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Research Article

Pregnancy in k/c/o SLE in remission with post renal transplant with acute graft rejection on superimposed preclampsia

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Abstract

BACKGROUND

Pregnancy with renal disease is associated with high risk for both mother and fetus with adverse outcomes. Criteria for considering pregnancy in k/c/o of SLE with renal transplanted patients include good post-transplant health for 2 years, stable allograft function with a serum creatinine <1.5 mg/dl, absence of rejection, control of blood pressure, absence of proteinuria and SLE under remission for past 6 months.

CASE

This is a case where 29yr old G2P1L1 with 26 weeks GA with SLE in remission and renal transplant recipient developed preclampsia and progressively increasing proteinuria and creatinine levels ending in acute graft rejection which was medical managed and pregnancy continued .Post natal period was uneventful and discharged on immunosuppressive therapy. With close medical and obstetric follow-up successful outcome of mother and infant is possible.

DISCUSSED AND CONCLUSION

A meticulous diagnostic approach is necessary to differentiate between lupus nephritis,preclampsia with severe features and acute graft rejection as preclampsia needs termination of pregnancy while graft rejection can be medically managed.Even with a stable graft function for 2yrs it is superimposed preclampsia that is increasing the risk of graft rejection.

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Keywords: Immunosuppressive,Acute graft rejection,lupus nephritis

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1. Introduction

BACKGROUND

Pregnancy following a kidney transplantation continues to remain challenging due to adverse effects of immunosuppressive medication,risk of deterioration of allograft function, risk of adverse maternal complications of preeclampsia and-hypertension, and risk of adverse fetal outcomes of premature birth, low birth weight, and small for gestational age .While SLE is TH2 mediated autoimmunity, in 10 to 50% of cases there is

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a risk of relapse thus making it a clinical challenge to differentiate between lupus nephritis ,severe preclampsia and acute graft rejection.1,2.

Ideal candidate for pregnancy after renal transplant are

1.sr creat<1.5mg/dl
2.proteinuria<500mg/dl
3.Normal /controlled BP
4.stable immunosuppression
5.No rejection for past 1-2yrs

maternal outcomes are LBR ~78%,preterm birth~50%,pre eclampsia ~15to 25%,PIH~70%,acute graft rejection ~8%

But in cases complicated with PIH graft rejection rate is increased.

CASE REPORT

Mrs X,29yr old,staff nurse by occupation with G1P1L0 with k/c/o SLE remission with h/o CKD 5 due to lupus nephritis with live donor kidney transplant on immunosuppresion (T.prednisolone5mg ,T.azathioprine 75mg) for booking visit at Gandhi hospital,secunderabd at 11 weeks GA .

Obstetric history:

G1: spontaneous conception at 5 yrs post -transplant

Booked at private tertiary hospital

Uneventful till 6 months gestation

At 6 months gestation-diagnosed as preclampsia with severe features

Emergency hysterotomy at 28 weeks GA for impending eclampsia with REDF ,delivered male baby of birth weight 700gms, expired on D-26 of life due to extreme prematurity.

Uneventful maternal recovery.

G2: spontaneous conception 6yrs post transplant.

Past history:

Diagnosed as SLE at 16 yrs of age,with episode of lupus nephritis landing in CKD -5,underwent live donor renal transplantation at 23yrs of age,maintaining on immunosuppressants, with no episodes of rejection and stable graft function since then

On examination:mild pallor +;PR-90bpm,BP- 120/80mmhg,CVS -normal findings,respiratory system -normal,urine proteins -ve,urine cultures - no bacterial growth.

NT scan /NB - normal,dual markers-normal ;Ut A Doppler - normal

Base line investigations-HB- 10gm/dl, Sr creatinine-1.1mg/dl,24hr UP - 111mg/dl,OGTT - Normal,ds dna +ve, LA - neg,anti RO/LA-ve,C3C4 levels-normal,ESR &CRP in normal limits

2decho-Normal,PFT -normal.

Pt started on T.ecospirin 150mg ,calcium 1.5gm /day and continued on immunosuppressants,regular antenatal visits with BPcheckups and urine dipstick for protein done

Repeat OGTT,TIFFA and fetal 2decho done at 22 weeks of GA.

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At 24 weeks GA : Pt developed BP of 150/100mg with PIH profile -normal,no proteinuria,diagnosed as GHTN and started on T,labetolol 100mg T.Regular growth scans done.

At 26 weeks GA ……..admission 1 : she developed increasing BP160/100 ,she was admitted and evaluated .
24hr UP -650mg/dl,
sr creatinine of 1.2
,SFLT/PIGF -120
,C3C4 -normal,dsdna levels in normal range .
Since lab parameters are in favour for preclampsia and chances of graft rejection are meagre she was managed as severe Preeclampsia .Antihypertensives escalated to t.labetotol 200mg TID,T.depine 10mg tid.Growth scan with Doppler showed IUGR with increased resistance in Umbilical artery ,strict fetal surveillance done,since bps were well controlled and no impending signs ,pt was advised for weekly follow ups and discharged.

At 30 weeks GA…….admission 2 :BPs we're well controlled but
pt developed increasing proteinuria ,raising creatinine levels and hematuria.
So biopsy was necessary to differentiate between,preeclampsia with renal involvement,LUPUS nephritis and acute GRAFT rejection.Biopsy showed acute B cell mediated rejection. Pt was started on bolus 500mg IV methyl prednisolone,IVIG immunoglobulins in total of 2g/kg over3 days.Renal function slowly improved over week with decreasing proteinuria and hematuria subsided and further doses were not necessary.

At 32 weeks GA :In view of REDF and DV changes , pt undertaken for EMLSCS under spinal anesthesia with precautions of stress dose of steroids;blood sugar monitoring,strict aseptic conditions and maintaining adequate renal perfusion.
Delivered a healthy female baby of btw-1.7kg with NICU admission and discharged healthy after 24days of life.

Pt continued on oral immunosuppressants and antihepertensives postnatally .Bps controlled ,proteinuria and creatinine levels normalized by 4weeks of pregnancy .

CASE DISCUSSION
Pregnancy confers a serious risk in women with moderateto severe kidney disease (defined as serum creatinine>1.3 mg/dl and >1.9 mg/dl respectively). The patientswith advanced chronic renal disease may present withhypothalamic-gonadal dysfunction leading to infertility.Due to rapid restoration of hypothalamic-pituitary-gonadal axis within 6 months after renal transplant, itbecomes imperative that contraception should be started
immediately after transplant in women with childbearingpotential.3 The best contraception has historically beenconsidered to be barrier methods, but because of potentialfor contraception failure, the American Society of
Transplantation Consensus Conference reportrecommended that transplant recipients be advised thatbarrier methods and intrauterine devices are not optimalforms of contraception. Intrauterine devices are notoptimal because they require an intact immune system forefficacy.5 Progestin-only oral contraceptives as well

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asestrogen/progestin are probably acceptable for use in thispatient population as long as hypertension is wellcontrolled.6-8 The best contraceptive agent to use aftertransplantation depends on considerations, made betweenthe patient and her physician, of the desirability of
pregnancy and considerations of the risks and benefits ofeach contraceptive method.4 The optimal timing ofpregnancy depends somewhat on individual
circumstances of the transplant recipient. Historically, therecommendation was to wait 2 years after successfultransplantation.7 This recommendation has been replacedby the American Society of Transplantation ConsensusOpinion that as long as graft function is optimal, definedas a serum creatinine <1.5 mg/dl, with <500 mg/24 hprotein excretion, and no concurrent fetotoxic infectionsor use of teratogenic or fetotoxic medications, andimmunosuppressive dosing is stable at maintenancelevels, the patient can safely proceed with the pregnancy.4
Given the increasing age of the transplant population,these recommendations might even be liberalized towaiting 6 months after transplantation in specific
situations.4,9 There have been no specificrecommendations for male transplant recipients withregard to post transplantation intervals and fathering achild.
The recommended maintenance immunosuppression inpregnant women is with calcineurin inhibitors(Tacrolimus/Cyclosporine), azathioprine, and low dose
prednisone; and it is considered safe. Sirolimus andMycophenolate mofetil should be stopped 6 weeks priorto conception.,It is recommend closely monitoring CNI(calcineurin inhibitors) levels every two to four weeks and maintaining them at the same levels as they were prior to pregnancy.

EFFECTS OF PREGNANCY ON RENAL GRAFT

In a normal pregnancy, glomerular filtration rate (GFR) increases by about 40%–60% due to hyperfiltration, vasodilation, and an increase in effective plasma flow which increases clearance of blood urea nitrogen and creatinine. During pregnancy, serum concentration of creatinine usually decreases below .8 mg/dl and blood urea nitrogen decreases below 12 mg/dl. Glomerular hyperfiltration also results in physiologic proteinuria of pregnancy.8,9,10 The kidney allograft adapts to these physiological changes of pregnancy. There is an increase in creatinine clearance by about 30% in the first trimester, a slight decrease in creatinine clearance in the second trimester, and a return of serum creatinine to pre-pregnancy level by the third trimester.12. absence of a decrease in serum creatinine in early pregnancy portends a poor prognosis and clinicians should consider careful evaluation of kidney transplant recipients whose creatinine does not decrease with expected physiologic changes of pregnancy. It has been demonstrated that among women with chronic kidney disease stages 3–5, a gestational fall in serum creatinine of <10% of the pre-pregnancy creatinine (as well as chronic hypertension, and proteinuria) were associated with adverse pregnancy and kidney outcomes (preterm delivery, low birthweight and loss of maternal kidney function). Additionally, an increase in the GFR causes physiological proteinuria of pregnancy, and women with kidney transplants have a higher 24-hour urine protein excretion as compared to healthy women. Protein excretion in pregnant kidney transplant recipients may increase up to threefold by the third trimester, exceeding 500 mg as compared to 200 mg in healthy pregnant women and returns to baseline levels by 3 months postpartum. abnormal increase in proteinuria from baseline during pregnancy in women with kidney transplant should trigger an evaluation for various causes of AKI including preeclampsia and urinary tract infection

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Among kidney transplant recipients, studies report thatapproximately 35% of pregnancies do not progressbeyond the 1st trimester due to spontaneous or

therapeutic abortion and that overall success rate is >90% after the 1st trimester.11 Most common maternalcomplication is hypertension. The prevalence ofhypertension in pregnant renal transplant patients (up to

73% in the National Transplantation Registry (NTPR),50% in Asia).

12-14 Alpha Methyl-dopa is considered thedrug of choice because of its well documented safety andlack of teratogenicity. Other antihypertensive agents

that are considered acceptable include Labetolol,Nifedipine, and Thiazide diuretics. Maternal renaltransplant patients with hypertension are at increased riskfor development of superimposed preeclampsia, with anincidence of 15 to 25% compared with 5% ofnormotensive pregnancies.Other comorbidities to beconsidered in the maternal transplant recipient includegestational diabetes,anemia, and infections such asurinary tract infections. Urinary tract infections occurin up to 42% of pregnant renal transplantpatients,although pyelonephritis is rare. The rates of pretermdelivery have been reported to beapproximately 50% inthe US and European and UK registries and even higher(64%) in recent center reports. Most deliveries occurearly because of maternal and/or fetal compromise, ratherthan spontaneous preterm labor.21

ACUTE REJECTION

Pregnancy is a state of immunological tolerance associated with decreased immune activity of lymphocytes which creates tolerance to the fetus and may benefit the kidney allograft. However, there is a possibility that the antigenic stimulus provided by the fetus may trigger graft rejection as well. Pregnancy in kidney transplant recipients poses a risk for acute rejection not only because of alterations in a previously stable immunosuppressive regimen but also due to the risk of sensitization. Gestational hypertension predisposes to pre eclampsia in 15 to 25% in renal transplant receipients while in normal pregnancies it is usually around 5%.

While In kidney transplant recipients who developed preeclampsia during pregnancy, a shorter time to graft loss and increased severe maternal and neonatal composite morbidity was observed15.In low risk pregnancies graft rejection rates are only 8%,while in pregnancies complicated by preclampsia the risk is increased.Human leukocyte antigen (HLA) allosensitization may occur during pregnancy but might not be detected since HLA antibodies are not routinely monitored during pregnancy. In the absence of risk factors, acute rejection rates are similar to the general transplant population, about 9.0% during pregnancy and 1.3% postpartum. 3 Acute cellular or antibody-mediated rejection can cause AKI in pregnancy. Rates of graft loss at 2 years postdelivery in pregnant kidney transplant recipients vary from 5% to 9%. 12 Woman' baseline calculated panel reactive antibody level or development of de-novo donor-specific antibodies, changes in dose of immunosuppression, poor medication adherence, or effect of pregnancy on

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immunosuppressive medication pharmacokinetics can predispose to acute rejection. Kidney biopsy is the gold standard for diagnosis of rejection. The availability of noninvasive biomarkers (genomic or donor derived cell-free DNA techniques) might be useful in kidney transplant recipients with advanced pregnancy or high risk for biopsy complications from a hematological perspective, however, these have not been studied in pregnant kidney transplant recipients. Third-generation genomics might be more useful compared to the cell-free DNA technique.

Diagnostic challenge is to differentiate between preclampsia vs graft rejection as preclampsia warrants termination of pregancy while cases of graft rejection can be medically managed and allowed for pregnancy continuation .Acute rejection is associated with higher creatinine levels while preeclampsia is associated with increased proteinuria.16 The sFlt-1/PlGF ratio has a very high negative predictive value in ruling out the development of preeclampsia within 7 days among women with suspected preeclampsia.17.Acute rejection in pregnancy carries a risk of prematurity and graft loss beyond that of preeclampsia for kidney transplant recipients.

MANAGEMENT OF REJECTION

While most patients are asymptomatic, presenting only with an elevation in serum creatinine and/or proteinuria, those with more serious rejection may present with fever, oliguria, and graft pain or tenderness. Occasionally, the diagnosis may be missed in patients with subtle increases in serum creatinine and/or proteinuria, which can be masked by the normal pregnancy-related changes in GFR and proteinuria. USG guide renal biopsy can be safelyl performed.

Treatment options are limited because of the potential fetotoxicity of many of the agents normally used to treat acute rejection. Augmentation of baseline immunosuppression and glucocorticoids are generally safe and are considered first-line therapy for both acute T cell-mediated (TCMR) and antibody-mediated rejection (ABMR) in pregnant recipients. In patients who are suspected of having rejection but cannot undergo a kidney allograft biopsy, glucocorticoids can be given as empiric treatment for rejection. Rabbit antithymocyte globulin (rATG), which is used to treat more severe forms of acute TCMR, is not recommended during pregnancy, as there are insufficient data regarding risk to the fetus. Patients with acute ABMR can receive intravenous immune globulin (IVIG), rituximab, and plasmapheresis, which have been used to treat pregnant patients with immune thrombocytopenia (ITP) and immune thrombotic thrombocytopenic purpura (TTP), respectively. However, there are limited data on fetal risk .12.In patients with rejection who are treated with high-dose glucocorticoids, we do not routinely give antibiotic prophylaxis against Pneumocystis pneumonia (PCP), since the risk of PCP in this setting is low and trimethoprim-sulfamethoxazole (TMP-SMX), dapsone, and inhaled pentamidine should all be avoided in pregnancy.

The doses used are as follows: IVIG for a total dose of 2 g/kg over 5–10 days, plasmapheresis for 5–6 treatments within 5–10 days And intravenous (iv) methyl-prednisolone bolus at a dose of 500 mg for 3 days.19.

In Successful treatment creatinine levels return to 25% of baseline value

CONCLUSION

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It is known that prepregnancy stable graft Function for 1-2 yrs a reduces the risk of rejection in pregnancy.But irrespective of the transplant -pregnancy interval and period of stable graft function transplant recipients who developed preeclampsia during pregnancy, a shorter time to graft loss and increased severe maternal and neonatal composite morbidity was observed. There was no difference in kidney graft survival based on a history of preeclampsia in a post-transplant pregnancy.

So irrespective of post transplant -pregnancy interval it is superimposed preclampsia that is increasing the risk of graft rejection .

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