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# FIRST EXPERIENCE IN TWO SUCCESSFUL CONSECUTIVE PREGNANCIES AFTER SIMULTANEOUS LIVER-KIDNEY TRANSPLANTATION WITH RENO-PORTAL TRANSPOSITION

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The paper presents the world's first clinical case of two full-term successive pregnancies in a patient following simultaneous liver-kidney transplantation with reno-portal transposition. Both pregnancies ended with the birth of healthy children and favorable course of postpartum and long-term periods. The features of management and childbirth are highlighted. Literature review on this problem is presented.

*Keywords: pregnancy, simultaneous liver-kidney transplantation, reno-portal transposition, severe portal vein stenosis, autosomal recessive polycystic kidney disease.*

## INTRODUCTION

At present, active development and wide interdisciplinary interaction between obstetrics, gynecology and transplantology have been promoting successful gestation not only after transplantation of individual solid organs, but also in the case of multivisceral transplantations with complex vascular reconstructions. This has ensured favorable pregnancy outcome in complex clinical situations. Highly trained transplant specialists have made it possible to perform complex simultaneous transplantations when existing vascular complications, such as total portal vein thrombosis, without high-tech vascular reconstructions, are absolute contraindications to transplantation due to the futility of restoring normal graft perfusion, impaired graft function and engraftment in the post-transplant period [1, 2]. Most researchers consider these methods as the most complicated, associated with high morbidity and risk of death in recipients in the early postoperative period [2–6]. Single cases of successfully performed similar operations with favorable long-term outcomes have been reported by world's leading transplantation centers [7]. There are no cases of gestation in patients after such interventions described in publications. The presence of a complex of transplanted organs and complex vascular reconstruction in a pregnant woman's body causes atypical course of adaptive gestational processes, high risk of pregnancy and delivery complications. It determines the need for highly skilled obstetric and gynecological care and personalized regimens for medical prevention, diagnosis and treatment of complications. In the Republic of Belarus, a patient successfully had full-term consecutive pregnancies after undergoing simultaneous liver-kidney (SLK) transplantation with reno-portal transposition. The situation was unique in that it involved managing both pregnancies to full-term and satisfactory condition of the newborns and mother in the postpartum period and beyond. Such a clinical situation, even with one pregnancy, is not described in any publications in international databases. This determines the need to highlight the principles of its management as a high-risk pregnancy with a favorable outcome, a unique situation, not found anywhere in the world.

## LITERATURE REVIEW

According to a meta-analysis by D'Amico et al. – employees at the Transplantation Center, Department of General Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA – published in February 2019 in Transplant International, a total of 66 patients who underwent liver transplantations combined with reno-portal transposition are currently registered worldwide. Among them are 50 (72.7%) male recipients, 15 (22.7%) women and 1 (1.5%) 14-year-old child. Reno-portal transposition was performed in 42 (63%) whole liver transplants, in 12 (18%) split liver transplants; 7.5% (5) of grafts were derived from living donor, and 4.5% (3) were domino grafts. Overall patient and graft survival were each 80%. Overall, 71% of patients developed postoperative complications, including

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ascites in 18 patients (27.2%), infectious complications in 13 patients (19.6%), transient renal dysfunction in 12 patients (18.1%), variceal hemorrhage in 2 patients (3%), bile leak/stenosis in 4 patients (6.1%), hepatic artery thrombosis in 3 patients (4.5%), early portal vein re-thrombosis in 2 patients (3%), chronic renal dysfunction in 2 patients (3%) and late (after 12 months) portal vein re-thrombosis in 1 patient (1.5%). Out of 3 patients with hepatic artery thrombosis, 2 required repeated vascular reconstruction, whereas the remaining patient required liver re-transplantation. One of the 2 patients with early portal vein thrombosis required portal angioplasty with stenting, which resulted in a satisfactory outcome, whereas the other patient died of multi-organ failure. A patient with late portal vein thrombosis required liver transplantation and died while awaiting re-transplantation as a result of multi-organ failure. Mortality was reported to be 19.6% (13 patients). Causes of death included sepsis (4 patients, 30.7%), cerebral hemorrhage (4 patients, 30.7%), hepatocellular carcinoma recurrence (2 patients, 15.4%), variceal hemorrhage (1 patient, 7.7%), and sudden cardiac arrest (1 patient, 7.7%) [1].

Since the model for end-stage liver disease (MELD) was introduced in 2002, there was been increased number of SLK transplantations [3, 4, 8–13]. However, reno-portal transposition during an SLK transplantation is described in only one source: Baker et al. – employees at the Northwestern University, Feinberg School of Medicine Department of Surgery, Division of Organ Transplantation, Chicago , USA – in their publication indicated that their experience was the only case of reno-portal transposition during an SLK transplantation [7].

In the case of our patient with SLK transplantation, the liver transplantation technique was complicated by the need for donor liver implantation against the background of critical portal vein stenosis and large spontaneous splenorenal shunts. Moreover, the use of a high-tech method for formation of reno-portal transposition was required.

Lai Q. et all. (2014), Starzl Unit of Abdominal Transplantation, University Hospitals Saint Luc, Brussels, Belgium, in a publication in World Journal of Hepatology, report that serious vascular complications such as portal vein thrombosis and critical portal vein stenosis were recently considered as an absolute contraindication for transplantation, and such patients were not operable. In recent years, due to improvements in surgical treatment methods, it has become possible to provide adequate hemodynamics in the portal vessels in patients with such vascular malformation by performing reno-portal or cavo-portal hemi-transposition [6]. Moreover, formation of a reno-portal transposition is the preferred method because it involves fewer complications if successful [1, 14]. However, these methods are considered by most researchers to be the most complicated, associated with high morbidity and risk of recipient death in the early postoperative period if there is incomplete correction of existing portal hypertension, leading to rapid hepatic graft dysfunction [2–6, 15–17]. To achieve satisfactory outcomes, patients should be referred to specialized centers, surgical strategy must be carefully planned before transplantation, high-tech vascular interventions may be required, and in some cases, individual transplantation technique that is unparalleled anywhere in the world may be required [5, 14, 18, 19].

Currently, there are international publications describing 6 pregnancies in 5 women after SLK transplantation. Not even a single pregnancy after SLK transplantation with renal portal transposition has been described. In the above cases, among the pregnancy complications, the following were indicated: fetal growth retardation in all patients, preeclampsia in two patients, premature birth zin four cases. Four patients were carrying pregnancy for the first time, one patient had 2 consecutive pregnancies with reversible renal transplant dysfunction during both pregnancies and a permanently impaired transplanted kidney function 17 months after delivery. These publications do not provide data on the condition of these women in the long-term period after delivery, as well as on the state of health and developmental characteristics of the newborns after the neonatal period [20–23].

Pregnancy in women after transplantation is always associated with increased risk of complications. Gestation after multivisceral transplantation is a more complicated and rarer situation. Complex vascular reconstruction during multivisceral transplantation during pregnancy is an unexplored situation requiring personalized management and an interdisciplinary approach. A physiological increase in the dynamics of pregnancy by almost 2 times the volume of circulating blood and the increasing effect of hormonal, neurogenic, and mechanical factors on the vascular wall lead to increased hemodynamic load on vascular anastomosis. At the same time, alternative blood flow in the vascular network of the transplanted complex, postoperative increase in the stiffness of the vascular wall at anastomosis sites, peculiarities of bile secretion, lipid, nitrogen metabolism and, in general, the functioning of the transplanted organs cause changes in the adaptation gestational processes, which increases the risk of pathological processes and complications.

Since 2008, 44 pregnant women with transplanted organs have successfully given birth at the Mother and Child Republican Centre for Applied Research [24–26]. We have presented the first pregnancy experience by this patient [27]. However, given the lack of such publications and the uniqueness of the clinical situation, and in order to highlight the therapeutic and diagnostic monitoring, as well as exchange of experience with foreign colleagues, the team of authors presents a clinical case of two successful full-term successive pregnancies in women after SLK transplantation with reno-portal transposition.

## CLINICAL CASE

*Patient A., born in 1985, was first diagnosed at the age of 10 months, when hepatosplenomegaly and kidney enlargement, accompanied by proteinuria and increased serum creatinine levels, were discovered during examination for pneumonia. The patient had a younger sibling sister, who had similar changes in internal organs. Although her parents and close relatives had no liver and kidney diseases, the disease was assumed to be hereditary. The family visited geneticists for consultations. In compliance with all K. Zerres criteria: 1) typical renal changes detected by imaging examination methods, 2) pathological and anatomical confirmation of the diagnosis in the patient's native siblings, 3) absence of polycystic kidney disease during ultrasound examination of the patient's parents above 30 years of age, 4) presence of clinically and histologically confirmed liver fibrosis, the patient was diagnosed with autosomal recessive polycystic kidney disease. Since this disease does not have any etiopathogenetic treatment and has a very unfavorable outcome in early childhood, despite symptomatic therapy, progressive deterioration of the patient's condition and development of end-stage of the disease led to the need for SLK transplantation. Final diagnosis at the time of inclusion in the waiting list: "Polycystic disease with liver and kidney injuries. Secondary chronic pyelonephritis, remission. End-stage chronic kidney failure, CKD 5D. Cryptogenic liver cirrhosis (Child-Pugh class B). MELD 19. Mixed portal hypertension. Splenomegaly. Hypersplenism. Grade 2 esophageal varices. Portal hypertensive gastropathy: chronic superficial gastritis and bulbitis. Ascites. Moderate symptomatic anemia".*

*Additional examination via CT angiography revealed critical portal vein stenosis and large spontaneous splenorenal shunts, formed against the background of portal hypertension. This anatomical feature significantly contributes to the hemodynamic characteristics of portal perfusion and requires vascular reconstruction at the hepatic graft implantation stage. This is necessary to prevent development of early graft dysfunction, which can occur against the background of changes in the volumetric blood flow through the portal vein due to stenosis and pronounced splenorenal discharge. In this case, reno-portal transposition becomes the optimal variant for vascular reconstruction (Fig. 1).*

*At the Minsk Applied Research Center for Surgery, Transplantology and Hematology (then known as Republican Scientific and Practical Center for Organ and Tissue Transplantation), on April 1, 2015, the patient underwent combined orthotopic liver transplantation with reno-portal transposition and heterotopic intra-abdominal kidney transplantation. The clinical characteristics of the disease and the surgical intervention performed are presented in table 1.*

*Good engraftment and graft functioning facilitated rapid recovery and achievement of high quality of life for the patient. They also restored fertility and the need for reproductive function. However, given the patient's genetically determined illness, the issue of gestation could only be resolved after genetic counseling. Based on the autosomal recessive type of inheritance of the*

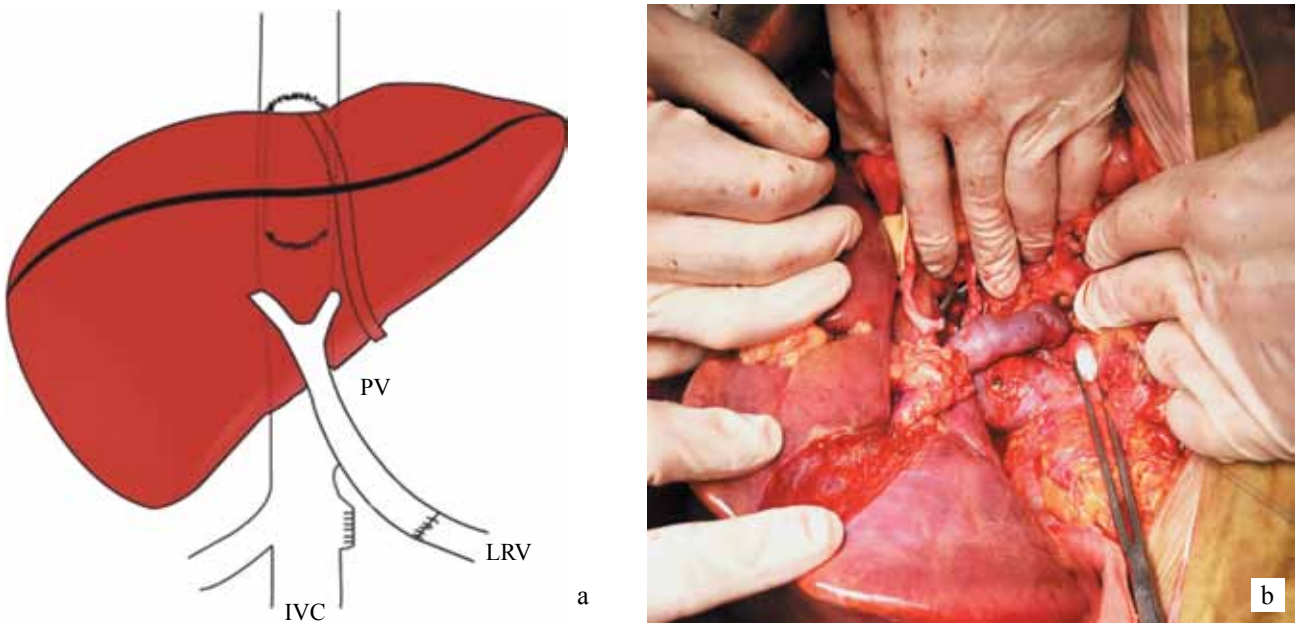


Fig. 1. Reno-portal transposition: a – graphic image of reno-portal transposition (J. P. Lerut, D. Mazza, V. VanLeeuwetal): PV – portal vein, IVC – inferior vena cava, LRV – left renal vein; b – final view of anastomosis between the portal vein of the liver graft and the recipient's (patient A) left renal vein (reno-portal transposition). Intraoperative photo from Prof. O. Rummo's archive

Table 1

**Patient A's anamnestic data. Surgical intervention peculiarities**

| Clinical characteristics | Personalized data | |
|---|---|---|
| Disease that necessitated multivisceral transplantation | Autosomal recessive polycystic kidney disease (ARPKD) | |
| Nature of disease | Congenital, genetically determined | |
| Disease manifestation period | Baby age | |
| Age at which end-stage disease manifested | 28 years | |
| Waitlist time | 11 months | |
| Vascular complication, a contraindication to transplantation | Critical portal vein stenosis, large spontaneous splenorenal shunts | |
| Cause of contraindication | Post-transplant impaired liver graft perfusion | |
| High-tech vascular reconstruction that allowed for transplantation | Reno-portal transposition (see Fig. 1) | |
| Type of transplantation performed | Combined orthotopic liver transplantation with reno-portal transposition and heterotopic intra-abdominal kidney transplantation | |
| Laboratory findings before and after transplantation: | Before transplantation | After transplantation |
| – serum creatinine | 479.2 μmol/L | 74.2 μmol/L |
| – urea | 40.0 mmol/L | 4.8 mmol/L |
| – uric acid | 595.6 μmol/L | 379.2 μmol/L |
| – alkaline phosphatase | 227.8 IU/L | 49.3 IU/L |
| – GFR by Cockcroft–Gault | 12.6 mL/min | 91.4 mL/min |

*disease and the probability of heterozygous carriage of a mutation in a healthy husband – 1:70 (population), the risk of having a baby with autosomal recessive polycystic disease was 0.7%, which is interpreted as a low degree of genetic risk and allows planning pregnancy for this couple.*

*Detailed characteristics of both pregnancies, as well as regimens for prevention and treatment of complications are presented in table 2.*

*During both pregnancies, the woman underwent prenatal examinations according to a pregnancy screening program: combined first trimester screening (ultrasound examination of the fetus with measurement of the thickness of the collar space and determination of three biochemical markers), ultrasound examination of the fetus at 20 and 32 weeks of gestation. Prenatal examination did not detect any fetal pathology. Doppler and cardiotocographic examinations showed that the condition of the fetus remained satisfactory throughout the observation period.*

*Delivery in both cases was performed through caesarean section in full-term pregnancy. Indications for caesarean delivery were: anatomically narrow pelvis, condition after multivisceral transplantation with vascular reconstruction, operated uterus (in the second pregnancy). Anesthetic management method included combined spinal and epidural anaesthesia. Given the undesirability of increasing the metabolic load when prescribing hormonal contraception and the risk of infection during installation of intrauterine systems, sterilization was performed during the second operation. Based on international data indicating the safety of breastfeeding when taking tacrolimus drugs, the patient was asked to continue to breastfeed the baby. But for her own reasons, she refused. Lactation was suppressed by administration of cabergoline. The postpartum period was uneventful. Both times, the sutures were removed on day 8, and the patient was discharged home with the child on day 9.*

*At present, it has been 2 years 7 months since the first and 5 months since the second birth. The patient feels well. Laboratory parameters correspond to the pregestational levels. Instrumental examinations revealed no pathology. Ultrasound examination of grafts with Doppler-measuring vessels and anastomosis was performed during both pregnancies and in the postpartum period – no dysfunction was detected. The data are presented in table 3 and in Fig. 2.*

*The condition of both children and the neonatal period are currently fully consistent with age characteristics. Examinations found that laboratory indicators correspond to that of the population. The boy is attending a standard-type preschool, he is active, 2 years 7 months of age, 94 cm tall and weighs 14.5 kg. The girl aged 5 months is 64 cm tall and weighs 7.2 kg. Cognitive development of both children with no abnormalities.*

*This family will be undergoing regular medical checkup: apart from general clinical examinations, diagnostic monitoring, as during pregnancy, includes in-depth examination of the urinary and digestive systems with identification of early markers of renal and hepatic injury, tumor markers. The children will continue to be monitored in order to determine if their health and development characteristics are normal.*

Table 2

**Clinical characteristics of pregnancy and childbirth, prevention and treatment regimens for complications in patient A during first and second pregnancy**

| Clinical characteristics | First pregnancy | Second pregnancy |
|---|---|---|
| **Pregnancy** | | |
| How long has the transplanted organ been in the body of the pregnant woman | 11 months | 3 years 1 month |
| Immunosuppressive therapy regimen | Tacrolimus (advagraf):<br>daily dose was increased with time from 5 to 7 mg,<br>methylprednisolone: from 2 to 4 mg | Tacrolimus (advagraf):<br>daily dose was increased with time from 7 to 8 mg |
| Pregnancy complication risk groups | Preeclampsia<br>Placental insufficiency,<br>Graft dysfunction/rejection,<br>Thromboembolic complications,<br>Severe anemia of combined genesis,<br>Gestational diabetes,<br>Infection | |
| Prevention regimens (drug groups) | Anticoagulant therapy (drugs with angio-protective effect in prophylactic doses);<br>Hepatoprotective agents: ursodeoxycholic acid, essential phospholipids;<br>Metabolic agents, amino acids and their derivatives: ademetionine;<br>Agents for treating liver diseases: artichoke leaf extract;<br>Phytopreparations for prevention of urinary tract infections in obstetrics;<br>Iron/folic acid/vitamin b drugs | |
| Pregnancy complications | Anemia of combined genesis,<br>Threatened miscarriage in the 18–19-week period,<br>Vaginitis | Anemia of combined genesis,<br>Placenta previa,<br>Hyperfermentemia<br>Asymptomatic bacteriuria |
| Treatment regimens (drug groups) | Combined antianemic agents of ferrous iron with folic, ascorbic acid, cyanocobalamin, parenteral administration of iron/vitamin B drugs;<br>Antispasmodic therapy: drotaverine / papaverine;<br>Vaginal suppositories with metronidazole and miconazole for vaginal sanitation | Parenteral administration of iron/vitamin B drugs; with decreased iron metabolism, hemoglobin concentration <90 g/L – subcutaneous injection of erythropoietin;<br>Hepatoprotective agents: ursodeoxycholic acid 250–500 mg/day, essential phospholipids 1800 mg/day,<br>Metabolic agents, amino acids and their derivatives: ademetionine Fosfomycin, phytopreparations for prevention of urinary tract infections |
| Delivery time | 38–39 weeks (268 days) | 37–38 weeks (262 days) |
| **Condition of the newborn and postpartum period** | | |
| Sex of newborn | male | female |
| Weight, g | 3030 | 2790 |
| Height, cm | 47 | 50 |
| Apgar score | 8/9 | 8/8 |
| Condition of newborn | Satisfactory | Satisfactory |
| Complications in newborn | – | – |
| Complications in mother | – | – |
| Rooming-in | + | + |
| Discharged home with the mother / transferred | Discharged | Discharged |
| Discharged on day ... | 9 | 9 |

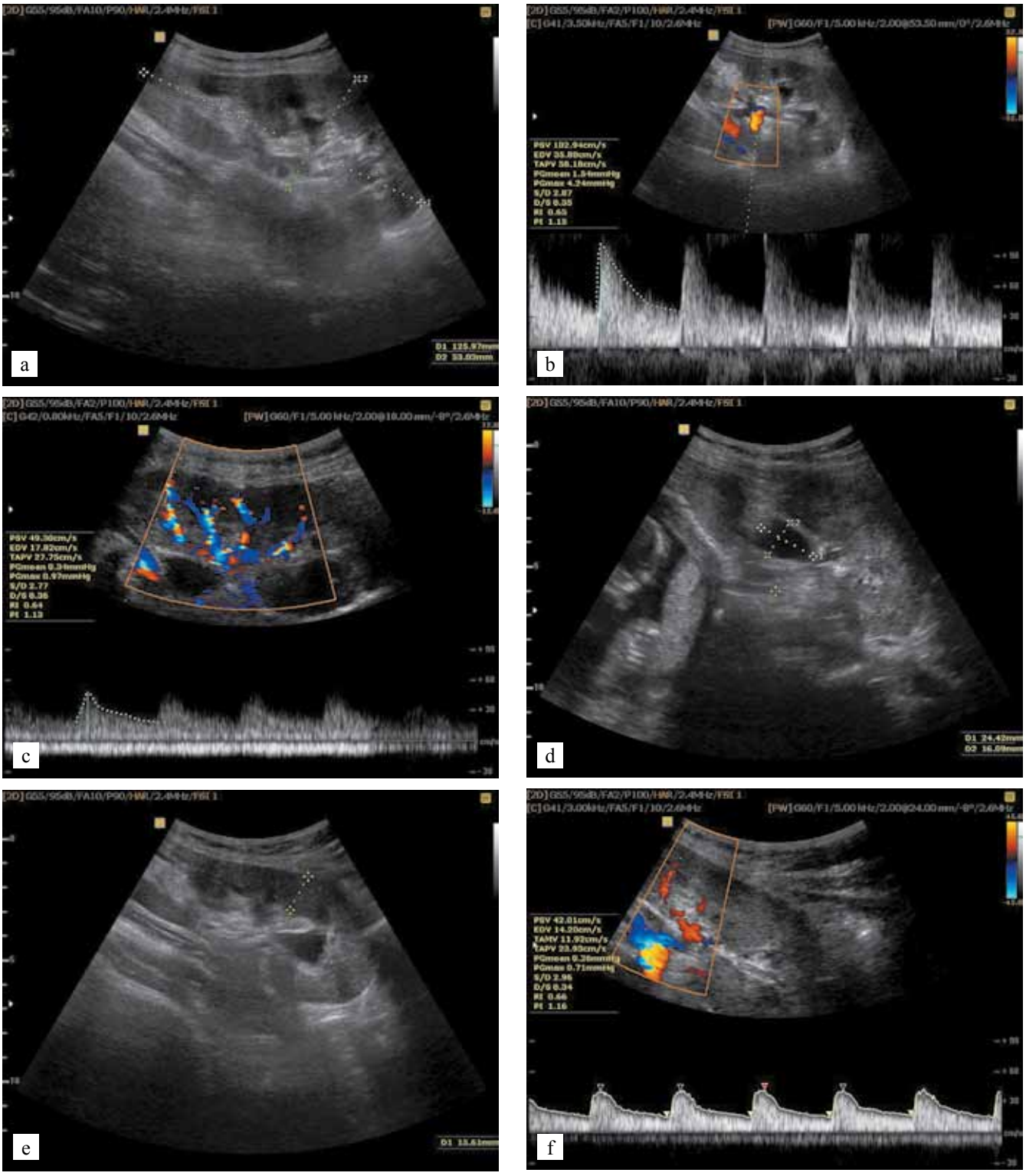


Fig. 2. Ultrasonic characteristics of transplanted complex on day 8 of the postpartum period. Transabdominal ultrasound with a 3.5–5 MHz transducer in the "abdomen" menu: 1–3 – ultrasound image of the renal graft: a – B-mode, b – Doppler ultrasound of blood flow in the main trunk of the graft renal artery, c – in the interlobar arteries of the renal graft; d–f – ultrasound image of the liver transplant gate structures: d – *vena portae*, B-mode, e – reno-portal anastomosis, B-mode, f – Doppler ultrasound of blood flow in *vena portae* and reno-portal anastomosis

Table 3

**Laboratory parameters for both pregnancies and after delivery**

| Parameters | Before pregnancy | 1st pregnancy | | | | After the 1st pregnancy (after 1 year) | 2nd pregnancy | | | | After 2nd pregnancy (after 5 months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 trimester | 2 trimester | 3 trimester | Postpartum period | | 1 trimester | 2 trimester | 3 trimester | Postpartum period | |
| Creatinine, μmol/L | 67.5 | 91.2 | 72.0 | 98.0 | 93.0 | 70.9 | 87.0 | 71.0 | 127.0 | 97.0 | 69.7 |
| Urea, mmol/L | 4.7 | 5.0 | 4.8 | 6.4 | 6.2 | 5.7 | 5.3 | 5.8 | 8.0 | 6.5 | 5.3 |
| Alt, IU/L | 19.0 | 15.1 | 18.1 | 17.0 | 15.0 | 9.0 | 8.0 | 9.0 | 35.1 | 18.0 | 19.0 |
| Ast, IU/L | 10.8 | 11.3 | 15.9 | 26.0 | 24.1 | 12.0 | 14.0 | 10.2 | 38.0 | 27.2 | 16.0 |
| Hgb, g/l | 118.0 | 102.1 | 96.4 | 92.9 | 104.3 | 108.2 | 107.0 | 92.8 | 92.4 | 103.0 | 114.0 |
| Platelets, 109/L | 79.6 | 67.1 | 102.0 | 129.1 | 185.0 | 72.4 | 82.5 | 87.3 | 95.6 | 119.0 | 91.4 |
| SPB, g/day | 0 | 0.06 | 0.08 | 0.13 | 0.03 | 0 | 0.022 | 0.06 | 0.125 | 0 | 0 |
| GFR by Cockcroft–Gault, mL/min | 94.0 | 88.2 | 74.1 | 57.4 | 89.3 | 97.0 | 87.6 | 88.1 | 86.4 | 92.3 | 93.0 |

## CONCLUSION

This case from practice represents a unique clinical situation where, despite the high risk of complications, a patient with multivisceral transplantation and high-tech vascular reconstruction, was able to endure two full-term consecutive pregnancies that ended in the birth of healthy babies. There was a favorable course of postpartum and long-term periods, reaching the pre-test level of laboratory indicators. There were no pathological changes in the morphological and functional characteristics of the formed complex. Due to absence of similar observations in international medical literature, we conclude that this is the first world experience of pregnancy in a patient with such diagnosis.

*The authors declare no conflict of interest.*

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