loss [6]. Furthermore, postoperative lymphoceles, which have an incidence of up to 20%, can worsen renal function by compressing the pelvicvicalyceal system, therewith also affecting the pregnancy [7,8]. Further complications in transplant recipients depend on the transplantation-to-conception interval, blood pressure control, and maternal renal function. Hence, high

Abbreviations: IUGR, intrauterine growth retardation; SGA, small for gestational age; UTI, urinary tract infection; VUR, vesicoureteral reflux.
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creatinine levels during pregnancy, maternal anemia, and uncontrolled hypertension are associated with a high incidence of premature deliveries, as well as SGA or IUGR of fetuses. Other serious comorbidities, including multi-organ transplantation, can potentially increase the risk of these pregnancies that are already at high risk.

The aim of this study was to evaluate pregnancy outcomes in renal transplant recipients who have additional risk factors.

**Materials and methods**

We retrospectively analyzed our prospective transplantation database, including 1537 consecutive adult patients who underwent renal transplantation at our tertiary referral center between January 1999 and December 2013. A total of 580 female transplant recipients were identified; 248 of these were of reproductive age, defined as age between 18 and 49 years. The data were matched with our obstetrical database to identify all women who had subsequently become pregnant and consulted our perinatal center. Additional risk factors and comorbidities were identified by the review of patient charts.

All women underwent renal transplantation at our tertiary referral center according to our routine protocol [9]. The medical care of patients followed the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the care of kidney transplant recipients by the American Society of Transplantation [10]. Immunosuppressive drug dosing was maintained at pre-pregnancy levels through frequent monitoring of blood levels [11]. Patient charts were electronically reviewed using View Point™ for Windows, version 5.6.16.917 (GE Healthcare®, Germany). Obstetrical information included gravidity, parity, assisted reproductive treatment, prenatal ultrasound data, date and mode of delivery, gestational week, and fetal outcome parameters. Gestational age was described as weeks plus days after the woman’s last menstrual period. Pre-existing or pregnancy-induced hypertension were defined as blood pressure higher than 140/90 mmHg diagnosed before or after 20 weeks of gestation, measured on two separate occasions more than six hours apart. Women were diagnosed with gestational diabetes, if the oral glucose tolerance test (75 g), showed a fasting blood sugar level of >92 mg/dL and/or postprandial blood sugar levels of >180 mg/dL and >153 mg/dL after one and two hours, respectively.

Study endpoints included pregnancy and perinatal outcome parameters, as well as graft function. Creatinine levels were measured at the time of admission for delivery and 12 months postpartum.

**Statistical analysis**

Descriptive data are presented as mean ± SD and median (range), unless otherwise stated. Discrete data are presented as n (%). Fisher’s exact test was used to compare groups of categorical data. Metric data were compared using the unpaired Student’s t-test or one-way analysis of the variance. A two-sided p-value <0.05 was considered statistically significant. Statistical calculations were performed using SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA). The study was approved by the appropriate ethics committee (Research ethics reference 1078/2012).

**Results**

**Obstetrical outcome**

The overall pregnancy rate in women who underwent renal transplantation at our tertiary referral center was 5% (n = 13). Ultra-high-risk pregnancies, defined as having at least one additional risk factor, were seen in, 77% (n = 10) of the patients. Risk factors included twin pregnancy, placenta previa/percreta, hypertension; previous heart transplantation, previous myocardial infarction; postoperative lymphocele, urinary leakage, hydrenephrosis, or vesico-ureteral reflux. In the ultra-high-risk group, two women had two consecutive pregnancies with an interval of 23 and 31 months between both deliveries. One patient had a dichorial twin pregnancy. A total of 13 neonates were born. The mean age of women at ultra-high-risk was 27 ± 3 years (median, 26; range, 22–34) at the time of transplantation and 34 ± 4 years (median, 33; range, 29–44) at the time of delivery. The mean transplantation-to-delivery time was 79 ± 36 months (median, 80; range, 26–148).

In our study, the preterm delivery rate prior to 37 + 0 (37 weeks and 0 days) gestational weeks was 50% (n = 6). Overall, the mean gestational week at the time of delivery was 36 ± 3 (median, 36; range, 30–40). The earliest time of delivery was 30 ± 1 gestational weeks in the patient with twins. Another very preterm birth at 31 + 3 gestational weeks occurred due to cervical insufficiency and preterm contractions after antenatal corticosteroid prophylaxis and intravascular tocolysis were administered. The mean birthweight in our cohort was 2467 ± 770 g (median, 2430; range, 1425–3956), corresponding to a mean percentile for gestational age adjusted birthweight of 37 ± 30 (median, 27; range, 11–74). Overall, the rates of pregnancy-induced hypertension, pre-existing hypertension and gestational diabetes were 42% (n = 5), 42% (n = 5) and 17% (n = 2), respectively. Cesarean section was performed in 67% of all women. Table 1 shows the detailed demographics of the patient population.

**Selected patients with ultra-high-risk pregnancies**

One patient had a myocardial infarction three years prior to the pregnancy (Table 1). At 38 + 0 gestational weeks, this patient presented with high blood pressure, rising levels of creatinine and consequently underwent cesarean section. Prenatal evaluation included three-dimensional-ultrasound and magnetic resonance imaging. Figs. 1 and 2 illustrate the proximity of the renal graft to the uterus. Another woman had undergone combined renal and cardiac transplantation at the age of 26 due to a congenital double-inlet, double-outlet right ventricle. Eight years later, she experienced an uneventful pregnancy and underwent cesarean section at 35 weeks of gestation due to deteriorating graft function.

A woman with placenta previa/percreta underwent hysterectomy due to unmanageable blood loss. Preoperative planning included three-dimensional-ultrasound and magnetic resonance imaging to identify the location of the transplanted ureters. Fig. 3 shows the renal graft in the patient’s left iliac fossa and the ureters weaving directly in front of the potential ureteromy site. Consequently, uterotomy for cesarean section was performed more cranially.

Regarding surgical and urological complications following renal transplantation, 20% (n = 2) of our patients were diagnosed with grade I VUR. One patient had both hydrenephrosis and ureteral leakage, which required further surgical intervention. Following this re-intervention, normal graft function was achieved without evidence of residual hydrenephrosis. The rate of postoperative lymphoceles, was 20% (n = 2) and could be managed conservatively. The overall incidence of UTIs was 50% (n = 6). No relation was found between the diagnosis of VUR and UTI incidence.

**Graft outcome**

After a mean post-transplantation follow-up period of 128 ± 50 months (median, 134; range, 32–179), all women had adequate graft function. Creatinine levels at the time of admission for delivery and 12 months postpartum were 1.32 ± 0.37 mg/dL (median, 1.1; range,
Table 1
Outcome of 12 ultra-high-risk pregnancies in 10 renal transplant recipients.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (yrs) at transplantation</th>
<th>Additional risk factor</th>
<th>Surgical</th>
<th>Urological</th>
<th>Obstetrical</th>
<th>Others</th>
<th>Hypertension</th>
<th>Partus</th>
<th>Age (yrs) at delivery</th>
<th>ART</th>
<th>GW</th>
<th>Mode</th>
<th>Indication for CS</th>
<th>Weight (grams)</th>
<th>Creatinine delivery^d</th>
<th>Creatinine 12 mts p.p.^d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>UTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>29</td>
<td>Yes^a</td>
<td>37w 3d</td>
<td>SD</td>
<td>–</td>
<td>3.110</td>
<td>0.97</td>
<td>1.29</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>UTI</td>
<td>IGDM</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>31</td>
<td>No</td>
<td>40w 3d</td>
<td>SD</td>
<td>–</td>
<td>3.956</td>
<td>0.89</td>
<td>1.05</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>UTI</td>
<td>VUR</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td>1</td>
<td>30</td>
<td>Yes^a</td>
<td>36w 2d</td>
<td>CS</td>
<td>N/A</td>
<td>2.430</td>
<td>1.08</td>
<td>1.4</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>UTI</td>
<td>IGDM</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td>1</td>
<td>31</td>
<td>Yes^b</td>
<td>38w 0d</td>
<td>CS</td>
<td>Unsuccessful labor induction</td>
<td>2.760</td>
<td>0.92</td>
<td>0.9</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>Uterus</td>
<td>IGDM</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>33</td>
<td>No</td>
<td>30w 1d</td>
<td>CS</td>
<td>Impaired renal function, twins DIP^c</td>
<td>1.425/1.709</td>
<td>1.72</td>
<td>1.85</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>UTI</td>
<td>Preterm contractions</td>
<td>–</td>
<td>Preexisting</td>
<td>1</td>
<td>30</td>
<td>No</td>
<td>31w 3d</td>
<td>CS</td>
<td>–</td>
<td>1.880</td>
<td>1.58</td>
<td>1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>UTI</td>
<td>SGA/IUGR</td>
<td>–</td>
<td>Preexisting</td>
<td>1</td>
<td>34</td>
<td>No</td>
<td>37w 3d</td>
<td>CS</td>
<td>Placenta previa and percreta</td>
<td>2.450</td>
<td>1.79</td>
<td>1.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>UTI</td>
<td>VTU, UTI</td>
<td>SGA/IUGR</td>
<td>Hysterectomy</td>
<td>1</td>
<td>37</td>
<td>No</td>
<td>35w 6d</td>
<td>CS</td>
<td>Acute renal failure</td>
<td>2.305</td>
<td>1.8</td>
<td>1.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ART – assisted reproductive treatment; GW – gestational week (weeks + days); HN – hydronephrosis; VUR – vesicoureteral reflux; UTI – urinary tract infection; RVHT – renal vascular hypertension; PIH – pregnancy induced hypertension; IGDM – Insulin dependent gestational diabetes; SGA – small for gestational age fetus; IUGR – intrauterine growth retardation; MI – previous myocardial infarction; HTX – previous cardiac transplantation; DIP – deceleration intra partu; SD – spontaneous vaginal delivery; CS – cesarean section; N/A – not available; p.p. – post partum.

^a Hormonal stimulation treatment received.
^b In vitro fertilization (IVF) performed.
^c Emergency cesarean section due to prolonged fetal heart rate deceleration and preterm contractions.
^d mg/dL.
0.89–1.80) and 1.37 ± 0.37 mg/dL (median, 113.52; range, 1.29–2.07), respectively. Creatinine levels in women who delivered spontaneously were comparable to those who underwent cesarean section (1.14 ± 0.36 mg/dL versus 1.42 ± 0.36 mg/dL). Women with preterm delivery had higher levels of creatinine at the time of admission for delivery (1.56 ± 0.29 versus 1.20 ± 0.35 mg/dL) and 12 months postpartum (1.58 ± 0.40 versus 1.27 ± 0.33 mg/dL). Women with elevated creatinine levels delivered in earlier weeks of gestation and their neonates had lower birthweights. Patients of advanced age at the time of delivery showed higher levels of creatinine at the time of delivery and 12 months postpartum. No rejection episodes occurred during follow-up, pregnancy, or within 12 months postpartum.

Comment

In this study, we investigated the outcomes of pregnancies in renal transplant recipients who had additional risk factors. Currently, the data available is poor and studies analyzing post-transplant pregnancies have not focused on patients who have experienced complications or on those with comorbidities. Pregnancies in renal transplant recipients with additional risk factors are often considered contraindicated, as they are already more susceptible to hypertension (54.2% versus 7.0% in healthy population), preeclampsia (27.0% versus 3.8%), and gestational diabetes (8.0% versus 3.9%), than their healthy counterparts [12,13]. Moreover, higher rates of cesarean section (56.9%), preterm deliveries (45.6%), and SGA/IUGR fetuses (40%) have been reported among this high-risk group [3].

According to the meta-analysis of Deshpande et al. [3] observing data of 4706 pregnancies in 3570 renal transplant recipients, the preterm delivery rate after renal transplantation is 45.6%, which is significantly above the general population. The preterm delivery rate of the general obstetrical population in Austria has been reported to be 8.3% [14]. In our cohort of women with ultra-high-risk pregnancies, 50% (n = 6) resulted in a premature delivery (median, 37 weeks; range 30–40), being consistent with previously published data for renal transplant recipients. Factors that can be controlled in order to reduce the risk for premature delivery in these patients are maternal blood pressure control, the transplantation-to-conception interval and the renal function, which is deteriorated by hypertension before and during pregnancy. Rates of hypertension, either pre-existing or pregnancy-induced, were higher in our cohort (80%; n = 8), than in literature [3]. The median transplantation-to-delivery interval was 80 months. According to the current guidelines, a minimum interval of one year is recommended [15].

In terms of the delivery mode, vaginal delivery has shown to be feasible after renal transplantation. In our cohort, the vaginal delivery rate was 33%. All vaginal deliveries were performed uneventful, even in a woman who experienced urinary leakage and underwent re-intervention after transplantation. Overall, the rates of elective, unplanned cesarean section and failed induction of labor in our study cohort were 43% (n = 3), 57% (n = 4) and 20% (n = 1), respectively. Current guidelines recommend vaginal delivery, but admit that cesarean section might be necessary in at least 50% of all cases [16,17].

The deterioration of the graft function during pregnancy seems to be a temporary effect [18]. In our study, graft function, indicated by creatinine levels, was stable until one year postpartum. From our data we cannot confirm that pregnancy negatively affects the
graft function. As graft function is essential for successful pregnancy outcomes, we also evaluated outcomes after urological complications, including VUR and hydronephrosis, which are known to have a significant impact on the graft. Studies evaluating voiding cystourethrocgraphies revealed rates of VUR and hydronephrosis of up to 86% and 33% after transplantation, respectively [19]. Thus far, no data exist in women who become pregnant after transplantation. In our cohort, VUR and hydronephrosis occurred in 15% and 8% of patients, respectively. No difference regarding graft function and perinatal outcomes between women with and without VUR or hydronephrosis can be reported. Female transplant recipients are known to be at high risk of developing UTIs [16]. Moreover, physiologic changes during pregnancy increase a woman’s susceptibility to UTIs [20]. In our study, the UTI rate was 46%, which is consistent with previously published data [21].

In this study, we report on a successful pregnancy in a woman who underwent combined renal and cardiac transplantation. Only few cases of pregnancies in cardiac transplant recipients have been described after the first among these women conceived in 1988 [22]. Pregnancy in cardiac transplant recipients has often been discouraged due to the elevated risk of maternal cardiomyopathy, subsequent mortality and the limited longevity of the cardiac graft [23]. In the woman who successfully conceived after combined renal and cardiac transplantation, the cardiac graft adapted well to the changes caused by pregnancy, including increased workload and cardiac output volume. Finally, we would like to discuss the obstetrical challenges in our renal transplant cohort. The patient with the dichorial twin pregnancy presented with deteriorating renal function at 30 gestational weeks. It has been reported that physiological changes in renal hemodynamics may assist in predicting a favorable outcome in twin pregnancies after renal transplantation [24]. Whether the impaired renal function occurred owing to the twin pregnancy remains unclear. The woman who had a placenta previa suffered from extensive intraoperative blood loss due to a placenta percreta. In this patient, the indication for hysterectomy would have been equal in non-transplanted women. However, since the incidence of multiples rises and the rates of abnormal invasion of the placenta are increasing, further cases are to be expected.

We are aware that our study has some limitations, including the retrospective design, the small number of cases, and the lack of follow-up data. Nevertheless, this is the first study to provide data on ultra-high-risk pregnancies and on the evaluation of the upper and lower urinary tract for the assessment of postoperative urological complications.

In conclusion, renal transplant recipients commonly present with additional risk factors during pregnancy. Although successful outcomes can be achieved in these ultra-high-risk pregnancies, higher rates of preterm delivery and low neonatal birthweight must be reported. Vaginal delivery is feasible in recipients with adequate graft function, but these patients need to be aware of the elevated risk for cesarean section. Preoperative evaluation of the urinary tract is recommended in order to avoid injury of the graft and the transplant ureter. A comprehensive multidisciplinary care throughout the pregnancy is mandatory.

Conflict of interest
None to declare.

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