27

Preconceptional optimization in the solid organ recipient

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INTRODUCTION

Impaired fertility is common in women with end-stage organ disease. Amenorrhea occurs in approximately 50% of patients with chronic liver disease[1], and in many women with advanced chronic kidney disease (CKD)[2]. Abnormalities of the hypothalamic–pituitary axis and hormonal abnormalities are commonly implicated. In women with end-stage renal disease (ESRD), subfertility may also occur due to hypothalamic–gonadal dysfunction[3]. For women with liver disease, menstrual dysfunction may be linked to the etiology of the underlying liver disease[1]. Pregnancy is an uncommon event in women with advanced CKD; each year pregnancy only occurs in 0.5% of women of childbearing age treated with dialysis[4]. Despite this, unplanned pregnancies do occur, and all women of childbearing age with end-stage organ disease should be provided contraceptive advice.

Following organ transplantation, fertility in women of childbearing age is usually swiftly restored, typically within 6 months[5]; for many young women with end-stage organ disease, transplantation offers the best chance of a successful pregnancy. The first successful pregnancy following renal transplantation was reported in 1958[6] and after orthotopic liver transplantation in 1978[7]. Since then, successful pregnancies have been reported in recipients of lung, heart and pancreas-liver transplants. Today approximately 2% of women of childbearing age with a renal transplant become pregnant[9], and the literature now contains reports of over 14,000 pregnancies worldwide[8]. The US National Transplantation Registry reported that more than 70% of post-transplant pregnancies result in a successful live birth[9].

Despite good pregnancy success rates, women with solid organ allografts are at increased risk of complications during pregnancy including hypertension, pre-eclampsia, preterm delivery and infection[1,10]. Because some immunosuppressive agents and other medications commonly used in transplant recipients are contraindicated in pregnancy, these issues merit discussion with women of childbearing age. Ideally such discussions should occur prior to transplantation in order for pregnancy to be planned at the optimum time in terms of maintaining good graft function and minimizing the likelihood of complications to mother and baby.

OPTIMAL TIMING OF PREGNANCY AFTER TRANSPLANTATION

Restoration of fertility, and hence the ability to conceive, usually occurs fairly rapidly following successful organ transplantation[8]. The recovery of fertility is less common in women who undergo transplantation towards the end

of their childbearing years[11], and irregular menstrual bleeding remains a major concern of women with a renal transplant. In one study of 114 patients, although 49% had normal menstruation, another 31.2% had oligomenorrhea, hypomenorrhea or amenorrhea[12]. In the early post-transplant period, pregnancy is less likely to be successful when the degree of immunosuppression and the risk of acute rejection and infection all are generally highest. It is therefore important that appropriate contraceptive advice be given to women prior to organ transplantation. Although the choice of contraceptive method is essentially arbitrary, many physicians prefer long-acting forms of contraception to ensure adequate protection[8]. Intrauterine devices are less likely to be effective in patients taking immunosuppressive agents because their efficacy depends on intact immunologic function[13]. They may also increase the risk of intrauterine infections[10].

Historically, most transplant centers have advised that pregnancy is safe after the second post-transplant year, providing that the graft is functioning well. For renal transplant recipients, this typically means a serum creatinine of less than 133 μmol/l (<1.5 mg/dl) and urine protein excretion of less than 500 mg/day[14]. In 2003, a consensus conference held by the Women's Health Committee of the American Society of Transplantation (AST) concluded that pregnancy is probably safe after the first transplantation year, providing that allograft function is stable and no episodes of rejection have occurred in the year preceding conception[15]. At this point the patient is usually stable, the risk of an acute rejection episode is generally low, immunosuppressive medication will have been reduced, and viral prophylaxis will have been completed[8].

Specific guidelines for recipients of other solid organ transplants regarding allograft function prior to conception are lacking[9]. Cardiac transplant recipients are advised to avoid pregnancy for at least 1 year post-transplantation and preferably 2 years[16]. For recipients of lung transplants, most expert opinion in published series recommends waiting at least 2 years before conception[17]. Acute rejection is common in the first year, with over 50% of patients requiring treatment. Two years after lung transplantation, however, the risk of acute rejection is reduced, and as with other solid organ transplants recipients, patients will be maintained on lower doses of immunosuppression[18].

The optimal timing for a pregnancy for a woman with a solid organ transplant is probably somewhere between 12 months and 5 years post-transplant[19]. In addition to stable graft function and absence of recent rejection episodes, immunosuppression should be at stable dosing, and acute infections which might affect the fetus should not be present (see Figure 1). A number of special circumstances can affect adherence to the published recommendations[15], including maternal age, medical noncompliance and additional comorbidity factors that may impact on graft function and pregnancy. On the occasions when women who do not fulfil the recommended criteria regarding timing of pregnancy choose to become pregnant or accidentally conceive, such cases must be assessed on an individual basis.

Any pregnancy in a solid organ transplant recipient should be considered high risk. The expectant mother should be managed by a multidisciplinary team including her transplant physician and an obstetric specialist with expertise in this field, and should be monitored on a frequent basis[20]. Particularly close surveillance is recommended for diabetic women with renal allografts, because complications are more frequent in this group[10]. Following a successful pregnancy, both allograft function and levels of immunosuppressive drugs require close monitoring; regular postpartum follow-up should be ensured.

Some transplant recipients desire more than one pregnancy. In this eventuality, it is important that the entire clinical picture be reassessed prior to each pregnancy, i.e. graft

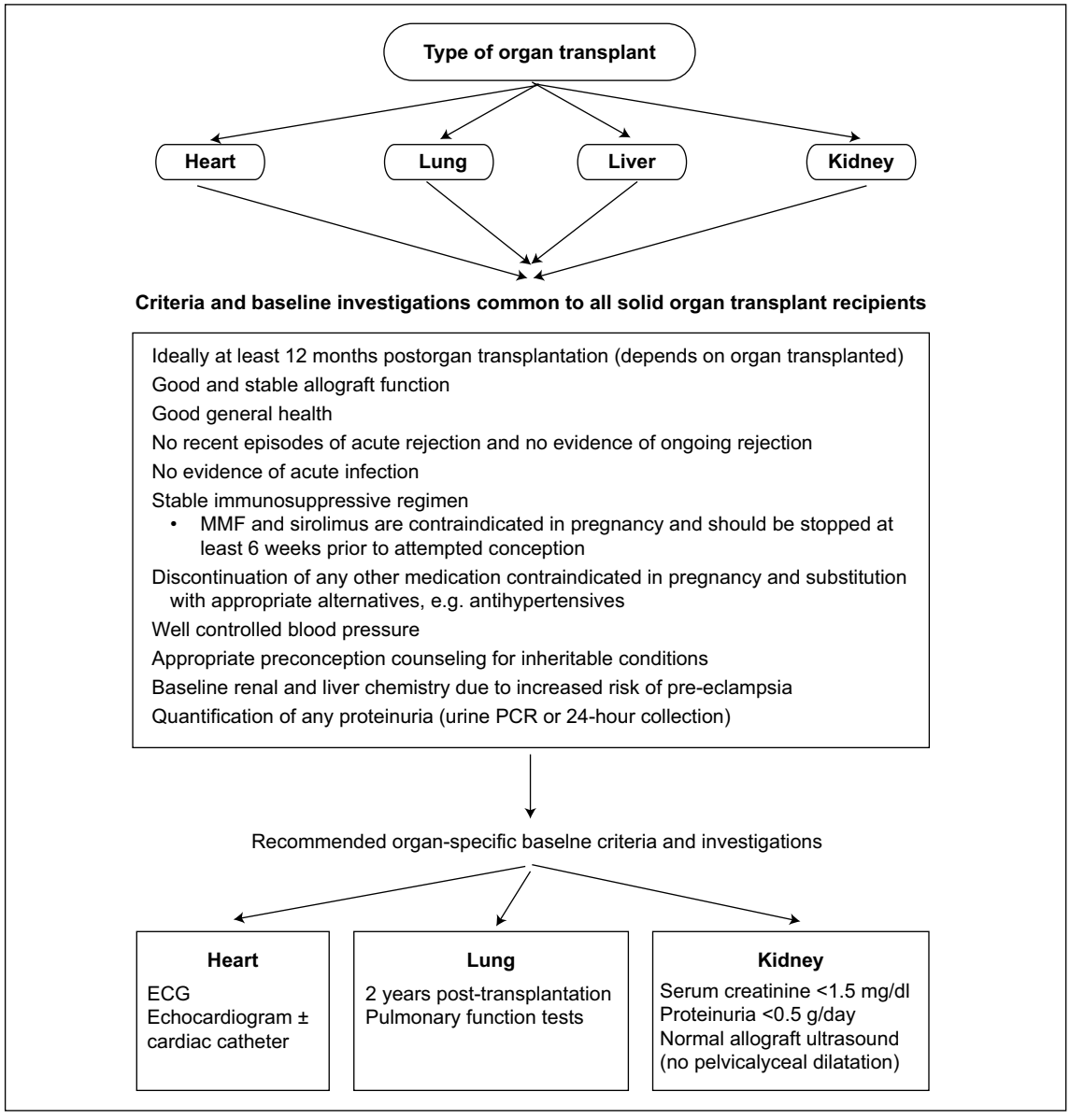

Figure 1 Criteria for considering pregnancy in solid organ transplant recipients. MMF, mycophenolate mofetil; PCR, protein to creatine ratio; ECG, electrocardiogram

function, hypertension, renal dysfunction and proteinuria, and that the risks posed by any new medical problems be assessed. Evidence from the European Dialysis and Transplant Association (EDTA) registry shows that further pregnancies do not adversely affect graft function provided that graft function is good at the onset of each pregnancy[21].

PRECONCEPTION COUNSELING

Preconception counseling, preferably offered by a multidisciplinary team including obstetricians, transplant physicians, midwives, pharmacists and other health professionals, should be offered to the solid organ transplant recipient and her partner, ideally prior

to transplantation[1,10,17]. All patients should be offered contraceptive advice. Any patients hoping for a future pregnancy should be counseled about the potential risks of pregnancy to the mother and child, timing of pregnancy and, if appropriate, alternative options.

Solid organ transplant recipients who have difficulty conceiving naturally are likely to seek access to assisted reproductive techniques such as ovulation induction, *in vitro* fertilization and embryo transfer[19]. In one study of 126 Iranian renal transplant recipients, the rate of infertility (10.4%) was similar to that of the general population[22]. There are case reports of successful *in vitro* fertilization in female renal transplant recipients[23,24] and also of intracytoplasmic sperm injection for male renal transplant recipients with infertility[25].

BASELINE PRECONCEPTION ASSESSMENT IN THE ORGAN TRANSPLANT RECIPIENT

For recipients of cardiac transplants, a number of baseline tests are required to assess cardiac status prior to pregnancy. All patients should have an electrocardiogram and an echocardiogram[17]. Some experts advocate coronary angiography (to exclude allograft coronary artery disease), right heart catheterization and cardiac biopsies, but these tests may not be required if the patient is stable from a cardiovascular point of view. Likewise, pulmonary function should be assessed with appropriate tests in the lung transplant recipient, and most experts recommend that spirometry should be performed regularly during the pregnancy[26,27]. Patients with a renal transplant should have an ultrasound of the allograft to ensure there is no pelvicalyceal dilatation[14].

It is not uncommon for recipients of both lung and heart transplants to have a degree of renal dysfunction which requires assessment prior to conception. Renal chemistry should be checked, and proteinuria quantified by either a urine protein to creatinine ratio (PCR), or a 24 hour urine collection[17]. Given the increased risk of pre-eclampsia in this group of patients, baseline liver chemistry should also be checked so comparison can be made to assist with diagnosis if pre-eclampsia is suspected[17]. Figure 1 summarizes the baseline and organ-specific investigations which should be undertaken when pregnancy in solid organ transplant recipient is being considered.

SPECIAL CIRCUMSTANCES

The underlying reason for organ transplantation may have implications for the pregnancy and well-being of the fetus[17]. A number of renal diseases have a hereditary component, and women need to be informed on how their kidney disease may affect their child. Vesicoureteric reflux (VUR) is one such condition and, in many cases, is probably inherited in an autosomal dominant manner. It is commonly diagnosed in pregnancy when often previously asymptomatic women develop recurrent urinary tract infections, hypertension and proteinuria[28]. Women with VUR must be advised that their child may inherit the same condition. If the maternal diagnosis is known during the pregnancy, antenatal ultrasound may be used to look for the typical changes of reflux nephropathy in the fetus[29]. Patients with adult polycystic kidney disease (APKD) or a family history of Alport's syndrome can be referred for genetic counseling[28].

For women whose underlying liver disease was caused by a genetic disorder such as alpha-1 antitrypsin deficiency and hemochromatosis, or even rarer conditions such as Alagille syndrome and Caroli syndrome, genetic counseling should be offered. Prenatal testing may be available for certain conditions[1].

Lung transplant recipients who had cystic fibrosis (CF) prior to transplantation should be offered genetic counseling as recommended by the American College of Obstetricians

and Gynecologists (ACOG)[30]. Their partners should be offered carrier testing to determine the risk of CF in any future offspring.

For patients who underwent cardiac transplantation due to peripartum cardiomyopathy (PPCM), there is a theoretical risk of recurrent PPCM. Some published case reports have not demonstrated any evidence of disease recurrence; however, the number of cases reported is currently too small to draw any conclusions[17].

For women with congenital heart disease the risk of recurrence in the offspring is up to 8%, depending on the nature of the maternal lesion[31]. Cardiac transplantation in patients with mitochondrial myopathies has been reported[32]. There is a risk that these and other conditions can be transmitted to offspring, and for this reason appropriate preconception genetic counseling should be offered to any woman who is at risk.

VACCINATION

Most patients should be offered appropriate vaccination as part of routine pretransplant medical care. If not already immunized, prior to conception the patient should be vaccinated against influenza, pneumococcus, hepatitis B and tetanus[17]. Women who are not rubella immune should receive the rubella vaccine before being transplanted, because live virus vaccines are contraindicated post-transplantation[11].

OPTIMIZATION OF IMMUNOSUPPRESSION

Immunosuppressive agents must be continued during the pregnancy to avoid graft rejection, but the benefits to the mother should be balanced with potential detrimental effects to the fetus. All medications used to prevent rejection of transplanted organs cross the maternal–placental–fetal interface[8], but fortunately the location of the fetal liver facilitates filtration of all pharmacological agents that cross the placenta.

To date the immunosuppressive regimens in most of the successful pregnancies in allograft recipients have consisted of a combination of prednisonlone, azathioprine and a calcineurin inhibitor (CNI) – either cyclosporine or tacrolimus[5]. Prednisolone should ideally be at a dose of less than 15 mg/day, and azathioprine less than 2 mg/day[14]. CNI dose adjustments are often required during pregnancy. Whilst the consensus from the literature is that acute rejection rates during pregnancy are low and are indeed no higher than in non-pregnant patients, CNI levels can fluctuate during pregnancy, a factor which can increase the likelihood of an acute rejection episode. Cyclosporine levels can fall during pregnancy, thus necessitating a 33% increase in dose after 20 weeks[33]. However, the authors of this same report found that postpartum drug levels can rise sharply, and further dose adjustments were necessary to avoid toxicity. It is mandatory that CNI levels are monitored closely both during pregnancy and in the immediate postpartum period. Although neither cyclosporine nor tacrolimus has been reported to be teratogenic or mutagenic, both have been associated with low birth weight, intrauterine growth retardation and small size for gestational age infants[5]. In this regard, patients with hyperemesis gravidarum may have inadequate immunosuppression levels due to reduced absorption.

Data regarding the safety of newer agents such as mycophenolate mofetil (MMF) (Cellcept) and sirolimus are more limited but progressively increasing. MMF, a prodrug of mycophenolic acid, is now used worldwide as an immunosuppressive agent following solid organ transplantation[34]. In combination with prednisolone and often tacrolimus it is typically used as first-line immunosuppression in the USA and mainland Europe following renal transplantation[35]. Systemic

lupus erythematosus (SLE) which commonly affects young women of childbearing age can be treated with MMF, particularly if there is severe renal involvement[36]. According to the annual report of the Organ Procurement and Transplantation Network in the United States, MMF use for immunosuppression after renal transplantation increased from 11.9% in 1995 to 79.6% in 2000[37]. This agent is known to have teratogenic properties in animals, with offspring of treated rats and rabbits showing increased frequencies of anophalmia, agnathia, hydrocephaly, cardiovascular and renal abnormalities, as well as umbilical and diaphragmatic hernias[38,39].

A number of case reports presently describe congenital abnormalities following human maternal mycophenolate use. In one report of a pregnancy terminated at 22 weeks during which the mother was treated with MMF at the time of conception and during organogenesis, the fetus exhibited multiple malformations[40] including cleft lip and palate, micrognathia, ocular hypertelorism, microtia and external auditory duct atresia and a left pelvic ectopic kidney. In addition, complete agenesis of the corpus callosum was present. In 2007, Perez-Aytes *et al*.[34] reported a newborn with a number of congenital abnormalities including cleft lip and palate, bilateral microtia, hypertelorism and micrognathia whose mother, a renal transplant recipient, had become pregnant whilst taking MMF. At that time an extensive literature review identified six other cases with similar malformations after *in utero* exposure to MMF.

The MMF manufacturer's Summary of Product Characteristics states that its use is not recommended during pregnancy and should be discontinued at least 6 weeks before conception is attempted, during which time effective contraception should be used. Therapy with MMF should not be initiated until a negative pregnancy test has been obtained. Female patients should be informed that congenital malformations, notably involving development of the ears, have been reported in children of patients exposed to MMF in combination with their other immunosuppressants during pregnancy. The manufacturers also advise that MMF is contraindicated in nursing mothers.

Sirolimus (rapamycin) is a potent macrolide immunosuppressive agent used frequently following organ transplantation. Currently data are limited on the impact of sirolimus on pregnancy outcomes. Studies in pregnant rats have shown that whilst sirolimus is not teratogenic, it caused reduced fetal weight and delays in ossification (Summary of Product Characteristics). A case was described wherein a 30-year-old renal transplant recipient delivered a healthy normal baby at term having taken sirolimus throughout the pregnancy[41]. However, based on the current available information, the most recent European Best Practice Guidelines recommend that sirolimus, like MMF, be discontinued 6 weeks before conception is attempted and avoided in breastfeeding mothers[14].

IMMUNOSUPPRESSION AND MALE FERTILITY

Fertility in male patients with end-stage organ disease is reduced for a number of reasons, including low testosterone levels, and high follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin levels which result in abnormalities in spermatogenesis and impotence[42,43]. As is the case in female patients, fertility improves following transplantation due to restoration of hypothalamic–pituitary function resulting in improved sperm motility, although sperm count and morphology are not completely restored to normal[44]. The true incidence and prevalence of male infertility is difficult to determine[43].

The effects of the different immunosuppressive agents on fertility in male transplant organ recipients are not entirely known[43]. Neither azathioprine nor calcineurin inhibitors

(cyclosporine, tacrolimus) are associated with male infertility after transplantation[45]. The effects of MMF on male fertility are largely unknown. The CellCept Summary of Product Characteristics states that MMF had no effect on the fertility of male rats at doses above those used in renal and cardiac transplant recipients. Isolated reported cases of male infertility exist in patients treated with MMF worldwide.

Reports indicate that sirolimus is associated with altered sex hormone levels (low testosterone and elevated LH and FSH) and impaired sperm quality. Deutsch *et al.* reported a case of sirolimus-associated infertility in a young male heart-lung recipient[46]. Sperm quality improved following the withdrawal of sirolimus and the patient subsequently reported fathering a successful pregnancy. The authors postulated that oligospermia is a possible and partly reversible side-effect of sirolimus and this eventuality should be taken into consideration when sirolimus is administered to young male patients. It is probably advisable to avoid sirolimus in male patients who wish to become fathers.

BREASTFEEDING

For most of the commonly used immunosuppressive agents, limited data are available on what to advise women about breastfeeding. Prednisolone appears to be safe to use in the breastfeeding mother[35]. The British National Formulary (BNF) states that systemic effects in an infant are unlikely with a maternal dose of prednisolone up to 40 mg daily[47]. With higher doses, however, it is advised that the infant's adrenal function should be monitored. Milk concentrations range from 5 to 25% of maternal blood levels, and only trace amounts are found in breast milk following a 10 mg dose[48].

Azathioprine has a toxic metabolite which is present in milk in low concentrations. However, small studies have shown no evidence of harm in the babies of azathioprine-treated lactating women[49], and consensus opinion is that breastfeeding is not absolutely contraindicated[15].

The BNF advises that breastfeeding should be avoided in women prescribed tacrolimus and cyclosporine, as both drugs appear in the breast milk[47]. Despite this, several experienced renal transplant units in the UK have permitted breastfeeding in women treated with cyclosporine and no drug-related problems have been noted in their babies[35]. Two reports have identified minimal transfer of tacrolimus to infants as a consequence of breastfeeding[50,51]. As with azathioprine, the consensus opinion for tacrolimus is that breastfeeding is not absolutely contraindicated, but babies should be closely monitored and immunosuppressive levels in the infant should be checked[15].

Given the lack of data on breast milk transfer in lactating women treated with MMF and sirolimus, it is advised that breastfeeding be avoided in women taking these drugs[35].

RISK OF REJECTION

It has been suggested that organ rejection during pregnancy should not occur, because non-specific systemic maternal immunosuppression exists to prevent the mother rejecting the fetus[52]. However, reports have indicated that rejection rates in solid-organ transplant recipients are no different to those in non-pregnant recipients[14,53]. If immunosuppression is reduced during pregnancy based on an assumption of natural non-specific maternal immunosuppression, organ rejection may ensue[8]. Two maternal deaths occurred when immunosuppression was discontinued during pregnancy[8,54]. In cardiac transplant recipients, there is a high risk of acute rejection in pregnancy if immunosuppression is not carefully monitored. It is difficult to confirm the diagnosis of acute rejection in this group of patients as a biopsy usually involves X-ray screening which is contraindicated in pregnancy.

It may be difficult to detect allograft dysfunction during a pregnancy. For recipients of a renal allograft, for example, there may only be a small increase in serum creatinine[55]. The increased glomerular filtration rate which occurs in pregnancy usually results in a fall in serum creatinine[19]. The magnitude of this decline in the renal transplant recipient is dependent upon pre-pregnancy renal function[56].

For patients with liver transplants, any deterioration in liver chemistry during the pregnancy requires aggressive evaluation. There is no contraindication to liver biopsy, if required, to look for evidence of rejection[1]. Derangement of liver chemistry can also occur during pregnancy with pre-eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome and cholestasis of pregnancy. It can be difficult to distinguish these complications from graft rejection and exacerbation of underlying liver disease such as hepatitis C[1].

Methylprednisolone is most commonly given to treat an acute rejection episode and is usually effective[57]. Newer agents such as basilixmab and antithymocyte globulin (ATG) may also be effective but data about their safety in pregnancy are limited[8]. The AST guidelines advise the use of intravenous immunoglobulin, but that ATG and rituximab should be avoided in pregnancy[15].

OPTIMIZATION OF COMORBID CONDITIONS

Many recipients of solid organ transplants often have one or more coexisting medical conditions which may influence the outcome of their pregnancy[58]. It is important that these conditions be identified, and that a management plan be formulated by the relevant multidisciplinary team for antenatal and postnatal care.

Hypertension

Hypertension is a common medical disorder of pregnancy, which affects approximately 10–15% of all pregnancies[59]. It is a major cause of maternal morbidity and mortality, both within the UK and worldwide[60]. As one of the most important factors contributing to pre-eclampsia and resulting increases in the risk of fetal growth restriction, placental abruption and preterm delivery, maternal hypertension is an important factor increasing perinatal morbidity and mortality.

Hypertension is common in the solid organ transplant recipient even before pregnancy, and particularly if the patient is receiving a calcineurin inhibitor such as cyclosporine[61]. The incidence rates of both hypertension and pre-eclampsia vary depending on the organ transplanted[8].

Forty-three to 73% of renal transplant recipients are hypertensive before pregnancy[62] and a further 25% become hypertensive during pregnancy[63,64]. Pre-eclampsia develops in 15–37% of renal transplant recipients[58] and is reportedly as common in recipients of pancreas-kidney transplants[8]. Lower rates have been reported in liver, heart and lung recipients[53]. Hypertension develops in 51% of patients within 1 year of lung transplantation, and by 5 years is present in 85% of these patients[17]. The National Transplantation Pregnancy Registry (NTPR) reported that hypertension during pregnancy occurs in 35% of liver transplant recipients[62]. In 2004 the NTPR reported a 46% rate of hypertension and a 10% rate of pre-eclampsia in pregnant heart transplant recipients[62]. This registry also reported 15 pregnancies and eight live births in lung transplant recipients, finding a 53% rate of hypertension and a 13% rate of pre-eclampsia among these individuals.

Table 1 shows the percentage of women who develop hypertension and pre-eclampsia during pregnancy according to the organ transplanted.

Good blood pressure control has a beneficial effect on both graft and patient survival for recipients of renal transplants[65,66]. There is no specific evidence regarding target blood pressure level in pregnancy, but recent UK consensus guidance recommends that it should ideally be maintained at less than 140/90 mmHg in order to minimize progression of any

Table 1 Characteristics of pregnancy among transplant recipients during pregnancy and of their infants, according to organ received

Characteristic	*Kidney*	*Liver*	*Pancreas and kidney*	*Heart*	*Lung*
No. of recipients	751	106	37	39	13
No. of pregnancies	1139	182	53	63	14
Hypertension during pregnancy (%)	28–72	22–42	75	47	50
Diabetes during pregnancy (%)	3–12	0–13	2	4	21
Rejection episodes (%)	2–12	0–11	6	22	31
Pre-eclampsia (%)	29–31	13–33	33	10	13
Graft loss within 2 years (%)	4–14	3–9	17	0	23
Live birth (%)	71–78	72–82	80	70–80	57
Mean duration of gestation (weeks)	35–36	37–38	34	37–38	35
Mean birth weight of infant (g)	2308–2493	2635–2802	2128	2717–2930	2285
Cesarean section (%)	46–92	22–42	52	29–100	38

Reproduced with permission from McKay and Josephson[8]

underlying renal impairment, reduce maternal cardiovascular risk and preserve graft function[58]. No formal guidelines exist for recipients of other solid organs, but it is universally accepted that blood pressure should be well controlled prior to conception[1].

Many solid organ transplant recipients who are planning pregnancy are prescribed one or more antihypertensive agents. It is essential that these are reviewed ideally before conception is attempted, or at the time pregnancy is confirmed, as some agents are contraindicated in pregnancy.

Methyldopa is usually recommended as the first-line treatment for hypertension in pregnancy[14]. Its safe use in pregnancy has been established in case–control studies, and long-term studies of children whose mothers took methyldopa during pregnancy have shown no adverse effects[67,68]. Women should be informed of its potential side-effects including drowsiness and depression[58].

Several other antihypertensive agents are considered safe in pregnancy. Atenolol is associated with small-for-gestational age babies and should be avoided in pregnancy[69]. Other beta blockers are safe in pregnancy and labetalol is typically used. This class of drug should be avoided in patients who are asthmatic. Calcium channel blockers appear to be safe and well tolerated[70], and follow-up at 18 months has shown no detrimental effects in the infants[71]. Although there have been few controlled trials to demonstrate its safety, hydralazine has been extensively used in pregnancy with few adverse events reported. It is commonly used as adjunctive therapy with methyldopa[72].

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARBs) are commonly used in renal transplant recipients to both control blood pressure and reduce proteinuria. Recent reports have linked their use to the development of congenital abnormalities during all three trimesters of pregnancy and these agents are therefore contraindicated in pregnancy[8]. Ideally they should be discontinued before conception is attempted or at the time a pregnancy is suspected or confirmed. A recent study reported a 2.7 times greater risk of serious congenital malformation following exposure to ACE

inhibitors during the first trimester of pregnancy[73]. During the second and third trimesters they are associated with a fetopathy comprising oligohydramnios, hypocalvaria, fetal growth restriction, renal dysplasia, anuria, renal failure and often intrauterine death[74].

Some renal transplant recipients take a diuretic to help control edema which may have arisen secondary to proteinuria, due to either recurrent disease or chronic allograft nephropathy[19]. Diuretics ideally should be avoided in pregnancy because they can cause hypovolemia and thus compromise placental blood flow. However, in cases of severe edema the risk–benefit ratio of diuretic therapy should be assessed on an individual basis.

REDUCING THE RISK OF PRE-ECLAMPSIA

Low-dose prophylactic aspirin helps prevent pre-eclampsia[75]. Few studies, however, have specifically examined the purported benefit in women with underlying renal disease or recipients of organ transplants. Solid organ transplant recipients are at increased risk of pre-eclampsia, and additionally may have other conditions such as diabetes, chronic hypertension and systemic lupus erythematosus that increase the risk further. It is generally recommended that aspirin be commenced after 12 weeks in the high-risk patient if there are no contraindications[58].

Diabetes

A patient with a renal transplant may have had end-stage renal disease due to diabetic nephropathy. Alternatively, a solid organ transplant recipient may have developed new-onset diabetes after transplantation (NODAT)[58]. Patients prescribed steroids and tacrolimus are at increased risk of glucose intolerance. One meta-analysis shows that the risk of post-transplant diabetes is five times greater in patients treated with tacrolimus rather than cyclosporine[76]. For this reason, glucose tolerance testing may be indicated during pregnancy for tacrolimus-treated patients. A recent review reported that 3–12% of pregnant renal transplant recipients had diabetes[8,62].

Pregnant solid organ transplant recipients with diabetes have a number of important issues to consider. For example, the risk of preterm delivery and pre-eclampsia is increased[58] and fetal growth restriction is less common. Significant proteinuria can be present in patients with diabetic nephropathy affecting a transplanted kidney, especially if ACE inhibitors and ARBs have been discontinued at conception. Thromboembolic risk is increased in these patients and prophylactic low-molecular-weight heparin (LMWH) may be necessary. Edema and severe nephrotic syndrome may require diuretic treatment[58].

A patient whose diabetes is normally treated with oral hypoglycemic agents may require insulin during pregnancy. Metformin, currently undergoing a clinical trial, has been used in pregnancy in Australia[77].

Systemic lupus erythematosus and other autoimmune conditions (see also Chapter 7)

Approximately 1–2% of patients on the renal transplant waiting list have end-stage renal disease secondary to lupus nephritis; pregnancy is often a consideration for this category of renal transplant recipients, because SLE commonly affects young women[58]. A number of potential problems need to be considered in the solid organ transplant recipient with an underlying diagnosis of SLE. Recurrent miscarriages can occur. The presence of lupus anticoagulant and anticardiolipin antibody may necessitate treatment with prophylactic LMWH during pregnancy. The presence of anti-Ro and anti-La antibodies increases the

risk of fetal cardiac problems, including complete heart block. As with diabetes, SLE is associated with increased risk of both preterm delivery and pre-eclampsia.

INFECTION

As a consequence of immunosuppression, all recipients of solid organ transplants are at increased risk of infections from bacterial, fungal and viral organisms. Any such infection may pose serious risk to both mother and fetus. The overall risk of infection during pregnancy varies according to the organ transplanted. In lung transplant recipients, it is about 20%[62] and respiratory infections occur most frequently. For recipients of cardiac transplants the infection risk is about 11%[62].

Bacterial infections

Asymptomatic bacteriuria is fairly common during pregnancy, affecting 2–10% of women. Untreated, approximately 30% will develop a symptomatic urinary tract infection (UTI)[58]. Acute pyelonephritis occurs relatively frequently in patients whose end-stage renal disease has been caused by chronic pyelonephritis or reflux nephropathy. The European Best Practice Guidelines (EBPG) recommend that all renal transplant recipients should be screened for bacteriuria on a monthly basis with a midstream urine sample. If asymptomatic bacteriuria is present, a course of antibiotics should be given[14]. Renal transplant recipients frequently suffer from recurrent UTIs, and it is necessary to commence or continue prophylactic antibiotics during pregnancy with a safe agent. Women prescribed trimethoprim should be advised prenatally about changing to alternative antibiotic prophylaxis as this drug should be avoided in early pregnancy[47]. Prophylactic antibiotics are recommended for organ recipients requiring invasive procedures during the pregnancy, including fetal monitoring with scalp electrodes or intrauterine pressure monitoring[72].

Viral infections

Following solid organ transplantation, recipients are potentially at risk of either primary cytomegalovirus (CMV) infection or of reactivation. CMV is the most common cause of viral infection post-transplantation, the risk of which is highest during the first post-transplantation year when levels of immunosuppression are commonly at their peak. The British Transplantation Society recommends that prophylaxis against primary CMV infection with ganciclovir, valganciclovir or valaciclovir should be offered to CMV seronegative patients who receive a solid organ transplant from a donor who is seropositive[78]. Prophylaxis is also advised in cases where the donor and recipient are both seropositive and the recipient is treated with ATG/ALG/OKT3. Ganciclovir is contraindicated in pregnancy as it is teratogenic. It is recommended that effective contraception (including barrier contraception for men) be used during the course of treatment and for at least 90 days afterwards[47]. The same applies to valganciclovir, as it is an ester pro-drug of ganciclovir. Valaciclovir is a pro-drug of aciclovir. Aciclovir is not known to be harmful in pregnancy, but its manufacturers advise that is only used during pregnancy when the potential benefits outweigh any risks[47].

The overall frequency of CMV infection in pregnant transplant recipients is unknown; the NTPR reported four such cases[20]. In pregnancy, CMV infection can result in prematurity and low birth weight. Approximately 90% of congenital infections are asymptomatic. Affected children typically present in childhood with impaired psychomotor development and neurological, hearing, visual or dental abnormalities. Infants with symptomatic CMV infection

can develop jaundice, splenomegaly and a petechial rash. Cytomegalovirus inclusion disease, a severe form of CMV infection, is characterized by multiorgan involvement including microcephaly, seizures and motor disability[58]. By delaying pregnancy for at least 12 months and thus avoiding the period when the need for heavy immunosuppression is greatest, female solid organ transplant recipients can reduce the risk of CMV infection and its potentially serious consequences.

If CMV infection is suspected, a blood sample should be sent urgently for detection and quantification of CMV DNA using quantitative polymerase chain reaction (PCR)[78]. Women who are not immune to cytomegalovirus should be counseled regarding preventative measures.

Herpes simplex virus (HSV) infection is one of a number of persistent viral infections that can occur in solid organ transplant recipients[58]. HSV infection prior to 20 weeks' gestation is associated with an increased risk of abortion[72]. Vertical transmission can occur at the time of vaginal delivery, and cesarean delivery reduces the risk of transmission. Aciclovir can be used in pregnancy[20].

Women not immune to varicella zoster should be advised to avoid contact with individuals with chicken pox. Should exposure occur, prophylactic intervention with intravenous immunoglobulin should be considered.

Hepatitis B and hepatitis C

The hepatitis B and C status of the female organ transplant recipient should be established prior to conception. The prevalence of both hepatitis B virus (HBV) and hepatitis C virus (HCV) infections is increasing in patients with end-stage renal disease on dialysis[58]. If a patient is found to be positive for hepatitis B or hepatitis C the management of a pregnancy should involve close liaison between hepatologists, obstetricians and transplant physicians.

Hepatitis B Patients positive for HBV but without evidence of liver disease are increasingly considered for renal and other organ transplantation[58]. Some patients acquire HBV following transplantation. For those patients who are HBV DNA positive, antiviral therapy is required which may need to be long term. Lamivudine should be avoided during the first trimester of pregnancy[47]. Renal transplant recipients with HBV infection have reduced survival and are at increased risk of graft loss, although outcomes are improving with new developments in antiviral therapy[79].

In general for women who are hepatitis B carriers, pregnancy is uneventful[58]. Exacerbation of disease during pregnancy is uncommon. There is, however, a significant risk of vertical transmission to the infant during delivery, which occurs in up to 80% of cases. The combination of hepatitis B vaccination and hepatitis B immunoglobulin is 95% effective in preventing infection in the neonate[19].

Hepatitis C Hepatitis C is now more common than hepatitis B in renal transplant recipients[19], in that 11–49% of the recipients are reported to be HCV positive[80,81]. The risk of post-transplant liver disease is increased in these patients, and viral replication, and hence viral load, can be increased as a consequence of immunosuppression. The effect of HCV infection on both patient and graft survival following organ transplantation is currently unclear. Ribavarin is commonly used to treat hepatitis C. It is contraindicated in pregnancy, however, as animal studies have shown it to be teratogenic. It is therefore advisable that effective contraception should be used during oral administration and for 6 months after treatment[47].

Newborn vertical transmission of hepatitis C occurs in 5–10% pregnancies of HCV RNA-positive mothers. As no means of preventing vertical transmission exists, pregnancy should be planned when the viral load is

low[20]. Interferon is generally avoided in renal transplant recipients.

The outcome of pregnancies in HCV-positive women without an organ transplant is usually good, but only a few cases of pregnancy in HCV-positive renal transplant recipients have been reported[58]. In Ventura *et al.*'s report of three cases of pregnancy in HCV-positive renal transplant recipients without chronic liver disease[82], no evidence of progression of liver disease was observed during 2 years of follow-up postpartum.

ANEMIA

Anemia is commonly present in normal pregnancy. It arises because although there is an increase in red cell mass under the control of erythropoietin, the relative increase in plasma volume causes hemodilution.

Patients with solid organ transplants may become anemic as a result of this normal physiological mechanism. In addition, however, anemia may occur due to bone marrow suppression by immunosuppressive agents such as azathioprine. (MMF can also cause this but as discussed earlier is contraindicated in pregnancy.) Patients with renal transplants also may have anemia related to chronic renal impairment. This may be treated with erythropoietin prior to a pregnancy, or it may be necessary to commence treatment with erythropoietin during the pregnancy if graft function has deteriorated. It is important to consider and exclude other causes of anemia in the solid organ transplant recipient such as bleeding, hemolysis and vitamin deficiencies[83].

The general aim is to maintain the hemoglobin level at approximately 11 g/dl[58]. If the hemoglobin falls below this level, the following investigations should be considered:

- Ferritin level and transferrin saturation ratio
- Serum vitamin B12 and folate
- Hemolysis screen including blood film to look for evidence of red blood cell fragmentation
- Parvovirus infection test.

Erythropoietin can be safely used in pregnancy[84,85], as it does not appear to cross the placenta and is not reported to be teratogenic[86]. It is, however, associated with increases in blood pressure which necessitates careful monitoring. Hou recommends that erythropoietin therapy should be commenced if the hematocrit falls below 30% and the dose titrated to maintain a hemoglobin of 10–12 g/dl[20].

POST-TRANSPLANT ERYTHROCYTOSIS

Post-transplant erythrocytosis (PTE) is defined as a hematocrit of greater than 51%. It occurs in up to 20% of renal transplant recipients and is most common within the first 2 years after transplantation[58]. The etiology of PTE is unclear, but may possibly be due to the oversecretion of erythropoietin by native kidneys, transplanted kidneys or the liver. Untreated, PTE is associated with increased risk of vascular and thromboembolic disorders. ACE inhibitors or ARBs are commonly used to treat PTE, but both are contraindicated in pregnancy. Pregnant transplant recipients known to have PTE should have their hematocrit monitored regularly together with assessment of thromboembolic risk. Venesection can be considered if the hematocrit rises significantly[87].

HYPERLIPIDEMIA

Many renal transplant recipients are prescribed statin therapy to treat hypercholesterolemia and reduce the risk of cardiovascular events and morbidity[88]. Animal studies suggest that statins are teratogenic, and case reports in humans have described central nervous system defects and limb abnormalities in newborns exposed to statins *in utero*[76,89–91]. Statins

are contraindicated in pregnancy, and should be discontinued prior to conception[47,58].

SKELETAL PROBLEMS

Abnormal parathyroid hormone concentrations are seen in 77% of renal transplant recipients[92], due either to impaired transplant function or to incomplete resolution of pre-transplant hyperparathyroidism. In general hyperparathyroidism in the renal transplant patient is mild and asymptomatic, but few published data describe the outcome of pregnancy[58]. In a single case report of a renal transplant patient with mild tertiary hyperparathyroidism, albeit with a stable serum calcium level despite a deterioration in renal function, the infant developed mild neonatal hypocalcemia requiring treatment with intravenous calcium gluconate[92].

A variety of medications may be prescribed for the management of skeletal problems in renal transplant recipients, including alfacalcidol, calcium supplements, phosphate binders, bisphosphonates and, more recently, cinacalcet. These should be reviewed prior to pregnancy with a view to stopping those that are not advised in pregnancy. Calcium supplements and alfacalcidol are safe in pregnancy and can be continued. Calcium-containing phosphate binders are also safe in pregnancy, but newer agents such as lanthanum carbonate and sevelamer (Renagel) should be avoided, although evidence regarding these drugs is scant at present. Bisphosphonates, which are used in the treatment and prevention of osteoporosis, are known to cross the placenta, but very little is known about their safety in pregnancy. In general bisphosphonates should be discontinued pre-pregnancy or as soon as pregnancy is suspected, and careful consideration should be given before these agents are prescribed to women of childbearing age[58].

Table 2 summarizes which commonly used drugs in solid organ transplant recipients are considered safe in pregnancy and which are not.

Table 2 Table of drugs and their use in pregnancy

Drugs considered safe in pregnancy	*Drugs not recommended for use in pregnancy*
Immunosuppressive agents	Immunosuppressive agents
Prednisolone	Mycophenolate mofetil (MMF)
Azathioprine	Sirolimus
Cyclosporine	
Tacrolimus	Antihypertensive agents
	Angiotensin converting enzyme (ACE) inhibitors
Antihypertensive agents	Angiotensin receptor blockers (ARBs)
Methyldopa	Furosemide
Labetalol	
Calcium channel blockers	Other drugs
Hydralazine	Ganciclovir, valganciclovir
	Bisphosphonates
Other drugs	Lanthanum carbonate, sevelamer
Aspirin	Statins, e.g. atorvastatin, simvastatin
Aciclovir	Lamivudine
Alfacalcidol	Ribavarin
Calcium-containing phosphate binders	Trimethoprim

CONCLUSION

Solid organ transplantation restores fertility to many women with end-stage organ disease and undoubtedly offers the best chance of a successful pregnancy to women of childbearing age. In order to make an informed decision, it is essential that women of childbearing age are counseled regarding contraception and pregnancy, ideally prior to transplantation. Pregnancy can then be planned at an optimum time to protect graft function and minimize risks to the fetus. Medications can be modified where necessary, and concurrent medical problems such as hypertension can be identified and a management plan during pregnancy formulated. Despite all efforts, pregnancy in a solid organ transplant recipient remains high risk, and should be managed by an appropriate multidisciplinary team as described above.

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