PREGNANCY IN RENAL TRANSPLANTATION

Clinical aspects

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SUMMARY

Following renal transplantation, it is often possible to achieve parenthood.

If a female recipient becomes pregnant she must be considered at high risk and so monitored.

The better the renal function before pregnancy, the more satisfactory the obstetric outcome.

Pregnancy in transplanted mothers presents many complex medical problems and is related to definite risks to both mother (toxemia, serious infections) and fetus (intrauterine growth retardation, premature labor).

If a renal function is compromised prior to conception and there is a further deterioration during pregnancy, termination of pregnancy or premature delivery should be considered to avoid permanent impairment of renal function.

Pregnancy is regarded as an immunologically privileged state and that is the reason why the incidence of rejection in pregnant patients is unusual. Rejection occasionally occurs in puerperium.

Immunosuppressive drugs must be continued during pregnancy to maintain the integrity of the transplanted kidney. There are no predominant or frequent developmental abnormalities in children of renal transplanted recipients treated with modest doses of immunosuppressive and steroid drugs.

Usually the transplanted kidney does not produce any mechanical dystocia in labor and during vaginal delivery there is no apparent mechanical injury to the kidney. Cesarean section is usually necessary for purely obstetric reasons.

The possibility of conception in kidney transplants recipients of childbearing age and the fact that pregnancy is not without significant maternal and fetal risks emphasizes the need for counseling, with regard to family planning, all such patients.

Chronic renal failure in women is usually associated with irregular or absent menstruation and impaired fertility.

Fertility can be restored by a successfull chronic haemodialysis or renal transplant and pregnancies are not at all uncommon in women receiving such treatment.

Pregnancy occurs in only about 1 of 200 women of childbearing age having dialysis therapy ([1]). Very few of these pregnancies result in live birth at term ([1, 2, 3]). However, the abnormal reproductive function of these patients is usually reversed by transplantation, resumption of regular menses and ovulation correlating closely with the level of function achieved by the graft ([4]). About 1 in every 50 women of childbearing age having a functioning renal transplantation becomes pregnant ([4]).

The population of fertile women with kidney transplantation continues to grow and gestation in these patients, once quite rare, has increased markedly during the past decade.

This paper reviews the obstetric problems of kidney transplant recipients.

Renal function during pregnancy in renal transplantation

If the transplant's renal function is adequate prior to pregnancy, the glomerular filtration rate is usually maintained throughout pregnancy with little or no deterioration. The glomerular filtration rate usually increases early in pregnancy, as it does in normal gestation ([5]).

The transplanted kidney can respond to the increased demands of pregnancy irrespective of the chronological age of the donor organ ([6]). Decreased renal function can be noted during the third trimester: a transient reduction in the glomerular filtration rate and proteinuria can occur during the third trimester in 30%-40% of patients but disappears postpartum and in absence of hypertension is not significant.

Clin. Exp. Obst. Gyn. - ISSN: 0390-6663
XI, n. 4, 1984

In about 15% of patients significant renal functioning impairment may develop during pregnancy and persist after delivery ([7, 8]). Therefore, an appropriate conservative approach is to consider that any renal compromise appearing during pregnancy should be considered as potentially deleterious to the continued survival of the transplant, even though this compromise may be entirely reversible following delivery. Compromise of renal function at any time during pregnancy should be considered as an indication for consideration of termination of the pregnancy or for premature delivery ([8]).

There is evidence that pregnancy has a better prognosis if a patient waits one-two years after transplantation before becoming pregnant. On the other hand, when pregnancy occurs five or more years after transplantation, then in 75% of patients the postpartum renal function is never as good as it was before pregnancy and never recovers ([9]).

As far as the allograft rejection is concerned, it must be considered that the incidence of rejection in pregnant patients is unusual. Pregnancy is regarded as an immunologically privileged state which protects the mother from rejecting the fetus who carries paternal histocompatibility antigens, although pregnancy frequently immunizes the mother against these histocompatibility antigens ([10]). Rejection occasionally occurs in the puerperium and may be the result of the return to a normal immune state (despite immunosuppression) or possibly a rebound effect from the altered immunoresponsiveness associated with pregnancy ([8]).

Although the mechanisms involved in this tolerance are not fully understood, studies have suggested the production of enhancing or blocking factors by the intrauterine allograft.

Recently, it has been suggested that the embryo might protect itself by suppression of T-cell colony formation during pregnancy, either by the release of soluble factors acting as lymphocyte suppressive agents or by the induction of suppressor cells ([12]).

The decreased incidence of rejection in transplant recipients during pregnancy suggests that the privileged immunologic state of the fetus may influence the mother's overall allograft response ([13]).

In fact, some women have a substantial reduction or even cessation of immunosuppressive therapy during pregnancy without deterioration of renal function ([10]).

However, immunosuppressive drugs must be continued during pregnancy to maintain the integrity of the transplanted kidney and to prevent rejection.

Although acute rejection may not be a problem, the process of chronic rejection may continue during pregnancy ([14]). Rejection can be difficult to diagnose and should be suspected when any of the clinical signs are present – fever, oliguria, hypertension and deteriorating renal function, often associated with renal enlargement and tenderness.

However, without biopsy confirmation rejection cannot be distinguished from acute pyelonephritis, recurrent glomerulopathy and possibly severe preeclampsia. The presence of pregnancy does not preclude biopsy which should be undertaken before one embarks upon antirejection therapy ([9]).

Maternal and fetal risks

Pregnancy in the recipient of a renal transplantation is related to significant maternal and fetal risks.

The medical problems occurring in the transplant recipient are undoubtedly of greater concern. They include mainly toxemia and bacterial, viral and fungal infections. Both these factors may contribute to the increased incidence of premature labor, premature rupture of the fetal membranes and low birth weight infants.

Toxemia is diagnosed clinically in about 30% of the pregnancies in transplant recipients. However, biopsy studies on wo-

men with renal parenchimal disease show that the clinical diagnosis of superimposed toxemia is wrong in about 50% of cases ([15]).

The ingestion of immunosuppressive agents predisposes pregnant women with renal transplantation to all types of infection. This is particularly true in relation to urinary tract infections, with potentially serious development of pyelonephritis.

In addition to normal pathogens, Candida Albicans, Aspergillus, M. Tuberculosis, Listeria, Monocytogenes could also be found ([16]).

Premature rupture of membranes leading to premature delivery is a complication of pregnancy in transplant recipients in 20%-40% of cases. Frequently, pregnancy is prematurely terminated due to deteriorating renal function or uncontrollable toxemia, accounting for a 50% overall incidence of premature deliveries ([11]).

Intrauterine growth retardation occurs in at least 20%-25% of these pregnancies and one might expect that these deliveries involve patients with severe renal impairment vascular disease or hypertension ([17, 18]). Non specific depression of the immune system by immunosuppressive drugs could result in such adverse effects as fetal growth retardation.

In rats, azathioprine causes fetal growth retardation and markedly decreases the chance of normal neonatal growth and development ([19]).

Another potential risk to the fetus is congenital defects caused by the immunosuppressive agents. Based on animal and human data, both of the commonly used agents, azathioprine and the corticosteroids, have been implicated ([20, 21, 22, 23]). However, congenital abnormalities result from very large doses of azathioprine and steroids ([24, 25, 26]). and that is the reason why there are no predominant or frequent developmental abnormalities in children of renal transplant recipients treated with modest doses of immunosuppressive and steroids drugs.

Most of liveborn infants of renal transplant recipients have no neonatal problems. However, there could be problems peculiar to the offspring of this group of patients. These include lymphoid hypoplasia, involving the lymphnodes, spleen, thymus, and adrenocortical insufficiency.

At the time of birth, a sample of umbelical cord blood should be examined for serum electrolytes and a complete blood count should be done to determine the absolute number of lymphocytes.

Antenatal care

Female patients should be instructed to consult the obstetric clinic as soon as pregnancy is suspected. Many patients are under the impression that they could not conceive and in many instances pregnancy is not diagnosed until the second or even third trimester.

All pregnancy transplant patients must be considered at high risk and so monitored. Such patients should be followed in conjunction with a nephrologist, at biweekly intervals until the 32 week of gestation and then weekly until the onset of labor ([9]). Management requires attention to serial assessment of renal function, diagnosis and treatment of rejection, blood pressure control, prevention and early diagnosis of anemia, and assessment of fetal well-being.

At each visit routine antenatal care should be supplemented with standard renal function tests, including determinations of blood urea nitrogen levels, serum creatinine levels, 24-hours creatinine clearance and protein. In addition, a full blood count, determination of electrolytes and midstream urine specimen for microscopy and culture are performed.

Plasma protein, calcium and phosphate levels and cytomegalovirus and herpes hominis virus titers should be checked at six-week intervals.

Serial ultrasound is the best method to monitor successfully fetal growth. Measurement of maternal urinary or plasma estriol levels is of no value because maternal administration of glucocorticoids suppresses fetal adrenal steroid precursors ([27]). Human placental lactogen is unaffected by maternal ingestion of glucocorticoids; however, it is an exclusive secretory product of the syncytiotrophoblast and the temporal relationship which falling values of the hormone bear to fetal jeopardy makes its value questionable for increasing fetal salvage.

Fetal cardiotocography is performed weekly in the third trimester.

Management of delivery

Vaginal delivery should be the aim in renal transplant recipients. The transplanted kidney is usually located in the false pelvis and thus dystocia is uncommon.

The renal homograft blood vessels and ureter may be subjected to compression during labor but without any harmful consequences as a result of this ([14]). If there is any question of homograft compression or of obstruction of labor by the transplantated kidney, intravenous pyelography and X-ray pelvimetry could be performed simultaneously at 36 weeks' gestation ([10]).

Careful monitoring of maternal fluid balance, cardiovascular status and temperature is essential and aseptic technique is mandatory for every procedure. Surgical induction of labor by amniotomy and performance of an episiotomy warrant antibiotic cover.

Because of stress of labor, the patients should receive supplemental corticosteroid therapy with 100 mg of hydrocortisone given i.v. every 8 hours for 24 hours, commencing with the onset of parturition ([14]).

Cesarean section in transplanted recipients should be performed mainly for purely obstetric reasons, i.e. cephalopelvic disproportion, fetal distress and previous abdominal delivery.

Transplant patients may have pelvic osteodystrophy as a result of previous renal failure (or dialysis) or prolonged steroid therapy; a vascular necrosis of the femoral head is a common problem ([28]).

Impaired abduction of both hips could be a reason for abdominal delivery. Cesarean section in transplant recipients should be infrequent. However, the high incidence (about 50%) is probably due to the frequent necessity of prematurely terminating the pregnancy for medical indications, i.e. deteriorating renal function, toxemia, etc. ([11]).

When operating, exposure of the lower uterine segment could be difficult owing to the previous urologic surgery and occasionally a classical incision may be needed to avoid bladder and/or ureter damage ([20]).

Pregnancy counseling

Pregnancy in the recipient of a renal transplant is not without significant maternal and fetal risks.

The factors which are mainly correlated to te good obstetric outcome are: a) the interval of time between renal transplantation and conception; b) normal renal function prior to pregnancy.

There is evidence that pregnancy has a better prognosis if a patient waits two years after transplantation before becoming pregnant. On the other hand, when pregnancy occurs five or more years after transplantation, then in 75% of patients the postpartum renal function is never as good as it was before pregnancy and never recovers. Thus, waiting too long may be disadvantageous even in presence of apparently stable renal function.

The better the renal function before pregnancy, the more satisfactory the obstetric outcome. Ideally, prior to conception there should be ne evidence of renal rejection, the serum creatinine should be $\leqslant 2$ mg/100 ml, there should be no pro-

teinuria and there should be no hypertension. Intravenous pyelography should demonstrate no evidence of dilatation of the renal pelvis and calyces. The dose of prednisone should be $\leqslant 15$ mg/day and dose of azathioprine 3 mg/kg/day or less ([28]).

After full prepregnancy assessment, advice can be given, but it can only be advice since the patients must ultimately decide for themselves what degree of risk is acceptable.

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