

ANAESTHESIA FOR PARTURIENT WITH RENAL TRANSPLANT

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A successful renal transplant in women of child bearing age is on an increase in recent years. A successful renal transplantation reverses the altered reproductive and sexual function of the recipient. The resumption of regular menstruation and ovulation correlate closely with the level of function achieved by the graft (1-3). These parturients present a unique challenge with their altered physiology and immunosuppression associated with the desire to have a normal child, to the obstetrician, the nephrologist and the anaesthesiologist. The anaesthesiologist is called to meet the challenges of the management at parturition for a successful outcome. The anaesthetic management requires an understanding of the physiological changes in a post renal transplant recipient and the subsequent changes that occur as the pregnancy progresses and the challenges of the immunocompromised patient.

The immune system and the immune mechanisms preserve the integrity of the body, and protect against invasion of the microbial agents and their toxic products. The immune system composed of cells, tissues and organs is scattered through out the body. The cells of the immune system recognize and destroy invading pathogens or non-self antigens. The immune system is classified into the humoral and the cell mediated. The changes in the maternal immune status, to infection and immunization are not often seen in a clinical situation. Humoral immunity to infectious disease can be assessed by measurement of total immunoglobulin levels and by the antibody response to immunization. Levels of IgA and IgM do not change significantly in pregnancy (4) and although there is a decrease in serum IgG, this could be as a result of haemodilution or redistribution. In addition the antibody response to a variety of immunizing agents such as influenza vaccine or tetanus toxoid is normal and it appears that pregnancy does not affect the humoral immune response to infection (4).

The effect of pregnancy on the cell-mediated immunity is less clear. There is considerable evidence (5) from clinical observations that infections such as listeriosis (6), malaria (7), and coccidioidomycosis (8) in which CMI is an important means of defense are more common and/or more severe in pregnancy. These findings have not been possible to correlate with laboratory evidence of depressed CMI. Even skin testing with a variety of antigens appears to be normal, as are T4/ T8 cell count (4). Some studies have shown reduction of lymphocyte responsiveness to phytohaemagglutination, but this may be due to increased monocyte activity during pregnancy. The depression of CMI in pregnancy may be of such a degree as to increase susceptibility to infection.

The depression of the cell mediated immunity is reflected by altered lymphocyte tests, decreased T:B lymphocyte ratios, increased suppressor:helper T cell ratios, and decreased lymphocyte:monocyte ratios (9-14). There is a selective depression of cutaneous and antibody responses, including responses to specific microbial antigens(15) as are cellular mediated inflammation (16).

The immunoglobulin secreting cells increase in pregnancy, (17,18). There is a decrease in inflammatory responses, with changes in plasma protein (19) and circulating immune complexes (20-26). Pregnant patients with collagen diseases have Hypergammaglobulinemia as a feature because of diffuse immunologic B cell hyper reactivity. Normal T suppressor cells function is diminished while T helper function is increased. A variety of cytokine abnormalities involving both decreased interferon and variably altered interleukins are reported, as are reductions of leukocyte and erythrocyte membrane receptors for complement and immune complexes. Each of

the collagen disease is associated with a specific HLA- DR or B type; some of the immunological abnormalities common to the collagen disease themselves may be HLA linked (27).

Clinically measured complement reflects the balance between synthesis and consumption of rate limiting complement components (28-32). In an uncomplicated pregnancy total C3, C4 and CH50 are normal or raised relative to normal non-pregnant states. The normal values in pregnancy of C3, C4 and CH50 are 80 to 120mg/dl, 15 to 50mg/dl, 150 to 300 units/ml respectively. This may be elevated to 200mg, 75mg, or greater than 300units/dl respectively. The normal clinical values imply increased synthesis of complement components. Patients with collagen disease in non-pregnant states, have activation of both the classic and the alternative complement pathways with decreased synthesis of complement components. Pregnant patients with collagen disease are often hypocomplementemic as in pre-eclampsia.

The immunosuppression in a pregnant woman can be the result of **physical** (stress), **chemical** (Corticosteroids, Anaesthetic agents- Nitrous Oxide, Isoflurane, Morphine), and **biological agents** (Pregnancy).

Renal Hyperfiltration

In normal pregnancy GFR increases by 30-50% during the first and second trimester and decreases during third trimester. Theoretically this additional hyperfiltration of pregnancy predisposes the patient to loss of renal function.

The transplanted kidney in the recipient also undergoes a process of hyper filtration. This is a maladaptive response that attempts to bring the glomerular filtration rate (GFR) toward the rate of nephric system. In the long term this hyperfiltration may lead to glomerular sclerosis and loss of renal function if it is associated with increased glomerular or capillary pressure (33).

Baylis et al (34,35) demonstrated, that the gestational hyperfiltration is not associated with increased glomerular pressure, because of matching afferent and efferent arteriolar vasodilation. They also demonstrated that glomerular pressure is lower in female rats than in male rats, 10 months after uninephrectomy. Hakim et al showed this gender advantage is present in humans also (36).

Effect of Pregnancy on the Renal Allograft

Pregnancy does not cause irreversible decline in renal function or affect the natural history of the allograft (37,38). Although Whetam et al showed that pregnancy had no effect on graft survival or function (39), the risk of graft rejection increases if there is preexisting renal insufficiency. A study at the Royal Hospital showed a 12% (n= 8) rejection of the allograft in 32 women who conceived after the transplant (personal communication). In a long term follow up of 36 renal transplant recipients, Sturgist and Davison (40) reported, that there was no significant difference between the pregnant and non pregnant group over the graft loss or chronic rejection over a mean follow up period of 12 years. The study at the Royal Hospital (personal communication) had three rejections in the antenatal period, three in the 6 weeks of the postnatal and two rejections after two years of childbirth.

In most women the allograft function is enhanced during early pregnancy and deteriorates briefly during late pregnancy. Only 15% of the parturients experience persistent renal impairment (41). In others, there may be transient deterioration in late pregnancy with or without proteinuria. It is also believed that every pregnancy reduces the renal function by about 15-20%. Hence it is often advocated that the number of pregnancies be limited to one or two for the fear of persistent renal impairment. However, the study at the Royal Hospital had five multiparous women with three of them having four, one had five and one with six pregnancies respectively with no deterioration in renal function (personal communication).

Effect on Foetus

Despite the effect of pregnancy on allograft being minimal, the associated foetal outcome is less favourable. 45% of the 22 pregnancies progressing beyond 28 weeks gestation have adverse perinatal outcome (42). Early onset of hypertension (before 28 weeks) have adverse outcome, even if it is treated. Chronic hypertension may lead to microvascular changes that compromise uteroplacental circulation. Creatinine clearance seems to be an important parameter influencing the effect on the foetus. The Royal Hospital study showed that creatinine clearance of less than 150mmol/min had better foetal outcome (personal communication).

A reasonable guide of the renal function of the parturient with renal transplant for a successful outcome is:

1. Good general condition for 2 years after transplantation
2. Stature compatible with good obstetric outcome
3. No proteinuria
4. No significant hypertension
5. No evidence of graft rejection
6. No evidence of pelvicalyceal distension on a recent excretory urogram
7. Plasma creatinine of 180mmol/L or less
8. Drug therapy- prednisolone.15mg/day or less and azathioprine 2mg/kg/day or less

Despite the advise that pregnancy is to be avoided for a period of two years after renal transplant, the survey at the Royal Hospital in Oman revealed that the earliest pregnancy was at 2months post renal transplant, although the mean period for conception was 14.4months (range 2 - 45 months) and included 76 pregnancies.

Despite transplacental exposure to immunosuppressive drugs, congenital anomalies and other adverse effects are infrequent. Azathioprine may give rise to neonatal leucopenia and thrombocytopenia unless the maternal leucocyte count is maintained at or above 10000cells/mm³ (43). Cyclosporine A has been associated with IUGR (44).

Transplant recipients may become infected with cytomegalovirus (CMV) at the time of transplantation or may get reactivated secondary to immuno suppression. Active CMV infection during pregnancy is associated with congenital anomalies and in neonate may lead to death.

The immunosuppressants such as prednisolone, azathioprine, cyclosporine are to be continued during pregnancy for fear of acute rejection of the transplant unless toxicity results. Cyclosporine requirements increase during pregnancy possibly because of enhanced metabolism (45).Recent recommendation of a single immunosuppressive therapy to the recipient is thought to decrease the incidence of graft rejection and needs further study.

Anaesthetic Management

Anaesthesia and Immune System

Exposure to anaesthesia and surgery alters many facets of immunocompetence (46). Depression of immune system by anaesthesia could increase the likelihood of the development of postoperative infections or of augmentation of a co-existing infection. Exposure to anaesthesia and surgery depress both T cell and B cell responsiveness, as well as nonspecific host resistance mechanisms, including phagocytosis (47).

Various anaesthetic drugs depress immune system. There is evidence that local and inhaled anaesthetics (nitrous oxide) produce dose dependent inhibition of mobilization and migration of polymorphonuclear leukocytes necessary for phagocytosis (46,48). But the effects produced by these drugs are probably clinically insignificant considering the usual duration of anesthesia and doses of drugs administered. The effects are transient and may be modified by various other factors during the perioperative period.

The anaesthetic drugs possibly have bacteriostatic effects. Local anaesthetics have been shown to have such effects on a wide variety of organisms at concentrations achievable with topical application (48). Conversely, concentrations of local anaesthetics in the circulation, in association with regional anesthesia or after intravenous administration, do not have bacteriostatic effects (49). Liquid volatile anaesthetics in doses as low as 0.2 MAC produce dose dependent inhibition of measles virus replication and reduce mortality in mice receiving intranasal influenza virus (49).

Immune competence during surgery can be affected by direct and hormonal effects of anaesthetic drugs, immunologic consequences of other drugs used, type of surgery and coincident infections. Although multiple studies demonstrated the invitro alterations of immune function, no studies have ever demonstrated the actual importance (47). The alterations are likely of minor importance when compared with the hormonal aspects of stress responses.

The incidence of postoperative infection seems to be related to surgical trauma and to an associated release of cortisol and catecholamines that are well known to inhibit phagocytosis. In the absence of surgical stimuli the anaesthetic drugs are not known to increase the circulating levels of cortisol or catecholamines. The present opinion is, that effects of anaesthetics on resistance to infection are transient, reversible, and of minor importance, unlike the prolonged immunosuppressive effects of cortisol and catecholamines released as part of the hormonal response to surgery (46). This hormonal response is mediated through the sympathetic nervous system.

The attenuation of the Sympathetic nervous system stimulation is desirable during surgery. This can be achieved by deepened plane of anaesthesia. A light plane of anaesthesia is not advocated during surgery. Unfortunately majority of the parturients in the early part of the caesarian section surgery are administered a light plane of anaesthesia due to the fear of the neonatal depression. Evidence suggests that about 1.5 MAC halothane or enflurane or greater than 1mg.-1 of morphine is necessary to prevent the sympathetic nervous system response to surgical skin incision in 50% of patients (50). Since the use of narcotic is not advocated prior to the delivery of the foetus, for the fear of neonatal depression and poor APGAR scores, the use of volatile anaesthetic agents can be an alternative under general anaesthesia. One has to consider the fact that high concentrations of volatile anaesthetic agents may have a tocolytic effect and contribute to the development of an atonic uterus after delivery. This was especially thought with the use of ether and halothane. The same may not be true with the use of isoflurane and sevoflurane. Regional anaesthesia may reduce the hormonal response to surgical stimulation (49).

Despite these observations there is no evidence that the incidence of postoperative infection can be altered by the depth of anesthesia or by the techniques selected to produce anaesthesia.

Preoperative Assessment

The preoperative assessment of these immunosuppressive patients should have an initial laboratory study that includes complete blood count, renal function test, serum electrolytes, blood glucose, viral serology for CMV, Hepatitis B Virus, Hepatitis C Virus, and HIV and coagulation profile. It is necessary to ascertain the availability of adequate amount of blood before the procedure.

Pregnancy induces changes in the coagulation systems (51-53) such as a decrease in the life span of the platelets. This is not apparent in a normal pregnant woman as an increased production of platelets maintains the peripheral platelet count. Pregnant patients with collagen diseases may manifest thrombocytopenia, an event that also occurs commonly in preeclampsia, abruptio placenta, amniotic fluid embolism and intrauterine foetal demise. Therefore the cause of decreased platelet count may be difficult to define.

Transplant patients may have pelvic osteodystrophy related to their previous renal failure and dialysis or protracted steroid therapy, particularly if it occurred before puberty (54). The incidence of avascular necrosis of the femoral head is about 20% in transplant patients (55).

Some of the patients may have diabetes mellitus (either steroid induced or NIDDM). In such cases a very strict diabetic management protocol is needed, because of the increased complication rate by two fold than that in other pregnant renal allograft recipients (56,57). This may be secondary to cardio vascular system (CVS) changes accompanying diabetes.

It is believed that every pregnancy may reduce the renal function by 15-20%. Hence it is essential to be cautious in dealing with a multiparous recipient. In the absence of renal dysfunction or hypertension anaesthetic management is similar to that in the normal parturient, except that prophylactic antibiotics and stress dose steroids are indicated. In all patients with renal transplant, strict aseptic precaution should be maintained during the intra vascular access and also while performing regional techniques. In the presence of renal dysfunction or hypertension one should be cautious in administration of regular dose of narcotic analgesic during the peri operative and postoperative periods. There may be an increased sensitivity to noxious stimulus and report more pain than non-transplant pregnant patients.

General Anaesthesia

General anaesthesia may have to be administered to patients including patients with PIH, if there is no acceptance for regional techniques due to local cultural influence and lack of education (personal experience). This may expose the patient to an increased risk of morbidity and mortality. There was a 8% incidence of Pregnancy induced hypertension at the Royal Hospital.

The anaesthetic management should consist of preanaesthetic evaluation of the biochemical parameters for the renal, and liver functions, with cardiovascular evaluation and pharmacotherapeutic status. It is advisable to administer all patients a gastropropulsive, and a H2 blocker as premedication on the previous night and 90 minutes before surgery. It is prudent to continue the morning doses of antihypertensives, steroid and the immunosuppressive drugs on the day of surgery. Despite the surgery being a planned one, the need for crash induction of anaesthesia is mandatory and is advisable to use short acting muscle relaxant followed by orotracheal intubation. The maintenance of anaesthesia can be with Nitrous oxide: Oxygen and atracurium/ cisatracurium along with a volatile agent. The narcotic analgesic is to be used intraoperatively after the birth of the child. It is advisable to use the tocomimetic drug such as pitocin (Syntocinon) as an infusion rather than the ergot alkaloid to prevent the hypertensive response after the delivery of the baby.

Regional Anaesthesia

Neuraxial blocks are not a contraindication. The use of xylocaine with adrenaline in the epidural space is not a contraindication. The use of a narcotic such as fentanyl in the epidural space is better than morphine, because of the rapid onset, increased duration and absence of delayed respiratory depression. (58). The presence of an epidural catheter in the postoperative period for the first 24-48 hrs has been beneficial with no untoward effect. The use of subarachnoid injection, or combined spinal epidural techniques may not be the best of options in these immunocompromised parturients.

The intraoperative monitoring should consist of noninvasive/invasive blood pressure, ECG, SaO₂, and ETCO₂.

Supplemental oxygen in the postoperative period is mandatory.

Caesarian sections are purely necessary from the obstetric reasons. Caesarian sections are also indicated in those with genital herpes simplex virus infection. There is an incidence of 25 percent caesarean section rate, which is much higher than expected, presumably reflecting fear of the unknown, rather than that vaginal delivery would be hazardous for mother and or child. The incidence for Caesarian section at Royal Hospital was 33%. When a caesarean section is done, lower segment approach is usually feasible but previous urological surgery may make this difficult (59). Care must be taken that the ureter and or the graft blood supply are not damaged or compromised. The position of the kidney does not obstruct the normal vaginal delivery, and 50% of women have normal delivery.

In conclusion a clear understanding of the physiological changes secondary to the renal transplantation and the changes brought about by the pregnancy on the renal recipient would contribute for the safe management of the parturient.

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