Intrauterine Growth Restriction in Pregnant Renal and Liver Transplant Recipients: Risk Factors Assessment


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ABSTRACT

Background. Nowadays pregnancy after organ transplantation is possible due to advances in surgical and immunosuppressive therapies. One of the possible complications in pregnancy after organ transplantation is intrauterine growth restriction (IUGR). This may lead to various adverse perinatal outcomes. Prevalence of IUGR in the general population is estimated at 3%–10% with smoking being the most frequent maternal risk factor. The aim of this study was to determine the risk factors of IUGR in pregnant renal transplant recipients (RTR) or liver transplant recipients (LTR) in comparison with healthy pregnant women.

Methods. Retrospective analysis included 48 RTR and 52 LTR. IUGR was defined as estimated fetal weight less than the 10th percentile for gestational age. IUGR was diagnosed in 15 (31.3%) pregnant RTR and in 10 (19.2%) LTR. The control group consisted of 60 healthy pregnant women diagnosed with IUGR. Fisher exact test and Student t test were used to assess the differences in fractions and means, respectively, between distinguished groups of patients. Test for fractions based on asymptotic normal distribution was used to compare the proportion of patients with IUGR with the proportion of 10% in the general population. The logistic regression model was used to assess the statistical significance of correlations between the assumed risk factors and the prevalence of IUGR in multivariate settings.

Results. Hypertension, anemia, and proteinuria were the most frequent complications in the study group. They were more prominent in RTR than in LTR. Hypertension was diagnosed in all RTR, whereas severe anemia requiring erythropoietin treatment or blood transfusion was found in 4 RTR and in 1 LTR.

Conclusion. IUGR is more common in organ recipients. Therefore, vigilant obstetric care is highly recommended in pregnant patients after renal or liver transplantation. Hypertension, severe anemia, and proteinuria proved not to be statistically significantly correlated with the prevalence of IUGR among patients after transplantation.
among patients after organ transplantation. So far the reasons for IUGR in organ transplant recipients have not been analysed and compared with normal pregnancies. It has not been determined yet which risk factor is the most important in triggering growth restriction and what is the impact of chronic immunosuppressive therapy on fetal growth. It is not obvious if growth restriction depends on the type of transplanted organ. The aim of this study was to determine the most important risk factors of fetal growth restriction in patients after kidney (renal transplant recipient [RTR]) or liver (liver transplant recipient [LTR]) transplantation.

METHODS

We analyzed retrospectively a group of pregnant patients, which consisted of 48 RTR and 52 LTR. The median age in the RTR group was 29.4 years and in the LTR group was 27.8 years. The median time between organ transplantation and delivery time in the RTR group was 4.5 years and in the LTR group was 6.2 years. In each group 7 patients were in her second or subsequent pregnancy. All patients had routine blood tests and ultrasound scans performed. They also had vireology tests done and extra growth scans at 28 weeks. If fetal growth was less than the 10th percentile, extra scans were offered. All patients in the RTR group received immunosuppressive therapy; prednisone combined with 1 or 2 other immunosuppressive drugs. In most cases it was azathioprine (n = 28; 58.3%), cyclosporine A (n = 22; 45.8%), or tacrolimus (n = 21; 43.7%). In the LTR group there were 35 patients who received prednisone (67.3%) combined with 1 or 2 other immunosuppressive drugs: tacrolimus (n = 40; 76.9%), cyclosporine A (n = 12; 23%), or azathioprine (n = 3; 5.7%).

The control group consisted of 60 normal pregnancies with a median age of 32.3 years. Only 2 patients in the control group were in their subsequent pregnancy. All patients in the control group were diagnosed with IUGR. All of those patients were hospitalized between 2010 and 2012.

RESULTS

IUGR was diagnosed in 15 fetuses (31.3%) of 48 in the RTR group, which accounts for 31.3% and is significantly higher than the 10% fraction in the general population (P < .001). Similarly, IUGR was diagnosed in 10 of 52 patients after liver transplantation and the fraction of 19.3% was significantly higher than the fraction in the general population (P = .013). Demographic characteristics of pregnant women after transplantations are given in Table 1. It appears that patients with lower body mass index (BMI) are more vulnerable to IUGR.

In both groups the most common complications were hypertension, anemia, and protein in urine sample. There were no smoking patients in this group. Hypertension was the only risk factor that turned out to statistically significantly influence the occurrence of IUGR in the whole sample of transplant recipients. The occurrence of anemia and proteinuria was higher among patients without IUGR as compared with patients with diagnosed IUGR. The results are given in Table 2.

Hypertension was diagnosed in all RTR. They received treatment with either 1 or 2 antihypertensive drugs (methyldopa, metoprolol). There were only 3 patients in the LTR group who needed treatment with only 1 antihypertensive drug (methyldopa). Among patients with diagnosed IUGR, anemia was diagnosed in 10 (66.7%) patients after kidney transplantation and in 6 (60%) after liver transplantation. All of them received iron supplements. In 4 RTR and 1 LTR hemoglobin (Hb) concentration was <8 g/dL. Three RTR received treatment with erythropoietin and the remaining 2 received blood transfusions. Protein in urine samples was detected in 9 patients (60%) after kidney transplantation and in 2 (20%) patients after liver transplantation. Protein concentration in a 24-hour urine collection test was higher in RTR with the highest values of 9.1 g/dL. The time of delivery in RTR was between 24 and 39 weeks and there were 9 patients who had premature delivery. There was only 1 patient who delivered naturally and the rest had cesarean section due to fetal distress (6 patients), pre-eclampsia (4 patients), or failure to progress. There were 6 patients after liver transplantation who had natural delivery and 6 were induced due to fetal hypotrophy. The time of delivery was between 33 and 41 weeks and 4 patients delivered prematurely in this group.

To identify risk factors of IUGR among patients after transplantation in a multivariate environment, a logistic regression model was implemented. Assumed risk factors of IUGR, demographic characteristics of patients, and type of transplantation were used as repressors. The only repressor that turned out to statistically significantly influence the chance for IUGR in patients after transplantations was BMI. It appears, that higher BMI values decrease the
patients were induced due to abnormal ultrasound findings: IUGR and/or abnormal Doppler results in umbilical arteries or median cerebral artery. There were 21 elective cesarean sections due to low Bishop score and premature delivery before 34 weeks. In 8 patients there was an emergency cesarean section due to fetal distress.

**DISCUSSION**

Early detection of risk factors of growth restriction in pregnancy is clinically important despite unknown treatment for IUGR. Detecting IUGR risk factors determines very careful obstetric care and helps to plan the best time of delivery, therefore improving neonatal outcome. The prevalence of IUGR in patients after liver or kidney transplantation is higher compared with the control group [4]. It is important to underline differences between LTR and RTR. The prevalence of IUGR in RTR is higher compared with LTR (31.3% vs 19.2%, respectively; \( P = 0.083 \)). This is likely to be a result of proteinuria and hypertension, which are more common in this group; however, in our sample, we were unable to statistically confirm the dependence between proteinuria and occurrence of IUGR. Kociaszewska-Najman et al [5] compared neonatal outcomes (including IUGR and premature delivery) in patients after liver and kidney transplantation. Interestingly they confirmed that the prevalence of adverse neonatal outcomes is higher in mothers after kidney transplantation. In this study all RTR had hypertension compared with only 30% in the LTR group, which is consistent with other research publications [6]. The incidence of proteinuria was higher in RTR compared with LTR (60% and 20%, respectively). Hypertension (18%) and proteinuria (30%) were also less frequent in the control group. There is no known treatment of IUGR. The results justify the need for careful blood pressure control and regular 24-hour urine collection tests. This enables early adjustment of hypertension treatment. Anemia is another complication described in a series of publications on pregnant RTR and LTR. According to the World Health Organization (WHO), anemia is described as hemoglobin concentration <11 g% in the first trimester and <10.5 g% in the second trimester. Anemia is common in both LTR and RTR (60% and 66.7%, respectively) compared with the control group (38%). Although in all RTR the function of the transplanted organ was satisfactory, the prevalence of severe anemia (Hb <8 g%) was high. This is likely to be related to disabled erythropoietin secretion. In the vast majority of them, treatment with iron supplements was sufficient. Erythropoietin was administered in 5 patients.

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**Table 2. Prevalence of Hypertension, Anemia, and Proteinuria in Pregnant Patients After Kidney and Liver Transplantation With and Without Diagnosed IUGR**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence of Risk Factors Among Patients With IUGR (n = 15) n (%)</th>
<th>Prevalence of Risk Factors Among Patients Without IUGR (n = 42) n (%)</th>
<th>( P ) in 1-sided Fisher Exact Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>15 (100%)</td>
<td>33 (100%)</td>
<td>–</td>
</tr>
<tr>
<td>Anemia</td>
<td>10 (66.7%)</td>
<td>22 (66.7%)</td>
<td>.624</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>9 (60%)</td>
<td>25 (75.8%)</td>
<td>.219</td>
</tr>
</tbody>
</table>

**Table 3. Logistic Regression Estimates for Assumed Risk Factors**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>( z )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTR</td>
<td>–0.50</td>
<td>0.70</td>
<td>–0.71</td>
<td>.477</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.91</td>
<td>0.79</td>
<td>1.14</td>
<td>.252</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.06</td>
<td>0.56</td>
<td>0.12</td>
<td>.908</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>–0.67</td>
<td>0.60</td>
<td>–1.12</td>
<td>.261</td>
</tr>
<tr>
<td>Age</td>
<td>–0.03</td>
<td>0.06</td>
<td>–0.52</td>
<td>.604</td>
</tr>
<tr>
<td>BMI</td>
<td>–0.15</td>
<td>0.09</td>
<td>–1.77</td>
<td>.076</td>
</tr>
<tr>
<td>Time from transplantation to delivery</td>
<td>–0.01</td>
<td>0.09</td>
<td>–0.16</td>
<td>.873</td>
</tr>
</tbody>
</table>

*LTR is the reference value.

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**Table 4. Risk Factors of IUGR in the Control Group**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Number of Patients (n = 60) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>23 (38.3)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>18 (30.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (18.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td>8 (13.3)</td>
</tr>
</tbody>
</table>

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Statistical analysis was performed using SPSS 25.0 (IBM Corp. Armonk, NY). The Fisher Exact Test was used for comparison in 1-sided \( P \) values.
Intrauterine Growth Restriction

This kind of treatment is described in the literature as more appropriate compared with blood transfusions (which carry major risks of immunization) [7–9]. Anemia in LTR is more likely to appear, which may be related to insufficient iron and transferrin concentration. In the study group, there were 4 patients after kidney transplantation who required treatment with erythropoietin and 1 had blood transfusions. There was also only 1 patient after liver transplantation who required blood transfusion. Anemia was less frequent in the control group (38%) and there was no need of either blood transfusions or erythropoietin administration. Interestingly anemia is the most common pregnancy complication in the study group. It is believed that anemia in pregnancy may involve up to 70% pregnant women depending on the region of the world and the socio-economic development. The most common causes of anemia in pregnancy are iron and folic acid insufficiency.

The most common immunosuppressive drugs used in pregnant women after liver and kidney transplantation are prednisone, azathioprine, cyclosporine A, and tacrolimus. Prednisone crosses the placenta and reaches 10% of maternal serum concentration after being metabolized with 1β-hydroxysteroid dehydrogenase in the placental tissue. Azathioprine and 6-methylmercaptopurine (its metabolite) also cross the placenta. Placental concentration of azathioprine reaches 64%–93% of maternal serum levels. Nevertheless, azathioprine concentration in fetal blood is low and reaches 1%–5% of maternal serum levels. Cyclosporine crosses the placenta and reaches only 5% of maternal blood concentration, most likely due to size of the molecule. Tacrolimus reaches up to 50% of maternal blood concentration [10]. Some authors underline possible hyperkalemia and kidney function impairment in fetuses of mothers treated with tacrolimus. Its concentration in the neonate is undetectable after 3 to 7 days after delivery [11,12]. Given that both LTR and RTR received similar immunosuppressive treatment, it seems that tacrolimus has little influence on fetal hypotrophy (compared with other significant risk factors like hypertension in RTR).

The risk of elective preterm delivery due to fetal hypotrophy is 3 times higher in RTR and 2 times higher in LTR compared with the control group. According to the WHO report from 1985, the rate of cesarean sections should not reach 10%–15% of all deliveries. In the last few decades, the cesarean sections rate increased significantly in all populations. Patients with growth-restricted fetuses are at higher risk of cesarean section due to higher risk of abnormal findings of fetal surveillance methods (median cerebral artery and umbilical artery Dopplers) [13]. RTR have an additional risk factor, which is high blood pressure. The cesarean section rate in RTR, LTR, and the control group was 93%, 40%, and 48.3%, respectively.

There is still little data on risk factors related to IUUGR in patients after liver and kidney transplantation, therefore, this subject needs further research and the number of citations in this article is limited.

In conclusion, the major risk factors of IUUGR in RTR and LTR are hypertension and proteinuria, whereas the major risk factor in the control group was anemia. The results of this study justify the need for careful blood pressure control. This enables early adjustment of hypertension treatment and reduction of IUUGR risk among women after organ transplantation. We were unable to prove that the proteinuria and anemia influence the probability of IUUGR; in fact, in our sample the occurrence of these 2 factors was higher among patients without IUUGR. There is no evidence that immunosuppressive drugs influence significantly the prevalence of IUUGR in both groups of transplant recipients.

REFERENCES