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# **Pregnancy Post Transplant**

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Rubina Naqvi

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## **1. Introduction**

Be a mother is natural desire in female belonging to any community world over. In most cultures, pregnant women have a special status in society and receive particularly gentle care. At the same time, they are subject to expectations that may exert great psychological pressure, such as having to produce a son and heir, and some societies increase female population to fulfill this demand. Rate of ovulation and thus fertility is decreased in female with end stage renal disease, even if pregnancy occurs in dialysis population, only about 23 % were successful till 1980s (European registry). Whereas, after successful renal transplantation not only fertility rate increases with reemergence of better ovulation, but rate of successful childbirth also increases to 70- 80 % (Naqvi 2006,Thompson 2003).

In this chapter, we aim to review the course of pregnancy and its outcome in renal allograft recipients, in backdrop of different social and cultural values, which we face in this part of world.

## **2. Status of pregnancy related issues in country**

The 2006-07 Pakistan Demographic and Health Survey (PDHS) was undertaken to address the monitoring and evaluation needs of maternal and child health and family planning programs. In 1992-96 marital fertility; reported as 7.6 children per married woman, with a decline of one child over the past decade, PDHS data 2006-2007 reports 6.6 children per married woman. Eight percent of ever-married women report that they had a miscarriage in the past five years; about 2 percent said they had an abortion, and 3 percent reported having a stillbirth. For the most recent five-year period preceding the survey, infant mortality is 78 deaths per 1,000 live births. In interpreting the mortality data, it is useful to keep in mind that sampling errors are

quite large. For example, the 95 percent confidence intervals for the under-five mortality estimate of 94 per 1,000 are 86 and 103 per 1,000 indicating that, given the sample size of the 2006-07 PDHS, the true value may fall anywhere between 86 and 103 per 1,000 births. As observed in most studies, the mother's level of education is strongly linked to child survival. Higher levels of educational attainment are generally associated with lower mortality rates because education exposes mothers to information about better nutrition, use of contraceptives to space births, and knowledge about childhood illness and treatment. Similarly, childhood mortality rates decline as the wealth quintile increases. Only 34 percent of births in Pakistan take place in a health facility. Eleven percent is delivered in a public sector health facility and 23 percent in a private facility. Three out of five births (65 percent) take place at home. (Pakistan Demographic and Health Survey 2006-07, National Institute of Population Studies Islamabad, Pakistan. Macro International Inc. Calverton, Maryland USA, published June 2008)

The incidence of low birth weight (defined <2.5 Kg by WHO) in general population reported as high as 31% from South Asia (Badshah, 2008) and 33.9% reported from West Bengal, India. (Pahari 1997)

### 3. Status of renal transplant in country

The incidence of ESRD in Pakistan and neighboring country India would be expected to be higher since poor socioeconomic status predisposes the population to a number of infection-related glomerulonephritides and the incidence of nephrolithiasis is higher in both countries as they fall in a "stone belt." (Sakhuja, 2003) In addition 6.9 million people in country are affected by diabetes with the International Diabetes Federation estimating that this number will grow to 11.5 million by 2025. With low literacy rate and poor health facilities complications and end organ failure with diabetes and hypertension are more prevalent. If the incidence of ESRD is indeed 100 patients per million population per year, this would mean 18,000 patients for a population of 180 million in Pakistan. There are very few state run dialysis centers and most of them are small units with minimal care facilities, < 5 dialysis stations. The number of patients maintained on dialysis is likely to be < 50 patients per million population since few patients can afford this form of therapy. Sindh Institute of Urology and Transplantation (SIUT) is a semi government organization in country which cater largest population of patients suffering from any kind of kidney ailment. It is running largest hemodialysis and live related renal program not only in country but the region. This organization is unique in terms of providing free health care services to all, be it pre operative preparation, surgical procedure, life long follow up and immunosuppression. ([www.siut.org](http://www.siut.org)) Because of lack of state provided health facilities number of patients seen and treated at this hospital is beyond imagination and for same reason patients do comply during follow up and long term data from this institution is more reliable and representative.

Renal transplant started in country in 1979 from living related donors, initially the activity was as low as < 50 /year, which rose to about 2500 kidney transplants / year in 2007. Most of these were unrelated donor transplants done at private sector. In March 2010 Pakistan was fortunate

to have been able to pass a viable and authentic transplant law and activity of unrelated donor transplant decreased. Deceased donor transplant yet has to take off in country, though few have been done from non heart beating donors, organs supplied by Euro-transplant foundation and five local deceased donors.

#### **4. End Stage Renal Disease (ESRD) affecting fertility**

Female with ESRD have hypothalamic-pituitary-gonadal dysfunction, associated with high follicle stimulating hormone, luteinizing hormone and prolactin levels. Ovulation is suppressed and menstruation is irregular. Additionally there is sexual dysfunction, suppressed desire and associated psychological factors resulting from chronic ailment. Women on dialysis if conceive present with challenges of worsening of blood pressure controls and anemia, and higher incidences or pre-eclampsia. In 1980, the European Dialysis and Transplant Association reported that only 23% of 115 pregnancies in dialysis ended with surviving infants (European Registry). In 1998, Bagon et al. described a national survey showing a successful outcome in approximately half of the pregnancies in dialysis patients. There are few case series in the new millennium, mainly from single experienced centers, many of which report a successful outcome rate of >70% (Romao 1998, Barua 2008). Our own experience is limited with very poor outcome. (Unpublished)

#### **5. Pregnancy post transplant**

Reversal of normal endocrine function has been reported within 4-6 months after renal transplantation. (Ha 1991, Ghafari 2008, McKay 2008) Thus kidney transplant offers best hope for ESRF patients who keen to conceive. First pregnancy in renal transplant recipient was reported by Murray in 1963, since then there are many published reports focusing on impact of pregnancy on renal graft outcome with a conclusion that pregnancy does not have an adverse effect on graft function provided recipient has stable graft function and no adverse event happens during pregnancy. (Table)

#### **6. Optimal timing for pregnancy post transplant**

Most transplant centers advise that women can conceive after 2 years of transplant provided graft function is stable i.e. serum creatinine is < 1.5 mg/dl and proteinuria <500 mg/day. At that time, risk of acute rejections generally low, immunosuppression has reduced to minimal, prophylactic anti bacterial and anti viral already completed and women are usually stable. All pregnancies should be considered as high risk and should be managed by multidisciplinary team.

Author	year	Duration	Country	No. of pregnancies reported	outcome
Cararach	1993	25 years	Spain	133	Abortions 10% Preterm 46% Full Term 53%
First	1995	23 years	USA	25	Abortions 3 Live births 22
Saber	1995	25 years	Brazil	25	Abortions 4 Preterm 14 Full term 7
Sturgiss	1996	23 years	UK	18 (compared with 18 non pregnant controls)	Long term graft survival compared in two groups.
Tan	2002	14 years	Singapore	42	Abortions 10 Still birth 1 Ectopic 2
Armenti	2004	14 years	USA NTPR	1125	Abortions 20% Still births 2.5% Ectopic 1% Premature births 53%
Kashanizadeh	2007	6 years	Iran	86	Abortions 24 Full term 62
Sibanda	2007	7 years	UK Transplant Pregnancy Registry	193	Abortions 32 IUDs 3 Ectopic 1 Live Births 149
Draihimh	2008	10 years	5 Middle East Countries	234	Abortions 19.3% Still births 7.3% Live births 74.4%
Naqvi	2010	24 years	Pakistan	68	Abortions 15 Preterm 8 Full term 45 (40 live, 5 IUD or FSB)

**Table 1.** Published results from world over

## 7. Risks for mother

Mothers who are renal transplant recipient have certain risks on graft function and survival. Many of renal transplant recipients have hypertension and some degree of renal dysfunction with GFR (Glomerular filtration rate) of not up to the mark, both are affected with pregnancy and blood pressure medications may require alterations and increment in dosages. Some may predispose to pre-eclampsia which is difficult to diagnose especially when few of these women already have some preexisting proteinuria and blood pressure frequently increases after 20<sup>th</sup> week of gestation. Poorly controlled hypertension can cause preterm delivery.

Women with preexisting graft dysfunction i.e. serum creatinine of > 1.5 mg/dl are at greater risk of developing irreversible worsening of graft function. (Davison 1976) Acute rejection can also occur as blood levels of immunosuppressant may alter with changing volume distribution during pregnancy, this phenomenon is more relevant with calcineurin inhibitors. (Donaldson 1996) However, available reports indicate that rejection rate in pregnant recipient not differ from non pregnant recipients. (Armenti 2004) In our experience of 68 pregnancies in renal transplant recipients, none experienced acute rejection during pregnancy. (Naqvi 2010)

Urinary tract infection rate also increases in pregnant renal transplant recipients, some have reported as high as 42%. (Oliveria 2007)

The transplant recipient is at increased risk for viral infections, therefore, maternal–fetal transmission of infectious agents needs to be considered as a potential risk not only to the mother but also to the fetus. Cytomegalovirus infection is particularly serious because it is associated with hearing/vision loss and mental retardation and can be transmitted from the mother to the fetus through a trans-placental route, as well as during delivery or in breast milk in case mother is feeding to infant. (del Mar Colon 2007, Ross 2006)

Other infections that may pose additional risks in the immunosuppressed mother include toxoplasmosis, primary herpes simplex infection, primary varicella infection, HIV infection, and infection with either hepatitis B or C virus (Gardella 2007, Shiono 2007)

As allograft recipients have increased risk for gestational diabetes, some have recommended that they should be screened every trimester with a 50-g oral glucose load. (del Mar Colon 2007)

## 8. Risks to fetus

Published reports from UK, USA and European registries persistently highlighted risk of low birth weight of fetus and pre term delivery in renal transplant recipients. (Sibanda 2007, Armenti 2004) Willis et al from Australia reported 44% with low birth weight. (Willis 2000) In our experience we found mean birth weight infants born to transplant recipients was  $2.4 \pm 0.57$  Kg, with 7 newborns <1.8 Kg. (Naqvi 2010)

Exposure to immunosuppressants: Adrenal insufficiency and thymic hypoplasia have occasionally been described in the infants of transplant recipients, but these problems are unlikely



if the dose of prednisone has been decreased to 15 mg (Penn I, 1980). Prednisolone traverses the placenta but 90 % of maternal dose is metabolized within the placenta and not reaching to fetus (Blanford 1977). In addition if pregnancy is occurring after 2 years of transplant, recipient already on very small dose of Prednisolone. Steroids can also aggravate hypertension in mother; mothers are more prone to infections if steroid dose is still high at time of conception. Premature rupture of membrane is another complication reported in relation of steroids. Therefore, it is recommended to get conceive when steroid dose is reduced to minimal. Reports from azathioprine era through cyclosporine era have not identified specific malformations among infants born to transplant recipients (Armenti 2000). Radioactive labeling studies in humans have shown that 64–93% of Azathioprine administered to mothers appears in fetal blood as inactive metabolites (Sarikoski S, 1973). Cyclosporine metabolism appears to be increased during pregnancy and higher doses may be required to maintain plasma levels in the therapeutic range (Muirhead N, 1992). Data concerning the effect of tacrolimus on pregnancy is scarce. A report of 100 pregnant women (which included all organ transplant recipients), among 84 treated with tacrolimus, 68 progressed to a live birth, with 60% of deliveries being premature (Kainz A, 2000). Teratogenicity of mycophenolate mofetil is not yet confirmed, therefore it is recommended to switch over to azathioprine in female who are planning to conceive. A study has reported low number of T and B cells at birth in infants born to mothers who were on immunosuppressants, but these were normalized after few months. (Di Paolo 2000) Most published studies related to subject have not described clear cut congenital malformations or autoimmune disorders to children born to transplant recipients, though sporadic case reports which could be related to exposure risk of disease in general population.

## 9. Breast feeding by transplant recipients

Sparse data is available on recommendations for breast feeding from immunosuppressant mothers. Study published on cyclosporine levels in breast milk reveals cyA levels in milk equivalent to mother's serum. (Moretti 2003) This leads to conclusion that females who are on cyclosporine should not feed their babies, whereas the fact that small amounts of azathioprine and Prednisolone are excreted in milk (Coulam 1982) can provide an opportunity to consider feeding those babies whose mothers are on these two agents only. French et al. reported the first case of measurement of tacrolimus levels in human milk; suggest that maternal therapy with tacrolimus may be compatible with breast-feeding. (French 2003). Level of Tacrolimus was calculated in breast milk in this case but this was single case report. Data on other drugs is still lacking.

## Recommendations

1. preconception counseling is a must
2. good general health for about 2 years after transplant

3. stature compatible with good obstetric outcome
4. no or minimal proteinuria
5. no hypertension or well controlled blood pressure on one agent
6. consider revising anti-hypertensive regimen when pregnant
7. no evidence of recent graft rejection
8. stable graft function with serum creatinine less than 1.5 mg/dl
9. drug therapy at maintenance levels
10. switch immunosuppressants to milder, e.g. MMF should be converted to AZA, Tacrolimus to CyA and Prednisolone in minimal doses
11. once pregnant, transplant recipient should be seen by multidisciplinary team with a frequency of 4 weeks during first trimester and 2 weeks later on.

## Author details

Rubina Naqvi\*

Nephrology Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan

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