Pregnancy in Renal Transplantation

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Pregnancy in kidney transplantation is, considering its numerous complications, listed in category of high-risk pregnancies. Complications occur as consequence of action of immunosuppressant drugs and mutual interactions of graft on pregnancy and pregnancy on graft.

To assess conception it is necessary for female patient to fulfill conditions after which planning and management of pregnancy are carried out. Planning means a list of actions which altogether have as a goal to decrease risk factors for future mothers and for babies as much as possible. Pregnancy management is also procedural, including numerous hospitalizations, in which pregnancy, fetus and renal function are controlled, on-time identifying potentially dangerous complications and solving ones that might have already occurred. With all given precautions there is still no guarantee for successful pregnancy termination, although given measurements significantly improve possibilities of normal childbirth, like those in general population. Keywords: renal transplantation, pregnancy.

1. INTRODUCTION

Most women who are dialysis-dependent have anovulation, amenorrhea and infertility although 75% of them are in reproductive stages of life. Transplantation decreases or removes these disorders. Ovulation is restored several months after successful renal transplantation, and that way fertility is re-gained. First successful well-known pregnancy in transplanted woman was described in 1958, and experiences after that listed this pregnancy as high-risk, with numerous complications occurring as a result of graft impairment/immunosuppressant drug activity (1).

2. CASE PRESENTATION

Twenty-six year old patient S.H. from Kakanj is hospitalized in Department of Nephrology, Dialysis and Transplantation, Sub-department of Transplantation of Clinic for Internal Diseases for planning of pregnancy. She was transplanted in 2005, her father was a donor of kidney, and before transplantation she was 6 months dialysis-dependent due to terminal renal impairment. She has been a renal patient since her high-school days, and pathohistological kidney biopsy finding was not sufficient for terminal diagnosis. Clinical and laboratory aspects imposed chronic proliferative glomerulonephritis as her main disease, with hypertension and progressive renal deterioration as main characteristics. After getting married the patient came to her regular specialist nephrological examination with her husband and showed interest in possibilities of pregnancy in transplanted patients. After thorough insight in her previous medical history, thorough anamnesis and actual health examinations it has been determined that patient fulfilled all criteria for conception (Table 1), with administration of mycophenolate mofetil (MMF, CellCept®) being discontinued right away with recommendations to start with conception 6 weeks after the drug has been discontinued. As soon as patient reported having symptoms and signs of pregnancy, with positive hormonal (β hCG) test, she was hospitalized and introduced to plan of pregnancy management.

• The plan implied:
  • Before transplantation:
    • Rubeola vaccine.
    • X-ray of the pelvic.
  • Before pregnancy:
    • RH compatibility of spouses.
    • Microbiological tests on hepatitis B and C, HIV, herpes viruses, rubeola and toxoplasmosis.
    • Glycaemia values.
    • Administration of ACE inhibitors and angiotensin receptors is stopped.
    • Administration of MMF and sirolimus is stopped.
  • During pregnancy:
    • Daily: blood pressure is controlled.
• Once in two weeks/monthly: control exams of nephrologist and perinatologist.
• Complete blood analysis, biochemical analysis and urine exams, urine for bacteria.
• Creatinine concentration in serum and creatinine clearance.
• Proteins in urine in 24h.
• Body Mass of mother.
• Concentration of calcineurin inhibitors in blood.
• Ultrasonographic and gynecological examination.
• Every trimester of pregnancy: IgM on CMV and toxoplasmosis in seronegative women.
• In last trimester: glucose tolerance test, IgM on herpes simplex in seropositive women.
• Biophysical profile on every two weeks.

Physical exam: Except of physiological development of osteomuscular aspect, other findings were normal, including general impression, findings on heart, lungs, abdomen and extremities. In left inguinal region there was post-operative scar under which transplanted kidney was palpable. Transplanted kidney was of normal size and consistency, with no pathological murmurs found by auscultation. On admission: blood pressure was 115/75 mm Hg, pulse was 78/min. All laboratory results (complete blood analysis, Fe, CRP, Glucose in blood, AST, ALT, bilirubines, HbA1C, ALP, LDH, ionogram, Acid-Base Status, lipid status, proteinogram, hepatitis markers, microbiological and virusological results) were in referent values of normal findings, except of: urea 8.2 mmol/L, creatinine 127 µmol/L, and proteins in urine were 1+, biuret reaction of urine was 0.24g/24h, with normal findings in urine sediments.

Shortly after admission a multidisciplinary team (nephrologist, gynecologist) was formed. Nephrologist controlled parameters of renal function, diagnosed and treated acute or chronic rejection and other complications, making corrections of immunosuppressant therapy, whilst perinatologist controlled pregnancy guided by protocol for high-risk pregnancy and

During pregnancy patient was hospitalized nine times in total, hospitalizations lasting three days in average. Protocolar examinations were performed as well as gynecological examinations. In fifth hospitalization urinary tract infection was determined caused by bacteria E. Coli, which was successfully treated by non-nephrotoxic antibiotics (ampicillin). All biochemical findings were in referral values, with values of serum creatinine and glomerular filtration rate not statistically significantly changed (Figure 1 and 2).

Toward the end of pregnancy there were no signs of preeclampsia, hypertension or ambiguous impairment of renal function and delivery was performed in 38th week of gestation via natural birth canal. Mother gave birth to a healthy baby girl. After delivery bromocriptine was included in therapy in order to induce termination of breast milk production because breastfeeding

Table 1. Criteria for pregnancy planning in renal transplantation
diagnosed preeclampsia and gestational metabolic disturbances.

Gynecological protocol was made of: bimanual exam, ultrasonographic exam, early amniocentesis (protocolar), color Doppler ultrasound of feto-placental flow (protocolar), biophysical profile (fetal tone, fetal movements, respiratory movements, quantity of birth water etc).

Before conception administration of drugs with potential teratogenic effects is discontinued, and dosage of calcineurin inhibitors is made carefully because of changes in concentration due to expanding of plasma volume and anemia.

Gestational age is precisely determined by routine ultrasonographic exams in first trimester of pregnancy (measuring crown-rump diameter). Afterwards additional perinatal examinations were performed, mostly hormonal, and early amniocentesis was performed for the purpose of detecting possible chromosome aberrations, which was done in our patient by protocol.

Table 2. Drug classification and levels of risk for fetus

<table>
<thead>
<tr>
<th>Category</th>
<th>Information</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled studies on human did not show risk of usage in first trimester. There are still a possibilities of time-advanced effects</td>
<td>Drugs can be used in pregnancy</td>
</tr>
<tr>
<td>B</td>
<td>Animal studies showed no risk for fetus but there are no controlled studies on humans, or: animal studies showed harmful effects on fetus but they were not confirmed in controlled studies on human</td>
<td>Usage of drugs is probably safe in pregnancy</td>
</tr>
<tr>
<td>C</td>
<td>Animal studies showed harmful effects but there are no controlled studies on human, or there are no controlled studies on animals or humans</td>
<td>Drugs can be used in pregnancy if potentially beneficial effect overcomes potential risk for fetus</td>
</tr>
<tr>
<td>D</td>
<td>There are evidences of risk for humans, but in some cases usage can be acceptable</td>
<td>Usage is allowed in life threatening situations and severe diseases where safer drugs are not available</td>
</tr>
<tr>
<td>X</td>
<td>There are evidences of risk for human usage and that risk overbalances any possible positive effect of drug</td>
<td>Usage of these drugs is contraindicated in pregnancy</td>
</tr>
</tbody>
</table>
is not recommended (immunosuppressants being transferred via breast milk).

3. DISCUSSION

Effect of pregnancy on graft function
Changes in force of glomerular filtration during pregnancy were considered as factor which can bring to shortening of long-term graft survival, but newer studies did not confirm this thesis (2). Current stands are that pregnancy has no effect on renal function as long as it is well conserved, but it deteriorates renal function if it was damaged previously. The loss of transplanted organ two years following pregnancy is around 8%, which is similar to other patients with transplanted kidney (3). The impairment of renal graft function in third trimester for more than 30% is found in around 20% of cases (4), and the reasons are: graft rejection, preeclampsia, acute pyelonephritis, re-current glomerulopathy, obstruction of urinary tract and nephrotoxic effect of calcineurin inhibitors. Almost half of pregnant women have proteinuria which is most commonly mild and it is evident or increased in third trimester (4). Nephrotic proteinuria is less commonly seen and it is mostly in relation to increased blood pressure (4).

Effect of graft on pregnancy
Data from large Davison study show that the incidence of artificial and spontaneous abortions in transplanted population is 34%, which is 14% more than in general population (5). Since most of abortions occur in first trimester, 94% of pregnancies that enter second trimester are delivered successfully. Perinatal mortality is high and it amounts 10%, the incidence of premature delivery is 55%, and average gestation age is 35 weeks. Premature delivery occurs due to weakened graft function, preeclampsia and suffering of unborn baby. Stagnation of fetal growth is noted in 20% of cases. Aforementioned cannot be always attributed to renal graft impairment. Nephrotic proteinuria is significant predictor of poor outcome of pregnancy, especially when it occurs in phase of conception or early pregnancy.

Immunosuppressant therapy
The combination of calcineurin inhibitors with corticosteroids and eventually azathioprine is continued during pregnancy. Micophenolat-mofetil and sirolimus are contraindicated in pregnancy (6). All immunosuppressant drugs reduce immunity against infections of pregnant woman as well as fetus. They also occur in breast milk and breastfeeding is therefore not recommended.

Prednisone has weaker mineralcorticosteroid action than cortisole and therefore is applicable in pregnancy, its side-effects depending of dosage and length of treatment. Concentration in fetus is ten times lower than in mother’s bloodstream so risk of adrenal insufficiency is not realistic, especially since it does not lead to suppression of corticotropin-releasing hormone. It is listed in group B of drugs, which can be given safely during pregnancy (7) (Table 2).

Azathioprine has its well known side-effects: hepatic lesions, depression of bone marrow, increased risk of malignancies and segmentation of chromosomes in lymphocytes. It transits through placental membrane, but in its inactive metabolite form. Teratogenic effect on fetus is weak because fetus does not have enzyme for conversion of drug into its active metabolite.

Cyclosporine acts as nephrotoxin on mother, increasing blood pressure and leading to frequent occurrence of malignant neoplasms. As nephrotoxicity implies decrement of glomerular filtration, some pregnant women have increased values of serum creatinine only because of this drug. Although almost half of women treated with cyclosporine have increased blood pressure, even 75% of them have increased blood pressure in pregnancy (8). Cyclosporine travels through placental membrane and can lead to reduction on number and irregularities in maturing of T and B lymphocytes.

Experiences with tacrolimus are mainly positive. Adverse effects for mother are nephrotoxicity and hyperkalemia. It travels through placentar membrane. Most of pregnant women have favorable outcome of pregnancy.

Family Planning
In order to reduce risks for mother and fetus it is necessary to plan the pregnancy, in other words it is necessary for all the conditions listed in Table 1 (9) to be met before conception. Afore pregnancy patients have to be warned and familiarized with effects of pregnancy on graft function, relatively shorter life span which is sometimes inadequate for child-raising, possible side-effects of drugs, common occurrence of viral infections which can endanger mother and the fetus, as well as complications during childbirth which are still more frequent than in general population.

Pregnancy Management
Pregnancy should be managed by team which not only includes experienced transplantation nephrologist but also includes gynecologist who is subspecialist in perinatology, thus the team should be opened to medical experts of other specialties. Prior to conception administration of drugs with potential teratogenic effects (ACE inhibitors, antagonists of angiotensin receptors, mycophenolat mofetil, sirolimus and oral antidiabetics), and doses of immunosuppressive drugs are reduced to the lowest levels of efficiency. In pregnancy, due to increase in volume
of plasma, levels of calcineurin inhibitors are lowered, and because of anemia they are increased, due to bonding to erythrocytes. Renal function tests are controlled at least once a month, favorably twice, blood pressure is measured on daily basis, and in case of decrease or impairment of graft function patient is hospitalized for differential diagnosis. Episodes of acute rejections are not more often reported in comparison to non-pregnant transplanted population if the graft function was satisfying before the conception. As long as precise diagnosis is not yet made, which should be done as soon as possible, dosage of calcineurin inhibitors should be lowered. If necessary, transplanted graft biopsy must not be delayed. The treatment is identical as in patients who are not pregnant. Preeclampsia occurs as part of syndrome of pregnancy induced or pregnancy worsened hypertension. Hypertension usually disappears after childbirth, and is often first reported after 20 weeks of gestation. Diagnosis of preeclampsia is made when we have increased blood pressure values, proteinuria and edema. Preeclampsia can be extra complicated with HELLP syndrome which implies hemolysis, increased values of hepatic enzymes and thrombocytopenia. Preeclampsia can be extra complicated with HELLP syndrome which implies hemolysis, increased values of hepatic enzymes and thrombocytopenia. Preeclampsia occurs around 30% more often in these patients than in general population, and differential diagnosis of disturbance in function of renal graft could be very difficult. One can not rely on determination of uric acid values as sign of preeclampsia because it can be increased due to usage of calcineurin inhibitors. Sometimes it is necessary to undergo planned preterminal labor which is indicated in cases of refractory preeclampsia, eclampsia, oliguria, pulmonary edema, HELLP syndrome, stagnation of fetal growth and oligohydramnion. Administration of small doses of Aspirin from second trimester of pregnancy can be used as prevention of preeclampsia.

Childbirth and puerperium

Delivery is performed in centers of tertiary health care levels and in periods of 38-42 weeks of gestation. Natural vaginal delivery is preferred except when mother has pelvic osteodystrophy, avascular necrosis of femoral head, and when there are indications for cesarean section. During childbirth stress-dose of corticosteroids is administered (hydrocortisone 100 mg). Impairment of renal function after childbirth can be evident in three critical months following childbirth. Experienced pediatrician neonatologist should be in charge of baby's health, and breastfeeding is not recommended.

4. CONCLUSION

Only regular monitoring, multidisciplinary and planned approach to pregnancy in renal transplantation enables that this high-risk pregnancy is maintained in settings in which the risk factors are significantly lowered and possibility of normal delivery without complications are similar to those in general population.

REFERENCES