Case Report

Maternal and perinatal outcome in post renal transplant patients on immunosuppressive therapy : a report of five cases

Kumkum Pahari[1], Chandrima Dasgupta[2], Dilip Kumar Pahari[3]

Infertility is common in patients with end stage renal disease because women do not ovulate and are unable to conceive[1,2]. But as renal function improves following kidney transplantation (KT), normal ovulatory cycles and fertility are usually resumed within a few months of KT[3,4]. However, the rates of both pregnancy and successful pregnancy remain lower than in general population. Because of the multiple risk factors like immunosuppressive agents and the already existing co-morbidities, pregnancy in a KT recipient is definitely considered a high risk situation for both the mother and the fetus and the timing of pregnancy following transplant is very important to reduce these risks.

[*J Indian Med Assoc* 2018; **116:** 51-3]

Key words : **Transplant, kidney transplant, pregnancy, graft failure, immunosuppression.**

Case Reports

(1) Mrs DS in her mid-thirties, attended after seven years of KT with an intention to conceive. She was hypertensive & at that time she was on Amlodipine, Azathioprine & Prednisolone. Her serum creatinine level was 1.2mg/dl & urine protein was <300 mg/24 hours. She was immediately advised to start Folic Acid 5mg daily & given assurance to proceed. She failed to conceive in six months & on preliminary investigations, her husband was found to be azoospermic. Her husband was treated for low sperm count and he responded to therapy& she conceived spontaneously. Her antenatal period was uneventful except mild growth retardation of the baby & her renal status remained stable throughout the pregnancy under guidance of her nephrologist. She was delivered at 38 weeks of gestation by elective Caesarean section giving birth to a baby weighing 2.4 kg without any immediate perinatal complication. Mother's post-delivery serum creatinine was 1.5 mg/dl & her recovery was uneventful. Serum creatinine stabilized to 1.3mg% at the end of three months following delivery.

(2) Mrs A R C, 33years, diabetic also presented with 4 years after KT. She was on Insulin, Mycofenolate & Cyclosporine. Mycofenolate was stopped; she was put on Azathioprine & Cyclosporine was continued. Folic acid 5mg/day was added. Pre-pregnancy status; serum creatinine-1.5, urine protein-400mg/day, blood glucose was controlled with Insulin. She was found to have PCO disease & treatment was started accordingly. After treatment, her 1st pregnancy unfortunately ended in spontaneous miscarriage. Consequently she conceived again in 2011 but during this pregnancy her blood sugar remained fluctuating throughout for which she was under supervision of a diabetologist to supervise the insulin dose. Her renal status also deteriorated to some extent during this period but the concerned nephrologist supervised it. Ultimately this pregnancy continued upto 36 weeks & she was delivered by elective caesarean section giving birth to a normal baby weighing 2.6 kg. Her serum creatinine stabilized to 1.4mg% three months after delivery.

(3) Mrs S M, 27years, presented in early 2016 at 14 weeks of pregnancy 3 years. after her kidney transplantation. She was on Amlodipine, Azathioprine, prednisolone & Folic acid. Her graft function status was within normal limits throughout pregnancy. At 38 weeks she was admitted with spontaneous rupture of membrane & early labour but labour did not progress satisfactorily even after acceleration with oxytocin drip & emergency caesarean section was done. Baby was normal & healthy weighing 2.8 kg. Her serum creatinine was 1.0mg% three months after kidney transplantation.

(4) Ms D P, attended at the age of 19 years for a second KT after the first transplant was rejected. She got married after a successful 2nd KT & after one & half years. She decided to conceive. She was on Mycofenolate, Tacrolimus & Prednisolone. She did not have any co-existing medical disorders. Mycofenolate was withdrawn & she was also put on Azathioprine; the dose being decided & monitored by the concerned nephrologist. Her pre-pregnancy graft function status were determined and serum creatinine was 1.1mg/dl. She conceived spontaneously & pregnancy continued almost uneventfully under regular supervision of nephrologist &

Department of Obstetrics & Gynecology, Medica Superspecialty Hospital, Kolkata 700099
[1]MD, Consultant Obstetrics & Gynecology
[2]MRCOG(UK), CCST(UK), DFFP(UK), Consultant Obstetrics &Gynecology
[3]MD, DM, DNB, FISN, FASN (USA) Nephrologist & Transplant Physician

was terminated by elective CS near term giving birth to a normal baby weighing 2.7 kg. Her serum creatinine was 1.0mg/dl at the end of three months.

(5) Mrs C D, presented after 2 years of KT with subfertility. She had hypertension & her B.P. at the time of presentation was 160/100 but serum creatinine was 1.5 & 24 hour urinary protein was <300mg/24 hours. She was on Prednisolone. Mycofenolate, and Cyclosporineas immunosuppressive agents & Amlodipine as antihypertensive. Mycofenolate was stopped & Azathioprine was started. Folic acid was started & husband was treated for oligo-asthenospermia.Her pre-pregnancy status; BP-130/80, serum creatinine-1.2, urine protein-240 to 250-mg/24 hours. BP was reasonably controlled with Amlodipine. She conceived after treatment with Clomiphene Citrate for her husband. She developed pre-eclamptic toxemia with significant proteinuria & her serum creatinine also increased upto 2.5mg%, which was treated accordingly by the transplant physician. She developed IUGR & other signs of placental insufficiency & was delivered by Caesarean section at 34 weeks of gestation. The baby weighing 1.8 kg was shifted to NICU & ultimately improved & survived. Her serum creatinine stabilized at 1.9mg% three months after transplantation (Table 1).

Table 1 — *Showing the overall immediate maternal & neonatal outcome*

Case No	Mode of Delivery	Time of delivery	APGAR score at birth	Fetal weight at birth in Kg	Maternal outcome
(1) DS	Elective LSCS	38	9	2.4	Uneventful
(2) ARC	Elective LSCS	36	9	2.8	Uneventful
(3) SM	Emergency LSCS	38	8	2.8	Uneventful
(4) DP	Elective LSCS	38	9	2.7	Uneventful
(5) CD	Elective LSCS	34	7	1.8	Renal status temporarily deteriorated

Discussion

Successful pregnancy in post kidney transplant patients depends on careful timing the renal functional status of the patient at the time of conception & throughout the antenatal period.

According to the American Society of Transplantation Consensus Opinion (ASTCO)[5,6,7], a post KT patient can safely proceed with pregnancy provided the following conditions are fulfilled:

(1) Graft function should be stable & adequate e.g. Serum creatinine level < 1.5 mg/dlNo or minimal proteinuria < 500mg/24 hours

(2) No concurrent fetotoxic infection such as Cytomegalovirus (CMV), Hepatitis C virus (HCV), Hepatitis B virus (HBV)

(3) Patient is not on any teratogenic or fetotoxic medicine

(4) Immunosuppressive regimen is stable at maintenance level

Other factors to be considered are absence of rejection in the past in the past one year, maternal age & co-morbid factors that may influence pregnancy outcome e.g.etiology of the original disease, diabetes mellitus, hypertension, inherited disease in mother or fetus, cardiovascular status, obesity in the mother etc.

Obstetric management includes preconception counseling which should be done to explain all the untoward consequences of pregnancy on mother & baby to both the prospective parents.

Actual obstetric management of all post KT pregnant patients should be done by expert obstetrician at a well-equipped center with all facilities to support the mother & the newborn in collaboration with the transplant physician, cardiologist, endocrinologist, neonatologist & other related personnel because even when all the necessary conditions are met, pregnancy may present some risks to the mother & allograft.

Major maternal complications include graft dysfunction & rejection, which may occur due to changes in metabolism of immunosuppressive medicatios & increased glomerular filtration that occurs during pregnancy. Hyperemesis gravidarum may also lead to decreased availability of orally administered immunosuppression resulting in reduced immunosuppression. So, immunosuppression must be maintained during pregnancy by proper monitoring of blood levels of immunosuppressive agents[+8,9,10]& graft dysfunction warrants appropriate investigations (by biopsy if necessary).

Other maternal complications include Preeclampsia, Fetal Growth Retardation, Intra Uterine Fetal Death, Preterm labour & complications related to associated medical disorders.

Major perinatal risks include effects of immunosuppressive medications, (Azathioprine & steroids are considered to be category II drugs & can be used safely), risk of transmission of infections like CMV & all the complications of growth & pre-term babies.

Regarding mode of delivery, spontaneous vaginal delivery & even induction of labour can be safely allowed in post KT patients unless there is any obstetric contraindication. Caesarean section should be done only for obstetric reasons whetheron elective or emergency grounds.

Long-term effects on offspring of post KT patients are not yet fully known. It is not yet clearly known whether infants born to renal transplant recipient mothers have an increased risk of any specific defects. There are many factors that might contribute to alterations in fetal neurological development specially some functional changes & neurocognitive defects[11,12] but there is no definite evidencefor the above. There are also concerns that there may be increased incidence of autoimmunity in offspring of post KT patients[13,14,15] but there is no definite evidence for the above. This is an area that requires more study by a long-term prospective analysis of children born to renal transplant recipient mothers.

References

1 Anantharaman P, Schmidt RJ — Sexual function in chronic kidney disease. *Adv Chronic Kidney Dis* 2007; **14:** 119-25.

2 Palmer BF — Sexual dysfunction in uremia. *J Am Soc Nephrol* 1999; **10:** 1381-8.

3 Laifer SA, Guido RS — Reproductive function and out-come of pregnancy after liver transplantation in women. *Mayo Clin Proc* 1995; **70:** 388.
4 Kim JH, Chun CJ, Kang CM — Kidney transplantation and menstrual changes. *Transplant Proc* 1998; **30:** 3057.
5 McKay D, Josephson M — Reproduction and transplantation: Report on the AST consensus conference on reproductive issues and transplantation. *Am J Transplant* 2005; **5:** 1-8.
6 EBPG Expert group in renal transplantation — European best practice guideline for renal transplantation. Section IV: long-term management of the transplant recipient: IV.10. Pregnancy in renal transplant recipients. *Nephrol Dial Transplant* 2002: **17:** 50.
7 Josephson MA, McKay DB — Considerations in the medical management of pregnancy in transplant recipients. *Adv Chronic Kidney Dis* 2007: **14:** 156.
8 Thomas AG, Burrows L, Knight R, Panico M, Lapinski R, Lockwood CJ — The effect of pregnancy on cyclosporine levels in renal allograft patients. *Obstet Gynecol* 1997; **90:** 916-9.
9 McKay DB, Josephson MA — Pregnancy in recipients of solid organs: Effects on mother and child. *N Engl J Med* 2006; **354:** 1281-93.
10 Armenti V, Moritz M, Davison JM — Drug safety issues in pregnancy following transplantation and immunosuppression: Effects and outcomes. *Drug Saf* 1998; **19:** 219-32.
11 Victor RG, Thomas GD, Marban E, O'Rourke B: Presynapticmodulation of cortical synaptic activity by calcineurin. *Proc Natl Acad Sci U S A* 1995; **92:** 6269-73.
12 Avramut M, Zeevi A, Achim CL — The immunosuppressant drug FK506 is a potent trophic agent for human fetal neurons. *Brain Res Dev Brain Res* **132:** 151-7.
13 Murthy V, Kennea NL — Antenatal infection/inflammation and fetal tissue injury. *Best Pract Res Clin Obstet Gynaecol* 2007; **21:** 479-89.
14 Talge NM, Neal C, Glover V — Antenatal maternal stress and long-term effects on child neurodevelopment: How and why? *J Child Psychol Psychiatry* 2007; **48:** 245-61.
15 Lozoff B, Georgieff MK — Iron deficiency and brain development. *Semin Pediatr Neurol* 2006; **13:** 158-65.

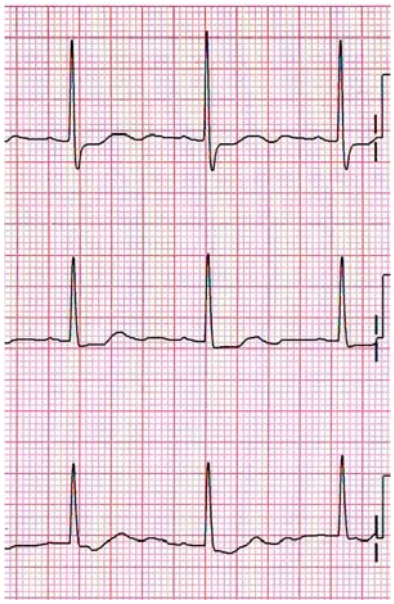
Answer : Pictorial CME (ECG Quiz) ***(Page no 37)***

ECG 1

Answer : (2) he is a genius

Patients presenting with chest pain, inverted U waves:

- **Are a very spe**cific sign of myocardial ischemia
- May be the earliest marker of unstable angina and evolving myocardial infarction
- May be observed during attacks of Prinzmetal angina
- Have been associated with LAD or LMCA occlusion and the presence of left ventricular dysfunction
- U wave inversion tends to occur mainly in the lateral leads (I, aVL, V5-6) and may be seen either during ischemic symptoms or at rest.



ECG 2

Answer :

ST Segment : The horizontal ST segment which hugs the baseline more than 3 small squares is the earliest sign of CAD. Please note the ST segment in V4,V5,V6. ST segment is horizontal and ST T angle is very short.

Normal ST segment smoothly ascends and merges with the T wave with a gentle concavity upwards (following figure)

CAVEATS

- BRADYCARDIA
- HYPOCALCEMIA (QTc)

These conditions also may produce horizontal ST segment

The above 2 ECGs show signs of Coronary Artery Disease which is usually missed and they are subtle ECG signs of CAD.