Pregnancy in Chronic Kidney Disease and Kidney Transplantation

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Pregnancy in Chronic Kidney Disease and Kidney Transplantation

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ABSTRACT

Chronic kidney disease (CKD) affects up to 6% of women of childbearing age in high income countries, and is estimated to affect 3% of pregnant women. Advanced renal dysfunction, proteinuria, hypertension and poorly controlled underlying primary renal disease are all significant risks for adverse maternal, fetal and renal outcomes. In order to achieve the best outcomes it is therefore of paramount importance that these pregnancies are planned, where possible, to allow the opportunity to counsel women and their partners in advance and to optimize these risks. These pregnancies should be deemed high risk and they require close antenatal monitoring from an expert multidisciplinary team.

We discuss the effect of pregnancy on CKD, and also current guidelines and literature with specific reference to transplantation, autoimmune disease and medication use in pregnancy. We also discuss the benefits of pre-pregnancy counselling and give practical recommendations to advise pregnant women with renal disease.

THE IMPACT OF KIDNEY FUNCTION ON PREGNANCY OUTCOME

CKD stage and outcomes

The pregnancies of most normotensive women with mild or even moderate renal dysfunction succeed, but are prone to more complications than those of gravidas with normal renal function. However, pregnancy is much more hazardous when kidney dysfunction is advanced. Women with advanced chronic kidney disease (CKD) have a lower likelihood of conceiving because of the decreased fertility associated with the hormonal changes of worsening kidney function and ESRD.[1] When they do conceive, advanced CKD predisposes to intrauterine growth restriction and preterm delivery,[2] and pregnancy has been blamed for hastening the rate of decline of kidney function, increasing proteinuria, and hypertension.[3] Such views however are based on insufficient data. Thus the level of kidney function/dysfunction and its effect on pregnancy remains a debated area.

An evolving state of understanding

Currently there is controversy reflecting the swinging pendulum of attitudes related to pregnancy in women with CKD, as well as the evolution of how the nephrology community assesses renal function. In 1975, an anonymously authored Lancet editorial noted that physicians in the past preferred avoiding pregnancy in women with any degree of CKD by noting: “Children of women with renal disease used to be born dangerously or not at all - not at all if their doctors had their way”.[4] The editorial took the then provocative stance that as most pregnancies succeed in the setting of mild kidney dysfunction, this attitude should be changed. Davison and Lindheimer[5] noted in 2010 that studies in the decades after the Lancet editorial led to a better understanding of outcomes for pregnancy in women with kidney dysfunction. Observational studies indicated that outcomes depended

on the degree of renal insufficiency pre-pregnancy, and the presence or absence of hypertension.[6] Based on these parameters, women were grouped into three categories: mild, moderate, or severe dysfunction. Normotensive women with preserved or mildly decreased but stable kidney function (defined as a serum creatinine (SCr) of ≤1.4 mg/dL) did well with over 95% live births, 75% of which were appropriate size for gestational age. However, prognosis worsened with moderate dysfunction (SCr ≥ 1.4 mg/dL-2.8 mg/dL) and more so with severe impairment (SCr level ≥ 2.8 mg/dL).[7] These estimates were based on a 26-year literature review (1984-2010), as well as personal patient files by John Davison, most recently published in a NephSAP editorial by Drs Lindheimer and Davison, in the issue devoted to renal disease and hypertension in pregnancy (reproduced with permission in Table 1).[8].

Creatinine vs eGFR

In 2002 the Kidney Disease Outcomes Quality Initiative (KDOQI) released a new chronic kidney disease (CKD) classification designating five categories based on estimated glomerular filtration rate (eGFR).[9] Ignoring the question of whether this classification system over-diagnosed kidney disease and dysfunction in some, the eGFR based system provided another filter through which to consider pregnancy outcomes. Piccoli and colleagues[10] used the classification and looked at pregnancy outcomes in 504 pregnancies in women with CKD compared with 836 low-risk pregnancies in women without CKD. They considered whether hypertension, proteinuria (> 1 gram/day), systemic disease, or CKD stage at baseline affected pregnancies. Outcomes assessed were: cesarean section, preterm delivery, early preterm delivery, small for gestational age, need for neonatal intensive care unit, new onset of hypertension, new onset/doubling of proteinuria, CKD stage shift, and a combined

outcome. The majority of patients in the study were classified as CKD stage 1. The authors concluded that adverse outcomes increased with increasing stage of CKD, including surprisingly stage 1, even in the absence of hypertension, baseline proteinuria, and systemic diseases. The eGFR was calculated based on the Cockcroft–Gault, Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas. As CKD-EPI and MDRD have been found to underestimate GFR in pregnancy[11,12] and Cockcroft-Gault has been demonstrated to both underestimate and overestimate GFR in hypertensive pregnant women,[13] it is possible that some of the patients in Piccoli's study had lower GFRs than the group in which they were classified. Some of the individuals reported to have CKD stage 1, could therefore have had a higher stage**.** While Piccoli *et al's* findings were primarily in women with mild and moderate dysfunction Imbasciati et al studied 49 women with preconception stage 3 to 5 CKD observed for a mean of 39 months after delivery. In the latter study only individuals with both GFR less than 40 ml/min/1.73m^2 and greater than 1 gram of proteinuria per day were noted to have poor fetal outcomes and accelerated kidney function loss.[14] A meta-analysis by Zhang et al of 23 studies that included 1514 pregnancies with CKD found no significant difference in renal outcomes in pregnant women with CKD compared with non-pregnant women with CKD. The study did however find that adverse pregnancy outcomes, including preeclampsia, premature births, SGA/low birth weight, cesarean section, stillbirth, fetal death, and neonatal death, were increased in women with CKD compared to those without. The conclusions that can be drawn from the meta-analysis must be put into context because the literature review focused on patients with CKD stages 1-3, thus excluding those with stage 4 or 5 who are most vulnerable for progression of disease.[15]

In their review and recent editorial Lindheimer and Davison[5,8] underscore that most eGFR formulae correlate poorly with measured GFR in pregnant women, and that obstetricians familiar with absolute values of creatinine may be unfamiliar with the nephrology community's CKD system . However, despite the seeming differences between those who are considering pregnancy outcomes through an eGFR based CKD stages filter, and those who are more comfortable with the serum creatinine based assessment, proponents of both agree that degree of kidney function plays an important role in outcome. Neither group advocates returning to the pre-1975 mindset of avoiding pregnancy in women with mild kidney dysfunction, however defined.

Additional contributing factors

Whilst clearly important, kidney function alone does not uniformly predict pregnancy outcomes. There are likely to be additional contributing factors to pregnancy outcomes, such as active systemic disease or endothelial injury. For example certain specific diseases such as Systemic Lupus Erythematosus (SLE) may exert a greater adverse effect on the pregnancy making it impossible to isolate the role of kidney function per se on outcomes.[16] Similarly kidney transplantation does not present a pristine model to look at kidney function alone because of the effects of immunosuppression.

Kidney transplantation and outcome

A national UK cohort study demonstrated that most pregnancies after renal transplantation are successful, although the risks of pre-eclampsia still remain higher than controls[17] and this higher risk of pre-eclampsia affects even those with good GFRs.[18] Patients should be counselled of this accordingly and the other precautions discussed in the pre-pregnancy

counselling section, initiated. How does the connection between kidney function and pregnancy outcomes relate to pregnancy outcomes in kidney transplant recipients? Similar to findings in advanced kidney failure, transplant patients appear to have a lower pregnancy rate than the general public.[19] Registry, cohort, and meta-analysis studies demonstrate that pregnancies in transplant recipients, which are more likely to be complicated by hypertension, are at greater risk for prematurity, small for gestational age, cesarean sections, the diagnosis of preeclampsia and perinatal mortality.[17,18,20] Of note while pregnancy and renal function outcomes in transplant recipients have been studied based on creatinine levels, we could locate no assessments based on the CKD staging system. In transplant recipients, there are the additional factors of immunosuppression medications. These factors make it hard to isolate and define the kidney function effect on pregnancy in this group. Long term follow-up of transplant recipients with and without a history of pregnancy supports the idea that pregnancy does not worsen long term outcomes.[21]

However, there may be subsets of transplant patients in whom pregnancy accelerates renal function decline. Data from the UK Pregnancy registry indicate that women with kidney allografts whose pre-pregnancy SCr is greater than 150µmol/L (approximately 1.7 mg/dL) have an increased serum creatinine after pregnancy, suggesting that the pregnancy itself may negatively affect graft function.[22] Despite limitations of available data in the transplant recipient, guidelines advise that amongst other factors, the basis for determining reasonable timing for pregnancy is the presence of adequate and stable graft function (arbitrarily set as a SCr<1.5 mg/dL).[23] The American Society of Transplantation recommends that prior to pregnancy there should be no rejection for one year, adequate and stable graft function, no acute infections, and stable immunosuppression dosing.[24] Pregnancy should be delayed until at least one year after renal transplantation[25] as postponement is associated with

better outcomes.[26] A recent study by Rose et al that examined allograft outcome and pregnancy timing in the first 3 post-transplant years of Medicare insured kidney transplant recipients suggests that pregnancy in the first 2 post-transplant years is associated with increased allograft loss compared with waiting an additional year.[27] Beyond optimal post-transplant pregnancy timing, there are many other unanswered questions about pregnancy in transplant recipients including the optimal pre-pregnancy kidney function and whether having pre-existent donor specific antibodies affects pregnancy outcomes, or the transplanted kidney. This last consideration is of particular concern given the usual pre-pregnancy modification of immunosuppression, with discontinuation of mycophenolic acid formulations.

Kidney donors

Pregnancy in kidney donors may be the perfect model in which to consider the role of kidney function. Donors are intensively medically screened and only allowed to donate a kidney if healthy. Their post-donation level of kidney function is approximately 75-80% of normal.[28] They do not have systemic disease and their remaining kidney, though hypertrophied and hyperfiltering, is normal. Three studies have found that post-donation pregnancies may be at increased risk for complications. Garg et al performed a population study and found a significantly higher incidence of gestational hypertension or preeclampsia in donors compared with matched non-donors.[29] Ibrahim et al's survey of previous kidney donors documented subjects reporting significant increases in diagnosed preeclampsia, hypertension, and gestational diabetes in pregnancies after donation compared with before.[30] Reisaeter et al found more pre-eclampsia diagnosed in women after donation compared with pregnancies before.[31]

Kidney function impact

Taken together the studies, case series, and registries indicate that kidney function alone plays a role in pregnancy outcomes, though usually limited unless kidney dysfunction is moderate and proteinuria is present. Whether pregnancy in women with CKD changes the course of their kidney disease, is less clear. Kidney donors aside, patients with CKD (with or without kidney transplants) have other factors that may independently influence pregnancy outcomes, be it underlying disease, medications, proteinuria, or hypertension.

BLOOD PRESSURE

Hypertension during pregnancy is an increasingly recognized problem, and one that has led to the creation of several management guidelines.[32–35] Using hospital discharge data from the Nationwide Inpatient sample (NIS) part of the Healthcare Cost and Utilization Project, a 2012 population-based study examined 56,494,634 deliveries between 1995 and 2008. During this period the prevalence of primary and secondary hypertension increased from 0.9% to 1.52% and 0.07% to 0.24% respectively.[36] Hypertension during pregnancy can be broken down into four types as outlined in Table 2: pre-eclampsia / eclampsia, chronic hypertension, chronic hypertension with superimposed pre-eclampsia, and gestational hypertension.[32] Management of hypertension during pregnancy differs from that in non-pregnant states. Blood pressure goals are more permissive during gestation. However the American College of Obstetricians and Gynecology (ACOG) recommends that if there is evidence of end organ damage, treatment goals should be as rigid as in the non-pregnant state.[32]

The reasoning behind why management in the pregnant and non-pregnant state differs is several-fold including that pregnancy is a time limited event in which the benefits of treatment are not easily realized,. and treatment exposes the fetus to medications which may affect intrauterine programming and may lead to reduced utero-placental blood flow with compromised fetal circulation.[37,38] Whether or not blood pressure management should differ in pregnancy from non-pregnant states is a point of current debate. Those who advocate that the 2 should not differ note that hypertension during pregnancy is not as benign as once thought. Hypertension during pregnancy has been associated with an increased risk for acute kidney injury (AKI), pulmonary edema, need for ventilator support, and cerebrovascular complications.[39,40] There is also now evidence that a hypertensive pregnancy is associated with later-in-life left ventricular hypertrophy.[41] An echocardiography study of pregnant and non-pregnant women who were normotensive or had essential hypertension suggested that pregnancy and hypertension have synergistic effects in causing myocardial hypertrophy.[42] This latter study indicates that cardiac changes may be seen not only years after delivery, but during the pregnancy too.

The debate over whether or not blood pressure goals in pregnant women with hypertension should be relaxed or stringent and the ACOG guidelines are timely as the Tight Control of Hypertension in Pregnancy Study (CHIPS) recently demonstrated that pregnancy outcomes and maternal complications were not significantly different in pregnant women whose hypertension was controlled more or less tightly.[43] However this debate is not germane to CKD because CKD *is* a form of end organ damage and the CHIPS trial excluded individuals with renal dysfunction. Consequently we suggest that such patients should be treated more aggressively, that is in a manner similar to the non-pregnant state i.e. aiming for tight control.

Fetal and maternal outcomes for pregnant women with CKD are markedly worse in the presence of hypertension. Bateman *et al* observed odds ratios of stillbirth, poor fetal growth, and spontaneous delivery <37 weeks gestation to be 7.29, 7.49 and 8.60 compared with 1.74, 2.29 and 2.25 respectively in women with CKD plus hypertension compared with those with CKD alone.[36] Maternal complications were also markedly increased in women with CKD who had chronic hypertension compared with those with CKD but without chronic hypertension. For example, preeclampsia and AKI odds ratios were 27.87 and 253.4 compared with 3.28 and 62.4 respectively. Whether or not blood pressure control in women with CKD and chronic hypertension would reduce these risks has not been studied. The United Kingdom's National Institute of Health and Clinical Excellence (NICE) clinical guidelines recommend keeping BP lower than 140/90 mmHg in pregnant women with target-organ damage, including CKD.[37] However, the evidence behind this blood pressure goal is scant at best.

The optimal blood pressure target for pregnant women with CKD and hypertension remains an unanswered question and important knowledge gap. Identifying that target is becoming increasingly important as the prevalence of CKD in pregnant women has increased from a range of 0.1% to 1% in the past to an estimated current prevalence of around 3%,[44] with recent literature suggesting that up to 6% of women of child-bearing age in high income countries are affected by CKD.[45]

PRE-PREGNANCY COUNSELLING

The value of pre-pregnancy counselling has been recognized in women with diabetes for several decades.[46] Pre-pregnancy counselling in women with chronic kidney disease offers

the opportunity to minimize disease activity, optimize blood pressure control and proteinuria, alter teratogenic medications and also to educate couples about potential fetal and maternal adverse events that may occur during pregnancy and the puerperium in this high risk group. It also allows discussion of the inheritance of genetic disorders of the kidney including cystic diseases, metabolic diseases and glomerular basement membrane disorders. The confidential enquiries into maternal deaths in the UK endorses that pre-pregnancy counselling should be routinely commissioned and offered to women with pre-existing medical illnesses in view of the morbidity and mortality triggered by these diseases.[47] The advice given is clearly dependent on underlying renal disease, baseline renal function, proteinuria and blood pressure at conception and this should be delivered in a patient focused, individualised manner. Women with chronic kidney disease should be counselled prior to pregnancy of the increasing risk of maternal and fetal complications as GFR declines. These risks include fetal growth restriction, pre-term birth, pre-eclampsia, fetal death and deterioration of maternal renal function / disease flare.[48]

Fertility

Women may need to be advised that advanced chronic kidney disease impairs fertility.[49] This is due to a multitude of reasons, although these are poorly characterized in the literature. Hyperprolactinemia is common in patients with CKD, due to reduced renal clearance and increased production from suppression of dopaminergic activity, and this inhibits gonadotropin secretion. This manifests as amenorrhea in women.[50,51]. Levels of leutinising hormone and follicle stimulating hormone are also elevated in CKD, although the physiological surge in LH usually seen during the mid-cycle of healthy women is not seen in those with CKD, and this can lead to anovulation.[51] These hypothalamic-pituitary axis

dysfunctions, in combination with the psychological impact of CKD causing depression and reduced libido, can significantly reduce the chances of conception. However, fertility can be restored after renal transplantation.[52] As pregnancy outcomes are progressively poorer with advancing chronic kidney disease, younger women who want to become pregnant are often advised to be transplanted first. If this is not possible, nocturnal haemodialysis may restore menses and improve the chances of pregnancy.[53,54]

Optimization Before Pregnancy

Blood pressure should be optimized before pregnancy. Both KDIGO and UK National Institute for Health and Care Excellence (NICE) recommend that adults with CKD, without proteinuria should aim for a blood pressure below 140/90mmHg. NICE recommend that those with CKD who have diabetes or those with proteinuria (ACR >70mg/mmol) aim for a blood pressure below 130/80mmHg. KDIGO also recommend this level for patients with an ACR >30mg/mmol. [55,56] These targets should be achieved prior to conception with drugs that are safe to continue during pregnancy (summarized in table 3). ACE inhibitors and angiotensin receptor blockers should be stopped prior to pregnancy or as early as possible after discovering pregnancy. A recent systematic review of the management of hypertensive disorders in pregnancy recommends the preventative use of low dose aspirin to reduce pre-eclampsia, and in severe hypertension. [57] UK NICE guidelines also advocate the use of aspirin from 12 weeks of gestation in women at high risk to reduce the incidence of pre-eclampsia.[58] Such risk factors include chronic kidney disease and autoimmune diseases such as systemic lupus erythematosus. This is based on a Cochrane review of 59 trials.[59]

Proteinuria may occur in 30% of women who do not have proteinuria before pregnancy,[60] and may confer poorer feto-maternal outcomes[61,62]. Proteinuria should therefore, where

possible, be controlled during pre-pregnancy counselling, and the main way to achieve this is through optimizing treatment of baseline renal disease and blood pressure control. Women with proteinuria should be counselled about the potential requirement for thromboprophylaxis during pregnancy.

. Systemic lupus erythematosus (SLE) affects women of child bearing age without affecting fertility and so pregnancy is not uncommon. A meta-analysis of 2751 women with SLE showed that those with active lupus nephritis (LN) had an increased risk of maternal hypertensive disorders and premature birth.[63] Disease flare, high initial creatinine and proteinuria at conception are predictive of worse outcomes. In addition, flares may cause a decline in renal function and accelerate progression to end-stage renal disease. Pregnancy should be planned and drugs altered accordingly prior to pregnancy, including stopping / substituting mycophenolic acid products. A minimum six month period of disease quiescence prior to pregnancy is therefore recommended.[64,65] The PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) study, a large prospective cohort study including 385 patients, recently demonstrated that 81% of pregnancies in women with inactive or stable mild/moderate disease were uncomplicated.[66] Features indicating a higher risk for adverse pregnancy outcomes, included a positive lupus anticoagulant, antihypertensive use, a low platelet count, Hispanic or non-white ethnicity, and a physician's global assessment score >1; and those women without these generally had favourable outcomes.

Pre-implantation diagnosis

It is important to discuss the option of preimplantation genetic diagnosis (PGD) with women whose CKD is secondary to a genetically inherited cause. Recent advances in techniques

used for in vitro-fertilisation allow removal of one or two cells at the eight cell stage of blastocyst formation.[67] These blastomeres can then be analysed for the mutations responsible for conditions such as Alports Syndrome or Adult Polycystic Kidney Disease.[68] Although there are limited data, initial reports suggest PGD is associated with similar success in pregnancy outcome when compared with routine IVF.

Pre-pregnancy counselling improves knowledge and changes behavior prior to pregnancy[69] which may help to reduce adverse events. The optimum way of offering pre-conception counselling has not been established. Patients with diabetes agreed that being informed of the risks prior to pregnancy is crucial, but existing childcare and work commitments prevented attendance to such services. They also stressed that the positive aspects of having children should be discussed rather than only medical complications.[70] In a retrospective analysis of 179 women with chronic kidney disease undergoing pre-pregnancy counselling in a large single centre, consultations included the multi-disciplinary team of a consultant obstetric physician, obstetrician and nephrologist.[71] These women had an overwhelmingly positive experience, with approximately 90% finding the clinic informative, with understandable information and helpful in deciding about pursuing pregnancy. However, 17% found the process intimidating, but this may prove difficult to abrogate in such a highly emotive situation. Clearly the inclusion of midwives, general practitioners, counsellors, psychologists and clinical geneticists when required, may prove an extremely useful addition to this team. Electronic media including the internet and DVDs have also proven beneficial.[72,73]

MEDICATIONS

Women with CKD including those with a kidney transplant are prescribed different types of medications that have the potential to adversely affect the pregnancy outcomes. These include immunosuppressive, anti-hypertensive and anti-viral medications. Each is important for the mother's overall health, but their effects on the pregnant woman and her developing fetus have been a concern for many practitioners. The major classes of medications used in women with CKD and in transplant recipients and their known effects on the mother and her offspring will be described below. See table 3.

Immunosuppressants:

Maintaining adequate immunosuppressive drug levels can be a challenge because drug levels change dramatically during gestation, primarily due to changes in blood volume and placental metabolism. Due to a natural increase in glomerular filtration rate, small changes in renal function can indicate significant rejection in pregnant transplant recipients[74] and close monitoring of renal function and drug levels is important. It is important to closely monitor drug levels throughout all phases of gestation and collaboration with the transplant center is mandatory during and immediately after the pregnancy.

There are no guidelines about dosing of immunosuppressant medications during pregnancy, but several studies have provided recommendations. Kim *et al* recently reported on blood levels of calcineurin inhibitors during gestation in 88 pregnancies from 75 transplant recipients.[75] In 80 cases the serum creatinine was decreased by an average of 0.14mg/dl during pregnancy and returned to pre-pregnancy levels after delivery. Tacrolimus blood trough levels decreased during the second trimester (from 5.8 ±2.8 ng/ml) to 4.2 ±1.8ng/ml). Likewise, cyclosporine levels decreased during the second trimester from 125.1

±65.1 ng/ml to 75.4 ±35 ng/ml. The recommendations of this study were to increase calcineurin inhibitor dose by approximately 20-25% during gestation to maintain optimal drug levels. Aktürk also reported on the pharmacokinetics of tacrolimus during pregnancy and recommended calcineurin inhibitor dosing is significantly increased in order to maintain adequate trough levels during pregnancy.[76] Women should be informed that tacrolimus levels need to be closely monitored in pregnancy. It is highly bound to plasma protein and erythrocytes, with complicated pharmacokinetics that are even further altered by normal physiological changes in pregnancy such as anaemia, hypoalbuminaemia and increased creatinine clearance. Maintaining whole blood tacrolimus levels after conception risks toxicity but no dose change may incur under-treatment. Unbound trough concentrations may be the most appropriate level to monitor during pregnancy,[77] but these are technically challenging to measure in routine practice.

Immunosuppressive medications cross the maternal-placental-fetal interface[74,78] and therefore there are always concerns about their effect on fetal development. The fetal liver, which is interposed between the umbilical vein and fetal inferior vena cava, filters the pharmacologic agents that pass through the placenta, including immunosuppressants. Calcineurin inhibitors are well-known to cross the placenta and enter the fetal circulation.[74] Zheng et al recently reported on tacrolimus concentrations in maternal and umbilical cord blood at delivery in eight transplant recipients and found that umbilical cord venous blood concentrations were 71% that of maternal concentrations. The lower fetal blood concentrations were proposed to be caused by the active transport of tacrolimus from the fetus toward the mother by placental P-glycoprotein.[79] Whether in utero exposure to tacrolimus has adverse effects on fetal development however is not known. In animal studies it was recently shown that rats treated with cyclosporine (CSA) during pregnancy

experienced impaired kidney development, suggesting a predisposition to chronic kidney disease and hypertension in adult life.[80] Despite this, tacrolimus is deemed safe in pregnancy[81] and breastfeeding.[82]

Corticosteroids pass through the placenta, but most of the maternal dose undergoes placental metabolism[74] and therefore the fetus is generally protected from adverse effects of corticosteroids. While adverse effects associated with in utero exposure to corticosteroids are rare, there have though been sporadic reports of adrenal suppression in newborns of pregnant transplant recipients particularly when the corticosteroids dose was high.

Azathioprine also passes into the fetal circulation, but the fetus lacks inosinate pyrophosphorylase, which is required for the conversion of azathioprine to its active metabolite 6-mercaptopurine.[74] Therefore, concerns about the use of azathioprine in pregnancy have been less than for other immunosuppressive.[83] Indeed, mycophenolic acid products are routinely substituted for azathioprine before and during pregnancy.[23] Substantial data have shown that mycophenolic acid products are associated with an increased incidence of spontaneous abortion and a distinct pattern of birth defects.[84] The spectrum of mycophenolate embryopathy includes ocular anomalies, corpus callosum agenesis, heart defects, kidney malformations, diaphragmatic hernia and skeletal deformities.[85] Numerous reports of mycophenolate-associated malformations led the FDA to issue a black box warning on its use during pregnancy.

Less is known about the effects of sirolimus in pregnancy. Sifontis reported on seven pregnancies with sirolimus exposure in seven pregnancies.[86] In three there were miscarriages and four resulted in live births. No malformations were observed but sirolimus

was switched to azathioprine during the first trimester in one case and in another the immunosuppressive regimen was switched from mycophenolate to sirolimus at 24 weeks. In the latter case the infant was born with features typical of mycophenolate embryopathy. There are several reports of sirolimus exposure during the whole pregnancy, without apparent adverse effects on the fetus.[87–90]

Recently there have been several reports about pregnancy in transplant recipients taking the mTOR inhibitor everolimus during their pregnancy.[91,92] One report of an unplanned pregnancy in a heart transplant recipient described a normal baby without obvious congenital defects. The fetus was exposed to everolimus as concentrations were similar in maternal and neonatal umbilical blood, and fetal blood levels were detected for 5 days after birth. In contrast CsA levels, which were also detected in umbilical blood, disappeared within 2 days of delivery in fetal blood.[93] Other reports have been published recently describing exposure to everolimus during pregnancies in kidney transplant recipients without apparent congenital malformations.[94,95] Although the few reports of unremarkable pregnancies with the use of mTOR inhibitors are encouraging, additional data are needed to confirm their safe use during pregnancy.

Treatment of rejection with corticosteroids is the mainstay during pregnancy and is generally considered safe to the fetus.[96] Recently Kutzler et al reported on the safe use of anti-thymocyte globulin (ATG) to successfully treat a pregnant renal transplant recipient with mixed acute cellular rejection and antibody-mediated rejection.[97] The patient was also treated with high-dose corticosteroids, intravenous immunoglobulin and plasmapheresis in addition to ATG; and she gave birth to a healthy baby boy. The safety of rejection treatment with ATG or other monoclonal or polyclonal antibodies has not been evaluated in clinical

trials in pregnant transplant recipients and only scattered case reports are available. There are no data on the long term impact on the exposed children's immune repertoire.

Management of lupus nephritis (LN) and other causes of autoimmune glomerulonephritides in pregnancy remains challenging due to limited safe therapeutic options. Cyclophosphamide and mycophenolate mofetil are teratogenic, and are generally to be avoided in pregnancy, although can be considered from the third trimester.[98] Steroids are often used in pregnancy as they are not associated with congenital abnormalities[99] but can cause premature rupture of membranes, preterm delivery, maternal sepsis and gestational diabetes.[100] Data on Rituximab use in pregnancy are limited but it does cross the placenta and lymphopaenia has been reported in new born children.[101] Hydroxychloroquine and azathioprine are safe in pregnancy and should be considered in treatment regimens prior to conception, along with aspirin. Hydroxychloroquine (HCQ) reduces the risk cardiac manifestations of neonatal lupus in anti-Ro-positive mothers and is actively recommended in women with LN before and during pregnancy.[102] Tacrolimus may be a useful alternative or adjunctive therapy for LN flare during pregnancy.[103]

Anti-Hypertensives:

Adverse effects of renin angiotensin system (RAS) blockade have been shown for some time, and ACE inhibitors and angiotensin receptor blockers are teratogenic.[104–107] In a recent retrospective study performed through the Midwest Pediatric Nephrology Consortium, RAS blocker fetopathy was identified and confirmed to depend on the timing of exposure, with the most severe renal manifestations occurring with exposure after the first trimester.[104] Beta blockers are commonly used during pregnancy and recent meta-analyses showed that first-trimester oral beta-blocker exposure was associated with no increase in major

congenital anomalies, but examination of organ-specific malformations revealed increased odds of cardiovascular defects, cleft lip/palate, and neural tube defects.[108] There is significant heterogeneity in the reports and thus it is not clear at this time whether beta-blockers are associated with these defects. Calcium channel blockers have recently been used in the management of hypertensive disorders of pregnancy and preterm labor. Teratogenicity with calcium channel blockers has been shown in animals, but no cases have yet been reported in humans and at this time are reported to be safe for use in pregnancy-associated hypertension.[109]

Antivirals:

Several antivirals have been used during pregnancy. The most commonly used antiviral agents target CMV infection. All of these have fetal toxicity. Valganciclovir should not be used as animal studies have revealed it can cause embryolethality, fetotoxicity, teratogenicity, and mutagenicity. Valganciclovir may cause impaired fertility in both males and females.[110] If CMV prophylaxis is required, valaciclovir is considered safe though possibly less effective. Lamivudine and tenofovir are safe for Hepatitis B prophylaxis. [111, 112]

CONCLUSIONS

Pregnancy in women with CKD and kidney transplant should be planned, considered high risk, and ideally managed by an expert multidisciplinary team. The best outcomes are likely seen where there has been careful pre-pregnancy evaluation and planning, and close monitoring during antenatal care. The outcomes for women and babies continue to improve

but we still need better biomarkers e.g. placental growth factor (PlGF) to identify those women at higher risk of developing superimposed pre-eclampsia.[113]

DISCLOSURES

Michelle A. Josephson is member of the Mycophenolate Pregnancy Registry Advisory Committee

REFERENCES

1. Shahir AK, Briggs N, Katsoulis J *et al.* An observational outcomes study from 1966-2008, examining pregnancy and neonatal outcomes from dialysed women using data from the ANZDATA Registry. *Nephrology (Carlton).* 2013;18:276–284.

2. Alkhunaizi A, Melamed N, Hladunewich MA. Pregnancy in advanced chronic kidney disease and end-stage renal disease. *Curr. Opin. Nephrol. Hypertens.* 2015;24:252–259.

3. Jones DC, Hayslett JP. Outcome of pregnancy in women with moderate or severe renal insufficiency. *N. Engl. J. Med.* 1996;335:226–232.

4. Pregnancy and renal disease. *Lancet (London, England)* 1975;2:801–802.

5. Davison JM, Lindheimer MD. Pregnancy and chronic kidney disease. *Semin. Nephrol.* 2011;31:86–99.

6. Jungers P, Chauveau D, Choukroun G *et al.* Pregnancy in women with impaired renal function. *Clin. Nephrol.* 1997;47:281–288.

7. Davison JM, Katz AI, Lindheimer MD. Kidney disease and pregnancy: obstetric outcome and long-term renal prognosis. *Clin. Perinatol.* 1985;12:497–519.

8. American Society of Nephrology | NephSAP - NephSAP Volume 15, Number 2 - Pregnancy and Kidney Disease.

9. K/DOQI clinical practice guidelines for chronic kidney disease:evaluation, classification, and stratification. *Am. J. Kidney Dis.* 2002;39:S1-266.

10. Piccoli GB, Cabiddu G, Attini R *et al.* Risk of Adverse Pregnancy Outcomes in Women with CKD. *J. Am. Soc. Nephrol.* 2015;26:2011–2022.

11. Smith MC, Moran P, Ward MK *et al.* Assessment of glomerular filtration rate during pregnancy using the MDRD formula. *BJOG* 2008;115:109–112.

12. Pamella S Ochoa JAV. Comparison of 24-Hour Urine to Estimated Renal Function using

CKD-EPI, MDRD4 and Cockcroft-Gault in Specific Patient Subsets. *J. Pharm. Care Heal. Syst.* 2015;2.

13. Côté A-M, Lam EM, von Dadelszen P *et al.* Monitoring renal function in hypertensive pregnancy. *Hypertens. pregnancy* 2010;29:318–329.

14. Imbasciati E, Gregorini G, Cabiddu G *et al.* Pregnancy in CKD stages 3 to 5: fetal and maternal outcomes. *Am. J. Kidney Dis.* 2007;49:753–762.

15. Zhang J-J, Ma X-X, Hao L *et al.* A Systematic Review and Meta-Analysis of Outcomes of Pregnancy in CKD and CKD Outcomes in Pregnancy. *Clin. J. Am. Soc. Nephrol.* 2015;10:1964–1978.

16. Clowse MEB, Jamison M, Myers E *et al.* A national study of the complications of lupus in pregnancy. *Am. J. Obstet. Gynecol.* 2008;199:127.e1-6.

17. Bramham K, Nelson-Piercy C, Gao H *et al.* Pregnancy in renal transplant recipients: a UK national cohort study. *Clin. J. Am. Soc. Nephrol.* 2013;8:290–298.

18. Deshpande NA, James NT, Kucirka LM *et al.* Pregnancy outcomes in kidney transplant recipients:a systematic review and meta-analysis. *Am. J. Transplant* 2011;11:2388–2404.

19. Gill JS, Zalunardo N, Rose C *et al.* The pregnancy rate and live birth rate in kidney transplant recipients. *Am. J. Transplant* 2009;9:1541–1549.

20. Coscia LA, Constantinescu S, Moritz MJ *et al.* Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clin. Transpl.* 2010:65–85.

21. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. *J. Am. Soc. Nephrol.* 2009;20:2433–2440.

22. Sibanda N, Briggs JD, Davison JM *et al.* Pregnancy after organ transplantation: a report from the UK Transplant pregnancy registry. *Transplantation* 2007;83:1301–1307.

23. McKay DB, Josephson MA, Armenti VT *et al.* Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. *Am. J. Transplant* 2005;5:1592–1599.

24. Deshpande NA, Coscia LA, Gomez-Lobo V *et al.* Pregnancy after solid organ transplantation: a guide for obstetric management. *Rev. Obstet. Gynecol.* 2013;6:116–125.

25. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. *Nephrol. Dial. Transplant* 2002;17 Suppl 4:50–55.

26. Fischer T, Neumayer H-H, Fischer R *et al.* Effect of pregnancy on long-term kidney function in renal transplant recipients treated with cyclosporine and with azathioprine. *Am. J. Transplant* 2005;5:2732–2739.

27. Rose C, Gill J, Zalunardo N *et al.* Timing of Pregnancy After Kidney Transplantation and Risk of Allograft Failure. *Am. J. Transplant* 2016;16:2360–2367.

28. Kasiske BL, Anderson-Haag T, Israni AK *et al.* A prospective controlled study of living kidney donors: three-year follow-up. *Am. J. Kidney Dis.* 2015;66:114–124.

29. Garg AX, McArthur E, Lentine KL. Gestational hypertension and preeclampsia in living kidney donors. *N. Engl. J. Med.* 2015;372:1469–1470.

30. Ibrahim HN, Akkina SK, Leister E *et al.* Pregnancy outcomes after kidney donation. *Am. J. Transplant* 2009;9:825–834.

31. Reisaeter A V, Røislien J, Henriksen T *et al.* Pregnancy and birth after kidney donation: the Norwegian experience. *Am. J. Transplant* 2009;9:820–824.

32. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet. Gynecol.* 2013;122:1122–31.

33. Krause T, Lovibond K, Caulfield M *et al.* Management of hypertension: summary of NICE guidance. *BMJ* 2011;343:d4891.

34. Lowe SA, Brown MA, Dekker GA *et al.* Guidelines for the management of hypertensive disorders of pregnancy 2008. *Aust. N. Z. J. Obstet. Gynaecol.* 2009;49:242–246.

35. Magee LA, Helewa M, Moutquin J-M *et al.* Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *J. Obstet. Gynaecol. Canada JOGC = J. d'obstétrique gynécologie du Canada JOGC* 2008;30:S1-48.

36. Bateman BT, Bansil P, Hernandez-Diaz S *et al.* Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. *Am. J. Obstet. Gynecol.* 2012;206:134.e1-8.

37. Redman CWG. Hypertension in pregnancy: the NICE guidelines. *Heart* 2011;97:1967–9.

38. von Dadelszen P, Ornstein MP, Bull SB *et al.* Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension:a meta-analysis. *Lancet (London, England)* 2000;355:87–92.

39. Ferrer RL, Sibai BM, Mulrow CD *et al.* Management of mild chronic hypertension during pregnancy: a review. *Obstet. Gynecol.* 2000;96:849–860.

40. Kuklina E V, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet. Gynecol.* 2009;113:1299–1306.

41. Scantlebury DC, Kane GC, Wiste HJ *et al.* Left ventricular hypertrophy after hypertensive pregnancy disorders. *Heart* 2015;101:1584–1590.

42. Zanati Bazan SG, Borges VM, Martin LC *et al.* Disproportionate pregnancy-induced myocardial hypertrophy in women with essential hypertension. *Am. J. Hypertens.* 2013;26:816–821.

43. Magee LA, von Dadelszen P, Rey E *et al.* Less-tight versus tight control of hypertension in

pregnancy. *N. Engl. J. Med.* 2015;372:407–417.

44. Hussain A, Karovitch A, Carson MP. Blood pressure goals and treatment in pregnant patients with chronic kidney disease. *Adv. Chronic Kidney Dis.* 2015;22:165–169.

45. Mills KT, Xu Y, Zhang W *et al.* A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int.* 2015;88:950–957.

46. Steel JM, Johnstone FD, Smith AF *et al.* Five years' experience of a "prepregnancy" clinic for insulin-dependent diabetics. *BMJ* 1982;285:353–356.

47. Wilkinson H. Saving Mothers' Lives. Reviewing maternal deaths to make motherhood safer:2006-2008. *BJOG An Int. J. Obstet. Gynaecol.* 2011;118:1402–1403.

48. Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ* 2008;336:211–215.

49. Hou S. Pregnancy in chronic renal insufficiency and end-stage renal disease. *Am. J. Kidney Dis.* 1999;33:235–252.

50. Meuwese CL, Carrero JJ. Chronic kidney disease and hypothalamic-pituitary axis dysfunction: the chicken or the egg? *Arch. Med. Res.* 2013;44:591–600.

51. Finkelstein FO, Shirani S, Wuerth D *et al.* Therapy Insight: sexual dysfunction in patients with chronic kidney disease. *Nat. Clin. Pract. Nephrol.* 2007;3:200–207.

52. Davison JM, Bailey DJ. Pregnancy following renal transplantation. *J. Obstet. Gynaecol. Res.* 2003;29:227–333.

53. Barua M, Hladunewich M, Keunen J *et al.* Successful pregnancies on nocturnal home hemodialysis. *Clin. J. Am. Soc. Nephrol.* 2008;3:392–396.

54. van Eps C, Hawley C, Jeffries J *et al.* Changes in serum prolactin, sex hormones and thyroid function with alternate nightly nocturnal home haemodialysis. *Nephrology (Carlton).* 2012;17:42–47.

55. Chronic kidney disease in adults: assessment and management | 1-recommendations |

Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/cg182/chapter/1-Recommendations. Last accessed 26/09/2016

56. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO_BP_GL.pdf. Last accessed 26/09/2016.

57. Gillon TER, Pels A, von Dadelszen P *et al.* Hypertensive disorders of pregnancy:a systematic review of international clinical practice guidelines. *PLoS One* 2014;9:e113715.

58. Hypertension in pregnancy: diagnosis and management | Guidance and guidelines | NICE. https://www.nice.org.uk/Guidance/CG107. Last accessed 26/09/2016.

59. Duley L, Henderson-Smart DJ, Meher S *et al.* Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane database Syst. Rev.* 2007:CD004659.

60. Stratta P, Canavese C, Quaglia M. Pregnancy in patients with kidney disease. *J. Nephrol.* 2006;19:135–143.

61. Ferrazzani S, Caruso A, De Carolis S *et al.* Proteinuria and outcome of 444 pregnancies complicated by hypertension. *Am. J. Obstet. Gynecol.* 1990;162:366–371.

62. Imbasciati E, Ponticelli C. Pregnancy and Renal Disease: Predictors for Fetal and Maternal Outcome. *Am. J. Nephrol.* 1991;11:353–362.

63. Smyth A, Oliveira GHM, Lahr BD *et al.* A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin. J. Am. Soc. Nephrol.* 2010;5:2060–2068.

64. Bramham K, Soh MC, Nelson-Piercy C. Pregnancy and renal outcomes in lupus nephritis:an update and guide to management. *Lupus* 2012;21:1271–1283.

65. Stanhope TJ, White WM, Moder KG *et al.* Obstetric Nephrology:Lupus and Lupus Nephritis in Pregnancy. *Clin. J. Am. Soc. Nephrol.* 2012;7:2089-2099.

66. Buyon JP, Kim MY, Guerra MM *et al.* Predictors of Pregnancy Outcomes in Patients With Lupus:A Cohort Study. *Ann. Intern. Med.* 2015;163:153–163.

67. Thornhill AR, deDie-Smulders CE, Geraedts JP *et al.* ESHRE PGD Consortium "Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)". *Hum. Reprod.* 2005;20:35–48.

68. De Rycke M, Georgiou I, Sermon K *et al.* PGD for autosomal dominant polycystic kidney disease type 1. *Mol. Hum. Reprod.* 2005;11:65–71.

69. Elsinga J, de Jong-Potjer LC, van der Pal-de Bruin KM *et al.* The effect of preconception counselling on lifestyle and other behaviour before and during pregnancy. *Womens. Health Issues* 2008;18:S117-125.

70. O'Higgins S, McGuire BE, Mustafa E *et al.* Barriers and facilitators to attending pre-pregnancy care services:the ATLANTIC-DIP experience. *Diabet. Med.* 2014;31:366–374.

71. Wiles KS, Bramham K, Vais A *et al.* Pre-pregnancy counselling for women with chronic kidney disease: a retrospective analysis of nine years' experience. *BMC Nephrol.* 2015;16:28.

72. Agricola E, Pandolfi E, Gonfiantini M V *et al.* A cohort study of a tailored web intervention for preconception care. *BMC Med. Inform. Decis. Mak.* 2014;14:33.

73. Hamill LL, McCance DR, Deery M *et al.* Impact of a preconception counselling resource (DVD) on preconception folic acid intake in women with diabetes. *Proc. Nutr. Soc.* 2014;73:E64.

74. McKay DB, Josephson MA. Pregnancy in recipients of solid organs - effects on mother and child. *N. Engl. J. Med.* 2006;354:1281–1293.

75. Kim H, Jeong JC, Yang J *et al.* The optimal therapy of calcineurin inhibitors for pregnancy in kidney transplantation. *Clin. Transplant.* 2015;29:142–148.

76. Aktürk S, Çelebi ZK, Erdoğmuş Ş *et al.* Pregnancy After Kidney

Transplantation:Outcomes, Tacrolimus Doses, and Trough Levels. *Transplant. Proc.* 2015;47:1442–1444.

77. Hebert MF, Zheng S, Hays K *et al.* Interpreting tacrolimus concentrations during pregnancy and postpartum. *Transplantation* 2013;95:908–915.

78. Ostensen M. Disease specific problems related to drug therapy in pregnancy. *Lupus* 2004;13:746–750.

79. Zheng S, Easterling TR, Hays K *et al.* Tacrolimus placental transfer at delivery and neonatal exposure through breast milk. *Br. J. Clin. Pharmacol.* 2013;76:988–996.

80. Slabiak-Blaz N, Adamczak M, Gut N *et al.* Administration of Cyclosporine A in Pregnant Rats - the Effect on Blood Pressure and on the Glomerular Number in Their Offspring. *Kidney Blood Press. Res.* 2015;40:413–423.

81. Armenti VT, Constantinescu S, Moritz MJ *et al.* Pregnancy after transplantation. *Transplant. Rev. (Orlando).* 2008;22:223–240.

82. Bramham K, Chusney G, Lee J *et al.* Breastfeeding and tacrolimus: serial monitoring in breast-fed and bottle-fed infants. *Clin. J. Am. Soc. Nephrol.* 2013;8:563–567.

83. McKay DB, Adams PL, Bumgardner GL *et al.* Reproduction and pregnancy in transplant recipients: current practices. *Prog. Transplant.* 2006;16:127–132.

84. Coscia LA, Constantinescu S, Davison JM *et al.* Immunosuppressive drugs and fetal outcome. *Best Pract. Res. Clin. Obstet. Gynaecol.* 2014;28:1174–1187.

85. Perez-Aytes A, Ledo A, Boso V *et al.* In utero exposure to mycophenolate mofetil:a characteristic phenotype? *Am. J. Med. Genet. A* 2008;146A:1–7.

86. Sifontis NM, Coscia LA, Constantinescu S *et al.* Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. *Transplantation* 2006;82:1698–1702.

87. Chu S-H, Liu K-L, Chiang Y-J *et al.* Sirolimus used during pregnancy in a living related renal transplant recipient:a case report. *Transplant. Proc.* 2008;40:2446–2448.

88. Guardia O, Rial MDC, Casadei D. Pregnancy under sirolimus-based immunosuppression. *Transplantation* 2006;81:636.

89. Framarino dei Malatesta M, Corona LE, De Luca L *et al.* Successful pregnancy in a living-related kidney transplant recipient who received sirolimus throughout the whole gestation. *Transplantation* 2011;91:e69-71.

90. Jankowska I, Oldakowska-Jedynak U, Jabiry-Zieniewicz Z *et al.* Absence of teratogenicity of sirolimus used during early pregnancy in a liver transplant recipient. *Transplant. Proc.* 2004;36:3232–3233.

91. Carta P, Caroti L, Zanazzi M. Pregnancy in a kidney transplant patient treated with everolimus. *Am. J. Kidney Dis.* 2012;60:329.

92. Margoles HR, Gomez-Lobo V, Veis JH *et al.* Successful maternal and fetal outcome in a kidney transplant patient with everolimus exposure throughout pregnancy:a case report. *Transplant. Proc.* 2014;46:281–283.

93. Fiocchi R, D'Elia E, Vittori C *et al.* First Report of a Successful Pregnancy in an Everolimus-Treated Heart-Transplanted Patient:Neonatal Disappearance of Immunosuppressive Drugs. *Am. J. Transplant* 2016;16:1319-1322.

94. Carta P, Zanazzi M, Minetti EE. Unplanned pregnancies in kidney transplanted patients treated with everolimus: three case reports. *Transpl. Int.* 2015;28:370–372.

95. Veroux M, Corona D, Veroux P. Pregnancy under everolimus-based immunosuppression. *Transpl. Int.* 2011;24:e115-7.

96. Josephson MA, McKay DB. Pregnancy and kidney transplantation. *Semin. Nephrol.* 2011;31:100–110.

97. Kutzler HL, Ye X, Rochon C *et al.* Administration of Anti-thymocyte Globulin (Rabbit) to Treat a Severe, Mixed Rejection Episode in a Pregnant Renal Transplant Recipient. *Pharmacotherapy* 2016;36:e18-22.

98. Østensen M, Khamashta M, Lockshin M *et al.* Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res. Ther.* 2006;8:209.

99. Anderson GG, Rotchell Y, Kaiser DG. Placental transfer of methylprednisolone following maternal intravenous administration. *Am. J. Obstet. Gynecol.* 1981;140:699–701.

100. Mariotti V, Marconi A, Pardi G. Undesired effects of steroids during pregnancy. *J Matern Fetal Neonatal Med.* 2004;16suppl2:5-7.

101. Hyrich KL, Verstappen SMM. Biologic therapies and pregnancy:the story so far. *Rheumatology (Oxford).* 2014;53:1377–1385.

102. Izmirly PM, Kim MY, Llanos C *et al.* Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. *Ann. Rheum. Dis.* 2010;69:1827–1830.

103. Webster P, Wardle A, Bramham K *et al.* Tacrolimus is an effective treatment for lupus nephritis in pregnancy. *Lupus* 2014;23:1192–1196.

104. Nadeem S, Hashmat S, Defreitas MJ *et al.* Renin Angiotensin System Blocker Fetopathy:A Midwest Pediatric Nephrology Consortium Report. *J. Pediatr.* 2015;167:881–885.

105. Cooper WO, Hernandez-Diaz S, Arbogast PG *et al.* Major congenital malformations after first-trimester exposure to ACE inhibitors. *N. Engl. J. Med.* 2006;354:2443–2451.

106. Tabacova S, Little R, Tsong Y *et al.* Adverse pregnancy outcomes associated with maternal enalapril antihypertensive treatment. *Pharmacoepidemiol. Drug Saf.* 2003;12:633–

646.

107. Velázquez-Armenta EY, Han JY, Choi JS *et al.* Angiotensin II receptor blockers in pregnancy: a case report and systematic review of the literature. *Hypertens. pregnancy* 2007;26:51–66.

108. Yakoob MY, Bateman BT, Ho E *et al.* The risk of congenital malformations associated with exposure to β-blockers early in pregnancy:a meta-analysis. *Hypertension* 2013;62:375–381.

109. Tranquilli AL, Giannubilo SR. Use and safety of calcium channel blockers in obstetrics. *Curr. Med. Chem.* 2009;16:3330–3340.

110. Valcyte® (valganciclovir hydrochloride) Patient Support. http://www.valcyte.com/patient. Last accessed 26/09/2016.

111. Yi W, Liu M, Cai H-D. Safety of lamivudine treatment for chronic hepatitis B in early pregnancy. *World J. Gastroenterol.* 2012;18:6645–6650.

112. Wang L, Kourtis AP, Ellington S *et al.* Safety of tenofovir during pregnancy for the mother and fetus:a systematic review. *Clin. Infect. Dis.* 2013;57:1773–1781.

113. Bramham K, Seed PT, Lightstone L *et al.* Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. *Kidney Int.* 2016;89:874–885.

Legends:

Table 1: Prepregnancy kidney function in patients with CKD with estimates of problems in pregnancy (fetal growth restriction, preeclampsia, preterm delivery, and significant kidney function loss in pregnancy [>25% SCr increment]), obstetric outcome, and loss of kidney function: The effect of altering cut-off between moderate and severe dysfunction from 2.8 mg/dL (≥250µmol/L) to 2.0 mg/dL (≥180µmol/L), respectively

Table 2: Hypertensive disorders of pregnancy

Table 3: Drug Safety in Pregnancy

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Pregnancy in Chronic Kidney Disease and Kidney Transplantation

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RUNNING HEADLINE: Pregnancy in CKD & Kidney Transplantation

ABSTRACT

Chronic kidney disease (CKD) affects up to 6% of women of childbearing age in high income countries, and is estimated to affect 3% of pregnant women. Advanced renal dysfunction, proteinuria, hypertension and poorly controlled underlying primary renal disease are all significant risks for adverse maternal, fetal and renal outcomes. In order to achieve the best outcomes it is therefore of paramount importance that these pregnancies are planned, where possible, to allow the opportunity to counsel women and their partners in advance and to optimize these risks. These pregnancies should be deemed high risk and they require close antenatal monitoring from an expert multidisciplinary team.

We discuss the effect of pregnancy on CKD, and also current guidelines and literature with specific reference to transplantation, autoimmune disease and medication use in pregnancy. We also discuss the benefits of pre-pregnancy counselling and give practical recommendations to advise pregnant women with renal disease.

THE IMPACT OF KIDNEY FUNCTION ~~IN AND OF ITSELF~~ON PREGNANCY OUTCOME

CKD ~~degree~~stage and outcomes

The pregnancies of most normotensive women with mild or even moderate renal dysfunction succeed, but are prone to more complications than those of gravidas with normal renal function. However, pregnancy is much more hazardous when kidney dysfunction is advanced. Women with advanced chronic kidney disease (CKD) have a lower likelihood of conceiving because of the decreased fertility associated with the hormonal changes of worsening kidney function and ESRD.[1] When they do conceive, advanced CKD predisposes to intrauterine growth restriction and preterm delivery,[2] and pregnancy has been blamed for hastening the rate of decline of kidney function, increasing proteinuria, and hypertension.[3] Such views however are based on insufficient data. Thus the level of kidney function/dysfunction and its effect on pregnancy remains a ~~hot~~ debated area~~topic~~.

An evolving state of understanding

Currently there is controversy reflecting the swinging pendulum of attitudes related to pregnancy in women with CKD, as well as the evolution of how the nephrology community assesses renal function. In 1975, an anonymously authored Lancet editorial noted that physicians in the past preferred avoiding pregnancy in women with any degree of CKD by noting: “Children of women with renal disease used to be born dangerously or not at all - not at all if their doctors had their way”.[4] The editorial took the then provocative stance that as most pregnancies succeed in the setting of mild kidney dysfunction, this attitude should be changed. Davison and Lindheimer[5] noted in 2010 that studies in the decades after the Lancet editorial led to a better understanding of outcomes for pregnancy in women with kidney dysfunction. Observational studies indicated that outcomes depended

on the degree of renal insufficiency pre-pregnancy, and the presence or absence of hypertension.[6] Based on these parameters, women were grouped into three categories: mild, moderate, or severe dysfunction. Normotensive women with preserved or mildly decreased but stable kidney function (defined as a serum creatinine (SCr) of ≤1.4 mg/dL) did well with over 95% live births, 75% of which were appropriate size for gestational age. However, prognosis worsened with moderate dysfunction (SCr ≥ 1.4 mg/dL-2.8 mg/dL) and more so with severe impairment (SCr level ≥ 2.8 mg/dL).[7] These estimates were based on a 26-year literature review (1984-2010), as well as personal patient files by John Davison, most recently published in a NephSAP editorial by Drs Lindheimer and Davison, in the issue devoted to renal disease and hypertension in pregnancy (reproduced with permission in Table 1).[8] ~~See Table 1~~.

Creatinine vs eGFR

In 2002 the Kidney Disease Outcomes Quality Initiative (KDOQI) released a new chronic kidney disease (CKD) classification designating five categories based on estimated glomerular filtration rate (eGFR).[9] Ignoring the question of whether this classification system over-diagnosed kidney disease and dysfunction in some, the eGFR based system provided another filter through which to consider pregnancy outcomes. Piccoli and colleagues[10] used the classification and looked at pregnancy outcomes in 504 pregnancies in women with CKD compared with 836 low-risk pregnancies in women without CKD. They considered whether hypertension, proteinuria (> 1 gram/day), systemic disease, or CKD stage at baseline affected pregnancies. Outcomes assessed were: cesarean section, preterm delivery, early preterm delivery, small for gestational age, need for neonatal intensive care unit, new onset of hypertension, new onset/doubling of proteinuria, CKD stage shift, and a combined

outcome. The majority of patients in the study were classified as CKD stage 1. The authors concluded that adverse outcomes increased with increasing stage of CKD, including surprisingly stage 1, even in the absence of hypertension, baseline proteinuria, and systemic diseases. ~~The study analysis had sufficient data to confirm that adverse outcomes increased with increasing stage of CKD, including surprisingly stage 1, even in the absence of hypertension, baseline proteinuria, and systemic diseases.~~ The eGFR was calculated based on the Cockcroft–Gault, Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas. As CKD-EPI and MDRD have been found to underestimate GFR in pregnancy[11,12] and Cockcroft-Gault has been demonstrated to both underestimate and overestimate GFR in hypertensive pregnant women,[13] it is possible that some of the patients in Piccoli's study had lower GFRs than the group in which they were classified. Some of the individuals reported to have CKD stage 1, could therefore have had a higher stage. While Piccoli *et al's* findings were primarily in women with mild and moderate dysfunction Imbasciati et al studied 49 women with preconception stage 3 to 5 CKD observed for a mean of 39 months after delivery. In the latter study only individuals with both GFR less than 40 ml/min/1.73m^2 and greater than 1 gram of proteinuria per day were noted to have poor fetal outcomes and accelerated kidney function loss.[14] A meta-analysis by Zhang et al of 23 studies that included 1514 pregnancies with CKD found no significant difference in renal outcomes in pregnant women with CKD compared with non-pregnant women with CKD. The study did however find that adverse pregnancy outcomes, including preeclampsia, premature births, SGA/low birth weight, cesarean section, stillbirth, fetal death, and neonatal death, were increased in women with CKD compared to those without. The conclusions that can be drawn from the meta-analysis must be put into

context because the literature review focused on patients with CKD stages 1-3, thus excluding those with stage 4 or 5 who are most vulnerable for progression of disease.[15]

In their review and recent editorial Lindheimer and Davison[5,8] underscore that most eGFR formulae correlate poorly with measured GFR in pregnant women, and that obstetricians familiar with absolute values of creatinine may be unfamiliar with the nephrology community's CKD system . However, despite the seeming differences between those who are considering pregnancy outcomes through an eGFR based CKD stages filter, and those who are more comfortable with the serum creatinine based assessment, proponents of both agree that degree of kidney function plays an important role in outcome. Neither group advocates returning to the pre-1975 mindset of avoiding pregnancy in women with mild kidney dysfunction, however defined.

Additional contributing factors

Whilst clearly important, kidney function alone does not uniformly predict pregnancy outcomes. There are likely to be additional contributing factors to pregnancy outcomes, such as active systemic disease or endothelial injury. For example cCertain specific diseases such as Systemic Lupus Erythematosus (SLE) may exert a greater adverse effect on the pregnancy making it impossible to isolate the role of kidney function per se on outcomes.[16] Similarly kidney transplantation does not present a pristine model to look at kidney function alone because of the effects of immunosuppression.

Kidney transplantation and outcome

A national UK cohort study demonstrated that most pregnancies after renal transplantation are successful, although the risks of pre-eclampsia still remain higher than controls[17] and

this higher risk of pre-eclampsia affects even those with good GFRs.[18] Patients should be counselled of this accordingly and the other precautions discussed in the pre-pregnancy counselling section, initiated. How does the connection between kidney function and pregnancy outcomes relate to pregnancy outcomes in kidney transplant recipients? Similar to findings in advanced kidney failure, transplant patients appear to have a lower ~~fertility~~ pregnancy rate than the general public.[19] Registry, cohort, and meta-analysis studies demonstrate that pregnancies in transplant recipients, which are more likely to be complicated by hypertension, are at greater risk for prematurity, small for gestational age, cesarean sections, the diagnosis of preeclampsia and perinatal mortality.[17,18,20] Of note while pregnancy and renal function outcomes in transplant recipients have been studied based on creatinine levels, we could locate no assessments based on the CKD staging system. In transplant recipients, there are the additional factors of immunosuppression medications. These factors make it hard to isolate and define the kidney function effect on pregnancy in this group. Long term follow-up of transplant recipients with and without a history of pregnancy supports the idea that pregnancy does not worsen long term outcomes.[21]

However, there may be subsets of transplant patients in whom pregnancy accelerates renal function decline.~~However, there may be subsets of transplant patients in whom it does.~~ Data from the UK Pregnancy registry indicate that women with kidney allografts whose pre-pregnancy SCr is greater than 150µmol/L (approximately 1.7 mg/dL) have an increased serum creatinine after pregnancy, suggesting that the pregnancy itself may negatively affect graft function.[22] Despite limitations of available data in the transplant recipient, guidelines advise that amongst other factors, the basis for determining reasonable timing for pregnancy is the presence of adequate and stable graft function (arbitrarily set as a SCr<1.5

mg/dL).[23] The American Society of Transplantation recommends that prior to pregnancy there should be no rejection for one year, adequate and stable graft function, no acute infections, and stable immunosuppression dosing.[24] Pregnancy should be delayed until at least one year after renal transplantation[25] as postponement is associated with better outcomes.[26] A recent study by Rose et al that examined allograft outcome and pregnancy timing in the first 3 post-transplant years of Medicare insured kidney transplant recipients suggests that pregnancy in the first 2 post-transplant years is associated with increased allograft loss compared with waiting an additional year.[27] Beyond optimal post-transplant pregnancy timing, t~~T~~here are many other unanswered questions about pregnancy in transplant recipients including the optimal pre-pregnancy kidney function and whether having pre-existent donor specific antibodies affects pregnancy outcomes, or the transplanted kidney. This last consideration is of particular concern given the usual pre-pregnancy modification of immunosuppression, with discontinuation of mycophenolic acid formulations.

Kidney donors

Pregnancy in kidney donors may be the perfect model in which to consider the role of kidney function. Donors are intensively medically screened and only allowed to donate a kidney if healthy. Their post-donation level of kidney function is approximately 75-80% of normal.[28] They do not have systemic disease and their remaining kidney, though hypertrophied and hyperfiltering, is normal. Three studies have found that post-donation pregnancies may be at increased risk for complications. Garg et al performed a population~~cohort~~ study and found a significantly higher incidence of gestational hypertension or preeclampsia in donors compared with matched non-donors.[29] Ibrahim et

al's survey of previous kidney donors documented subjects reporting significant increases in diagnosed preeclampsia, hypertension, and gestational diabetes in pregnancies after donation compared with before.[30] Reisaeter et al found more pre-eclampsia diagnosed in women after donation compared with pregnancies before.[31]

Kidney function impact

Taken together the studies, case series, and registries indicate that kidney function alone plays a role in pregnancy outcomes, though usually limited unless kidney dysfunction is moderate and proteinuria is present. Whether pregnancy in women with CKD changes the course of their kidney disease, is less clear. Kidney donors aside, patients with CKD (with or without kidney transplants) have other factors that may independently influence pregnancy outcomes, be it underlying disease, medications, proteinuria, or hypertension.

BLOOD PRESSURE

~~Using hospital discharge data from the Nationwide Inpatient sample (NIS) part of the Healthcare Cost and Utilization Project, a 2012 population-based study examined 56,494,634 deliveries between 1995 and 2008. During this period the prevalence of primary and secondary hypertension increased from 0.9% to 1.52% and 0.07% to 0.24% respectively.~~[25] Hypertension during pregnancy is an increasingly recognized problem, and one that has led to the creation of several management guidelines.[32–35] Using hospital discharge data from the Nationwide Inpatient sample (NIS) part of the Healthcare Cost and Utilization Project, a 2012 population-based study examined 56,494,634 deliveries between 1995 and 2008. During this period the prevalence of primary and secondary hypertension increased from 0.9% to 1.52% and 0.07% to 0.24% respectively.[36] Hypertension during

pregnancy can be broken down into four types as outlined in Table 2: pre-eclampsia / eclampsia, chronic hypertension, chronic hypertension with superimposed pre-eclampsia, and gestational hypertension.[32] ~~Women who require antihypertensive medications before pregnancy or whose hypertension begins before the 20th week of pregnancy, or whose hypertension continues for more than 12 weeks following delivery are defined as having chronic hypertension. By contrast gestational hypertension is diagnosed when blood pressure elevation occurs after the 20th week of pregnancy in the absence of proteinuria or thrombocytopenia, impaired liver function, new onset of kidney dysfunction, pulmonary edema, or new cerebral or visual disturbances.[30]~~ Management of hypertension during pregnancy differs from that in non-pregnant states. Blood pressure goals are more permissive during gestation. ~~Furthermore, there are substantial differences as to when to start pharmacological therapy between the American College of Obstetrics and Gynecology (ACOG) and several other National and International guidelines.[31] The report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy recommends "For women with chronic hypertension and BP less than 160 mm Hg systolic or 105 mm Hg diastolic that they not be treated with pharmacologic antihypertensive therapy." However, for those women who have chronic hypertension and are already treated with antihypertensive medications, the target range is 120-160 mm Hg systolic and 80-105 mm Hg diastolic."~~ However the American College of Obstetricians and Gynecology (ACOG) ~~They also~~ recommend~~ed~~ that if there is evidence of end organ damage, treatment goals should be as rigid as in the non-pregnant state.[32]

The reasoning behind why management in the pregnant and non-pregnant state differs is several-fold including that~~. This includes at least in part that as~~ pregnancy is a time limited

event in which, the benefits of treatment are not easily realized~~appreciated during the time~~. ~~Another guiding principal behind the more relaxed blood pressure thresholds is that~~ and ~~medication~~ treatment exposes ~~not only the mother, but also~~ the fetus to medications which may affect intrauterine programming and may lead to reduced utero-placental blood flow with compromised fetal circulation.[37,38] Whether or not blood pressure management should differ in pregnancy from non-pregnant ~~these 2~~ states is a point of current debate. Those who advocate that the 2 should not differ ~~lower thresholds for treatment~~ note that hypertension during pregnancy is not as benign as once thought. Hypertension during pregnancy has been associated with an increased risk for acute kidney injury (AKI), pulmonary edema, need for ventilator support, and cerebrovascular complications.[39,40] There is also now evidence that a hypertensive pregnancy is associated with later-in-life left ventricular hypertrophy.[41] An echocardiography study of pregnant and non-pregnant women who were normotensive or had essential hypertension suggested that pregnancy and hypertension have synergistic effects in causing myocardial hypertrophy.[42] This latter study indicates that cardiac changes may be seen not only years after delivery, but during the pregnancy too.

The debate over whether or not blood pressure goals in pregnant women with hypertension should be relaxed or stringent and the ACOG guidelines are timely as the Tight Control of Hypertension in Pregnancy Study (CHIPS) recently demonstrated that pregnancy outcomes and maternal complications were not significantly different in pregnant women whose hypertension was controlled more or less tightly.[43] However this debate is ~~but are~~ not germane to CKD~~. This is~~ because CKD *is* a form of end organ damage and the CHIPS trial excluded individuals with renal dysfunction. ~~, and~~ Consequently we suggest that such

patients should be treated more aggressively, that is in a manner similar to the non-pregnant state i.e. aiming for tight control.

Fetal and maternal outcomes for pregnant women with CKD are markedly worse in the presence of hypertension. Bateman *et al* observed odds ratios of stillbirth, poor fetal growth, and spontaneous delivery <37 weeks gestation to be 7.29, 7.49 and 8.60 compared with 1.74, 2.29 and 2.25 respectively in women with CKD plus hypertension compared with those with CKD alone.[36] Maternal complications were also markedly increased in women with CKD who had chronic hypertension compared with those with CKD but without chronic hypertension. For example, preeclampsia and AKI odds ratios were 27.87 and 253.4 compared with 3.28 and 62.4 respectively. Whether or not blood pressure control in women with CKD and chronic hypertension would reduce these risks has not been studied. ~~Nevertheless, the treatment goals for blood pressure during pregnancy in the setting of CKD are lower.~~ The United Kingdom's National Institute of Health and Clinical Excellence (NICE) clinical guidelines recommend keeping BP lower than 140/90 mmHg in pregnant women with target-organ damage, including CKD.[37] However, the evidence behind this blood pressure goal is scant at best.

The optimal blood pressure target for pregnant women with CKD and hypertension remains an unanswered question and important knowledge gap. Identifying that target is becoming increasingly important as the prevalence of CKD in pregnant women has increased from a range of 0.1% to 1% in the past to an estimated current prevalence of around 3%,[44] with recent literature suggesting that up to 6% of women of child-bearing age in high income countries are affected by CKD.[45]

PRE-PREGNANCY COUNSELLING

The value of pre-pregnancy counselling has been ~~recognised~~recognized in women with diabetes for several decades.[46] Pre-pregnancy counselling in women with chronic kidney disease offers the opportunity to ~~minimise~~minimize disease activity, ~~optimise~~optimize blood pressure control and proteinuria, alter teratogenic medications and also to educate couples about potential fetal and maternal adverse events that may occur during pregnancy and the puerperium in this high risk group. It also allows discussion of the inheritance of genetic disorders of the kidney including cystic diseases, metabolic diseases and glomerular basement membrane disorders. The confidential enquiries into maternal deaths in the UK endorses that pre-pregnancy counselling should be routinely commissioned and offered to women with pre-existing medical illnesses in view of the morbidity and mortality triggered by these diseases.[47] The advice given is clearly dependent on underlying renal disease, baseline renal function, proteinuria and blood pressure at conception and this should be delivered in a patient focused, individualised manner. Women with chronic kidney disease should be counselled prior to pregnancy of the increasing risk of maternal and fetal complications as GFR declines. These risks include fetal growth restriction, pre-term birth, pre-eclampsia, fetal death and deterioration of maternal renal function / disease flare.[48]

Fertility

Women may need to be advised that advanced chronic kidney disease impairs fertility.[49] This is due to a multitude of reasons, although these are poorly characterized in the literature. Hyperprolactinemia is common in patients with CKD, due to reduced renal clearance and increased production from suppression of dopaminergic activity, and this inhibits gonadotropin secretion. This manifests as amenorrhea in women.[50,51]. Levels of

leutinising hormone and follicle stimulating hormone are also elevated in CKD, although the physiological surge in LH usually seen during the mid-cycle of healthy women is not seen in those with CKD, and this can lead to anovulation.[51] These hypothalamic-pituitary axis dysfunctions, in combination with the psychological impact of CKD causing depression and reduced libido, can significantly reduce the chances of conception. However, fertility can be restored after renal transplantation.[52] As pregnancy outcomes are progressively poorer with advancing chronic kidney disease, younger women who want to become pregnant are often advised to be transplanted first. If this is not possible, nocturnal haemodialysis may restore menses and improve the chances of pregnancy.[53,54]

Optimization Before Pregnancy

Blood pressure should be optimized before pregnancy. Both KDIGO and UK National Institute for Health and Care Excellence (NICE) recommend that adults with CKD, without proteinuria should aim for a blood pressure below 140/90mmHg. NICE recommend that those with CKD who have diabetes or those with proteinuria (ACR >70mg/mmol) aim for a blood pressure below 130/80mmHg. KDIGO also recommend this level for patients with an ACR >30mg/mmol.[55,56] These targets should be achieved prior to conception with drugs that are safe to continue during pregnancy (summarized in table 3). ACE inhibitors and angiotensin receptor blockers should be stopped prior to pregnancy or as early as possible after discovering pregnancy. A recent systematic review of the management of hypertensive disorders in pregnancy recommends the preventative use of low dose aspirin to reduce pre-eclampsia, and in severe hypertension.[57] UK NICE guidelines also advocate the use of aspirin from 12 weeks of gestation in women at high risk to reduce the incidence of pre-

eclampsia.[58] Such risk factors include chronic kidney disease and autoimmune diseases such as systemic lupus erythematosus. This is based on a Cochrane review of 59 trials.[59]

Proteinuria may occur in 30% of women who do not have proteinuria before pregnancy,[60] and may confer poorer feto-maternal outcomes[61,62]. Proteinuria should therefore, where possible, be controlled during pre-pregnancy counselling, and the main way to achieve this is through optimizing treatment of baseline renal disease and blood pressure control. Women with proteinuria should be counselled about the potential requirement for thromboprophylaxis during pregnancy.

~~There are a number of clinical practice guidelines for the management of hypertensive disorders of pregnancy worldwide. A recent systematic review showed that there is good inter-guideline consistency for the definitions of chronic hypertension, proteinuria and gestational hypertension. Also consistent were the preventative use of low dose aspirin to reduce pre-eclampsia, and in severe hypertension.[52] Prior to conception, women should be educated about the symptoms of pre-eclampsia. ACE inhibitors and angiotensin receptor blockers should be stopped prior to pregnancy or as early as possible after discovering pregnancy.~~

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Systemic lupus erythematosus (SLE) affects women of child bearing age without affecting fertility and so pregnancy is not uncommon. A meta-analysis of 2751 women with SLE showed that those with active lupus nephritis (LN) had an increased risk of maternal hypertensive disorders and premature birth.[63] Disease flare, high initial creatinine and

proteinuria at conception are predictive of worse outcomes. In addition, flares may cause a decline in renal function and accelerate progression to end-stage renal disease. Pregnancy should be planned and drugs altered accordingly prior to pregnancy, including stopping / substituting mycophenolic acid products. A minimum six month period of disease quiescence prior to pregnancy is therefore recommended.[64,65] The PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) study, a large prospective cohort study including 385 patients, recently demonstrated that 81% of pregnancies in women with inactive or stable mild/moderate disease were uncomplicated.[66] Features indicating a higher risk for adverse pregnancy outcomes, included a positive lupus anticoagulant, antihypertensive use, a low platelet count, Hispanic or non-white ethnicity, and a physician's global assessment score >1; and those women without these generally had favourable outcomes.

~~Women with chronic kidney disease should be counselled prior to pregnancy of the increasing risk of maternal and fetal complications as GFR declines. These risks include fetal growth restriction, pre-term birth, pre-eclampsia, fetal death and deterioration of maternal renal function / disease flare.[56] Advanced chronic kidney disease impairs fertility[88] which can be restored after renal transplantation.[89] As pregnancy outcomes are progressively poorer with advancing chronic kidney disease, younger women who want to become pregnant are often advised to be transplanted first. A national UK cohort study demonstrated that most pregnancies after renal transplantation are successful, although the risks of pre-eclampsia still remain higher than controls[15] and this higher risk of pre-eclampsia is even in those with good GFRs.[17] Patients should be counselled of this accordingly and the other precautions discussed here initiated. Pregnancy should be delayed until one year after renal transplantation[90] as postponement is associated with better outcomes.[91] The American~~

~~Society of Transplantation recommend that prior to pregnancy there should be no rejection for one year, adequate and stable graft function, no acute infections, and stable immunosuppression dosing.~~[92]

Pre-implantation diagnosis

It is important to discuss the option of preimplantation genetic diagnosis (PGD) with women whose CKD is secondary to a genetically inherited cause. Recent advances in techniques used for in vitro-fertilisation allow removal of one or two cells at the eight cell stage of blastocyst formation.[67] These blastomeres can then be analysed for the mutations responsible for conditions such as Alports Syndrome or Adult Polycystic Kidney Disease.[68] Although there are limited data, initial reports suggest PGD is associated with similar success in pregnancy outcome when compared with routine IVF.

Pre-pregnancy counselling improves knowledge and changes behavior prior to pregnancy[69] which may help to reduce adverse events. The optimum way of offering pre-conception counselling has not been established. Patients with diabetes agreed that being informed of the risks prior to pregnancy is crucial, but existing childcare and work commitments prevented attendance to such services. They also stressed that the positive aspects of having children should be discussed rather than only medical complications.[70] In a retrospective analysis of 179 women with chronic kidney disease undergoing pre-pregnancy counselling in a large single centre, consultations included the multi-disciplinary team of a consultant obstetric physician, obstetrician and nephrologist.[71] These women had an overwhelmingly positive experience, with approximately 90% finding the clinic informative, with understandable information and helpful in deciding about pursuing pregnancy. However, 17% found the process intimidating, but this may prove difficult to abrogate in

such a highly emotive situation. Clearly the inclusion of midwives, general practitioners, counsellors, psychologists and clinical geneticists when required, may prove an extremely useful addition to this team. Electronic media including the internet and DVDs have also proven beneficial.[72,73]

MEDICATIONS

Women with CKD including those with a kidney transplant are prescribed different types of medications that have the potential to adversely affect the pregnancy outcomes. These include immunosuppressive, anti-hypertensive and anti-viral medications. Each is important for the mother's overall health, but their effects on the pregnant woman and her developing fetus have been a concern for many practitioners. The major classes of medications used in women with CKD and in transplant recipients and their known effects on the mother and her offspring will be described below. See table 3~~2~~.

Immunosuppressants:

~~These are routinely required by women with renal transplants and often in women with various systemic diseases affecting the kidney as well as those with primary glomerulonephritis. The mother must maintain adequate immunosuppressive drug levels during her pregnancy, otherwise she risks rejection of her allograft or a flare of her underlying disease.~~ Maintaining adequate immunosuppressive drug levels can be a challenge because drug levels change dramatically during gestation, primarily due to changes in blood volume and placental metabolism. Due to a natural increase in glomerular filtration rate, small changes in renal function can indicate significant rejection in pregnant transplant recipients[74] and close monitoring of renal function and drug levels is important. It

is important to closely monitor drug levels throughout all phases of gestation and collaboration with the transplant center is mandatory during and immediately after the pregnancy.

There are no guidelines about dosing of immunosuppressant medications during pregnancy, but several studies have provided recommendations. Kim *et al* recently reported on blood levels of calcineurin inhibitors during gestation in 88 pregnancies from 75 transplant recipients.[75] In 80 cases the serum creatinine was decreased by an average of 0.14mg/dl during pregnancy and returned to pre-pregnancy levels after delivery. Tacrolimus blood trough levels decreased during the second trimester (from 5.8 ±2.8 ng/ml) to 4.2 ±1.8ng/ml). Likewise, cyclosporine levels decreased during the second trimester from 125.1 ±65.1 ng/ml to 75.4 ±35 ng/ml. The recommendations of this study were to increase calcineurin inhibitor dose by approximately 20-25% during gestation to maintain optimal drug levels. Aktürk also reported on the pharmacokinetics of tacrolimus during pregnancy and recommended calcineurin inhibitor dosing is significantly increased in order to maintain adequate trough levels during pregnancy.[76] Women should be informed that tacrolimus levels need to be closely monitored in pregnancy. It is highly bound to plasma protein and erythrocytes, with complicated pharmacokinetics that are even further altered by normal physiological changes in pregnancy such as anaemia, hypoalbuminaemia and increased creatinine clearance. Maintaining whole blood tacrolimus levels after conception risks toxicity but no dose change may incur under-treatment. Unbound trough concentrations may be the most appropriate level to monitor during pregnancy,[77] but these are technically challenging to measure in routine practice.

Immunosuppressive medications cross the maternal-placental-fetal interface[74,78] and therefore there are always concerns about their effect on fetal development. The fetal liver, which is interposed between the umbilical vein and fetal inferior vena cava, filters the pharmacologic agents that pass through the placenta, including immunosuppressants. Calcineurin inhibitors are well-known to cross the placenta and enter the fetal circulation.[74] Zheng et al recently reported on tacrolimus concentrations in maternal and umbilical cord blood at delivery in eight transplant recipients and found that umbilical cord venous blood concentrations were 71% that of maternal concentrations. The lower fetal blood concentrations were proposed to be caused by the active transport of tacrolimus from the fetus toward the mother by placental P-glycoprotein.[79] Whether in utero exposure to tacrolimus has adverse effects on fetal development however is not known. In animal studies it was recently shown that rats treated with cyclosporine (CSA) during pregnancy experienced impaired kidney development, suggesting a predisposition to chronic kidney disease and hypertension in adult life.[80] Despite this, tacrolimus is deemed safe in pregnancy[81] and breastfeeding.[82]

Corticosteroids pass through the placenta, but most of the maternal dose undergoes placental metabolism[74] and therefore the fetus is generally protected from adverse effects of corticosteroids. While adverse effects associated with in utero exposure to corticosteroids are rare, there have though been sporadic reports of adrenal suppression in newborns of pregnant transplant recipients~~.~~ particularly when the corticosteroids dose was high.

Azathioprine also passes into the fetal circulation, but the fetus lacks inosinate pyrophosphorylase, which is required for the conversion of azathioprine to its active

metabolite 6-mercaptopurine.[74] Therefore, concerns about the use of azathioprine in pregnancy have been less than for other immunosuppressive.[83] Indeed, mycophenolic acid products are routinely substituted for azathioprine before and during pregnancy.[23] Substantial data have shown that mycophenolic acid products are associated with an increased incidence of spontaneous abortion and a distinct pattern of birth defects.[84] The spectrum of mycophenolate embryopathy includes ocular anomalies, corpus callosum agenesis, heart defects, kidney malformations, diaphragmatic hernia and skeletal deformities.[85] Numerous reports of mycophenolate-associated malformations led the FDA to issue a black box warning on it's use during pregnancy.

Less is known about the effects of sirolimus in pregnancy. Sifontis reported on seven pregnancies with sirolimus exposure in seven pregnancies.[86] In three there were miscarriages and four resulted in live births. No malformations were observed but sirolimus was switched to azathioprine during the first trimester in one case and in another the immunosuppressive regimen was switched from mycophenolate to sirolimus at 24 weeks. In the latter case the infant was born with features typical of mycophenolate embryopathy. There are several reports ~~were~~ of sirolimus exposure during the whole pregnancy, without apparent adverse effects on the fetus.[87–90]

Recently there have been several reports about pregnancy in transplant recipients taking the mTOR inhibitor everolimus during their pregnancy.[91,92] One report of an unplanned pregnancy in a heart transplant recipient described a normal baby without obvious congenital defects. The fetus was exposed to everolimus as concentrations were similar in maternal and neonatal umbilical blood, and fetal blood levels were detected for 5 days after birth. In contrast CsA levels, which were also detected in umbilical blood, disappeared within 2 days of delivery in fetal blood.[93] Other reports have been published recently

describing exposure to everolimus during pregnancies in kidney transplant recipients without apparent congenital malformations.[94,95] Although the few reports of unremarkable pregnancies with the use of mTOR inhibitors are encouraging, additional data are needed to confirm their safe use during pregnancy.

Treatment of rejection with corticosteroids is the mainstay during pregnancy and is generally considered safe to the fetus.[96] Recently Kutzler et al reported on the safe use of anti-thymocyte globulin (ATG) to successfully treat a pregnant renal transplant recipient with mixed acute cellular rejection and antibody-mediated rejection.[97] The patient was also treated with high-dose corticosteroids, intravenous immunoglobulin and plasmapheresis in addition to ATG; and she gave birth to a healthy baby boy. The safety of rejection treatment with ATG or other monoclonal or polyclonal antibodies has not been evaluated in clinical trials in pregnant transplant recipients and only scattered case reports are available. There are no data on the long term impact on the exposed children's immune repertoire.

Management of lupus nephritis (LN) and other causes of autoimmune glomerulonephritides in pregnancy remains challenging due to limited safe therapeutic options. Cyclophosphamide and mycophenolate mofetil are teratogenic, and are generally to be avoided in pregnancy, although can be considered from ~~in~~ the third trimester.[98] Steroids are often used in pregnancy as they are not associated with congenital abnormalities[99] but can cause premature rupture of membranes, preterm delivery, maternal sepsis and gestational diabetes.[100] Data on Rituximab use in pregnancy are limited but it does cross the placenta and lymphopaenia has been reported in new born children.[101] Hydroxychloroquine and azathioprine are safe in pregnancy and should be considered in treatment regimens prior to conception, along with aspirin. Hydroxychloroquine (HCQ) reduces the risk cardiac manifestations of neonatal lupus in anti-Ro-positive mothers and is actively recommended

in women with LN before and during pregnancy.[102] Tacrolimus may be a useful alternative or adjunctive therapy for LN flare during pregnancy.[103]

Anti-Hypertensives:

Adverse effects of renin angiotensin system (RAS) blockade have been shown for some time, and ACE inhibitors and angiotensin receptor blockers are teratogenic.[104–107] In a recent retrospective study performed through the Midwest Pediatric Nephrology Consortium, RAS blocker fetopathy was identified and confirmed to depend on the timing of exposure, with the most severe renal manifestations occurring with exposure after the first trimester.[104] Beta blockers are commonly used during pregnancy and recent meta-analyses showed that first-trimester oral beta-blocker exposure was associated with no increase in major congenital anomalies, but examination of organ-specific malformations revealed increased odds of cardiovascular defects, cleft lip/palate, and neural tube defects.[108] There is significant heterogeneity in the reports and thus it is not clear at this time whether beta-blockers are associated with these defects. Calcium channel blockers have recently been used in the management of hypertensive disorders of pregnancy and preterm labor. Teratogenicity with calcium channel blockers has been shown in animals, but no cases have yet been reported in humans and at this time are reported to be safe for use in pregnancy-associated hypertension.[109]

Antivirals:

Several antivirals have been used during pregnancy. The most commonly used antiviral agents target CMV infection. All of these have fetal toxicity. Valganciclovir should not be used as animal studies have revealed it can cause embryolethality, fetotoxicity,

teratogenicity, and mutagenicity. Valganciclovir may cause impaired fertility in both males and females.[110] If CMV prophylaxis is required, valaciclovir is considered safe though possibly less effective. Lamivudine and tenofovir are safe for Hepatitis B prophylaxis. [111, 112]

~~**PRE-PREGNANCY COUNSELLING**~~

~~The value of pre-pregnancy counselling has been recognised in women with diabetes for several decades.[78] Pre-pregnancy counselling in women with chronic kidney disease offers the opportunity to minimise disease activity, optimise blood pressure control and proteinuria, alter teratogenic medications and also to educate couples about potential fetal and maternal adverse events that may occur during pregnancy and the puerperium in this high risk group. It also allows discussion of the inheritance of genetic disorders of the kidney including cystic diseases, metabolic diseases and glomerular basement membrane disorders. The confidential enquiries into maternal deaths in the UK endorses that pre-pregnancy counselling should be routinely commissioned and offered to women with pre-existing medical illnesses in view of the morbidity and mortality triggered by these diseases.[79] The advice given is clearly dependent on underlying renal disease, baseline renal function, proteinuria and blood pressure at conception and this should be delivered in a patient focused, individualised manner.~~

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CONCLUSIONS

Pregnancy in women with CKD and kidney transplant should be planned, considered high risk, and ideally managed by an expert multidisciplinary team. The best outcomes are likely seen where there has been careful pre-pregnancy evaluation and planning, and close monitoring during antenatal care. The outcomes for women and babies continue to improve but we still need better biomarkers e.g. placental growth factor (PlGF) to identify those women at higher risk of developing superimposed pre-eclampsia.[113]

DISCLOSURES

Michelle A. Josephson is member of the Mycophenolate Pregnancy Registry Advisory Committee

REFERENCES

1. Shahir AK, Briggs N, Katsoulis J *et al.* An observational outcomes study from 1966-2008, examining pregnancy and neonatal outcomes from dialysed women using data from the ANZDATA Registry. *Nephrology (Carlton).* 2013;18:276–284.

2. Alkhunaizi A, Melamed N, Hladunewich MA. Pregnancy in advanced chronic kidney disease and end-stage renal disease. *Curr. Opin. Nephrol. Hypertens.* 2015;24:252–259.

3. Jones DC, Hayslett JP. Outcome of pregnancy in women with moderate or severe renal insufficiency. *N. Engl. J. Med.* 1996;335:226–232.

4. Pregnancy and renal disease. *Lancet (London, England)* 1975;2:801–802.

5. Davison JM, Lindheimer MD. Pregnancy and chronic kidney disease. *Semin. Nephrol.* 2011;31:86–99.

6. Jungers P, Chauveau D, Choukroun G *et al.* Pregnancy in women with impaired renal function. *Clin. Nephrol.* 1997;47:281–288.

7. Davison JM, Katz AI, Lindheimer MD. Kidney disease and pregnancy: obstetric outcome and long-term renal prognosis. *Clin. Perinatol.* 1985;12:497–519.

8. American Society of Nephrology | NephSAP - NephSAP Volume 15, Number 2 - Pregnancy and Kidney Disease.

9. K/DOQI clinical practice guidelines for chronic kidney disease:evaluation, classification, and stratification. *Am. J. Kidney Dis.* 2002;39:S1-266.

10. Piccoli GB, Cabiddu G, Attini R *et al.* Risk of Adverse Pregnancy Outcomes in Women with CKD. *J. Am. Soc. Nephrol.* 2015;26:2011–2022.

11. Smith MC, Moran P, Ward MK *et al.* Assessment of glomerular filtration rate during pregnancy using the MDRD formula. *BJOG* 2008;115:109–112.

12. Pamella S Ochoa JAV. Comparison of 24-Hour Urine to Estimated Renal Function using CKD-EPI, MDRD4 and Cockcroft-Gault in Specific Patient Subsets. *J. Pharm. Care Heal. Syst.* 2015;2.

13. Côté A-M, Lam EM, von Dadelszen P *et al.* Monitoring renal function in hypertensive pregnancy. *Hypertens. pregnancy* 2010;29:318–329.

14. Imbasciati E, Gregorini G, Cabiddu G *et al.* Pregnancy in CKD stages 3 to 5: fetal and maternal outcomes. *Am. J. Kidney Dis.* 2007;49:753–762.

15. Zhang J-J, Ma X-X, Hao L *et al.* A Systematic Review and Meta-Analysis of Outcomes of Pregnancy in CKD and CKD Outcomes in Pregnancy. *Clin. J. Am. Soc. Nephrol.* 2015;10:1964–1978.

16. Clowse MEB, Jamison M, Myers E *et al.* A national study of the complications of lupus in pregnancy. *Am. J. Obstet. Gynecol.* 2008;199:127.e1-6.

17. Bramham K, Nelson-Piercy C, Gao H *et al.* Pregnancy in renal transplant recipients: a UK national cohort study. *Clin. J. Am. Soc. Nephrol.* 2013;8:290–298.

18. Deshpande NA, James NT, Kucirka LM *et al.* Pregnancy outcomes in kidney transplant recipients:a systematic review and meta-analysis. *Am. J. Transplant* 2011;11:2388–2404.

19. Gill JS, Zalunardo N, Rose C *et al.* The pregnancy rate and live birth rate in kidney transplant recipients. *Am. J. Transplant* 2009;9:1541–1549.

20. Coscia LA, Constantinescu S, Moritz MJ *et al.* Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clin. Transpl.* 2010:65–85.

21. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. *J. Am. Soc. Nephrol.* 2009;20:2433–2440.

22. Sibanda N, Briggs JD, Davison JM *et al.* Pregnancy after organ transplantation: a report from the UK Transplant pregnancy registry. *Transplantation* 2007;83:1301–1307.

23. McKay DB, Josephson MA, Armenti VT *et al.* Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. *Am. J. Transplant* 2005;5:1592–1599.

24. Deshpande NA, Coscia LA, Gomez-Lobo V *et al.* Pregnancy after solid organ transplantation: a guide for obstetric management. *Rev. Obstet. Gynecol.* 2013;6:116–125.

25. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. *Nephrol. Dial. Transplant* 2002;17 Suppl 4:50–55.

26. Fischer T, Neumayer H-H, Fischer R *et al.* Effect of pregnancy on long-term kidney function in renal transplant recipients treated with cyclosporine and with azathioprine. *Am. J. Transplant* 2005;5:2732–2739.

27. Rose C, Gill J, Zalunardo N *et al.* Timing of Pregnancy After Kidney Transplantation and Risk of Allograft Failure. *Am. J. Transplant* 2016;16:2360–2367.

28. Kasiske BL, Anderson-Haag T, Israni AK *et al.* A prospective controlled study of living kidney donors: three-year follow-up. *Am. J. Kidney Dis.* 2015;66:114–124.

29. Garg AX, McArthur E, Lentine KL. Gestational hypertension and preeclampsia in living kidney donors. *N. Engl. J. Med.* 2015;372:1469–1470.

30. Ibrahim HN, Akkina SK, Leister E *et al.* Pregnancy outcomes after kidney donation. *Am. J. Transplant* 2009;9:825–834.

31. Reisaeter A V, Røislien J, Henriksen T *et al.* Pregnancy and birth after kidney donation: the Norwegian experience. *Am. J. Transplant* 2009;9:820–824.

32. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet. Gynecol.* 2013;122:1122–31.

33. Krause T, Lovibond K, Caulfield M *et al.* Management of hypertension: summary of NICE guidance. *BMJ* 2011;343:d4891.

34. Lowe SA, Brown MA, Dekker GA *et al.* Guidelines for the management of hypertensive disorders of pregnancy 2008. *Aust. N. Z. J. Obstet. Gynaecol.* 2009;49:242–246.

35. Magee LA, Helewa M, Moutquin J-M *et al.* Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *J. Obstet. Gynaecol. Canada JOGC = J. d'obstétrique gynécologie du Canada JOGC* 2008;30:S1-48.

36. Bateman BT, Bansil P, Hernandez-Diaz S *et al.* Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. *Am. J. Obstet. Gynecol.* 2012;206:134.e1-8.

37. Redman CWG. Hypertension in pregnancy: the NICE guidelines. *Heart* 2011;97:1967–9.

38. von Dadelszen P, Ornstein MP, Bull SB *et al.* Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension:a meta-analysis. *Lancet (London, England)*

2000;355:87–92.

39. Ferrer RL, Sibai BM, Mulrow CD *et al.* Management of mild chronic hypertension during pregnancy: a review. *Obstet. Gynecol.* 2000;96:849–860.

40. Kuklina E V, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet. Gynecol.* 2009;113:1299–1306.

41. Scantlebury DC, Kane GC, Wiste HJ *et al.* Left ventricular hypertrophy after hypertensive pregnancy disorders. *Heart* 2015;101:1584–1590.

42. Zanati Bazan SG, Borges VM, Martin LC *et al.* Disproportionate pregnancy-induced myocardial hypertrophy in women with essential hypertension. *Am. J. Hypertens.* 2013;26:816–821.

43. Magee LA, von Dadelszen P, Rey E *et al.* Less-tight versus tight control of hypertension in pregnancy. *N. Engl. J. Med.* 2015;372:407–417.

44. Hussain A, Karovitch A, Carson MP. Blood pressure goals and treatment in pregnant patients with chronic kidney disease. *Adv. Chronic Kidney Dis.* 2015;22:165–169.

45. Mills KT, Xu Y, Zhang W *et al.* A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int.* 2015;88:950–957.

46. Steel JM, Johnstone FD, Smith AF *et al.* Five years' experience of a "prepregnancy" clinic for insulin-dependent diabetics. *BMJ* 1982;285:353–356.

47. Wilkinson H. Saving Mothers' Lives. Reviewing maternal deaths to make motherhood safer:2006-2008. *BJOG An Int. J. Obstet. Gynaecol.* 2011;118:1402–1403.

48. Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ* 2008;336:211–215.

49. Hou S. Pregnancy in chronic renal insufficiency and end-stage renal disease. *Am. J. Kidney Dis.* 1999;33:235–252.

50. Meuwese CL, Carrero JJ. Chronic kidney disease and hypothalamic-pituitary axis

765 dysfunction: the chicken or the egg? *Arch. Med. Res.* 2013;44:591–600.

766 51. Finkelstein FO, Shirani S, Wuerth D *et al.* Therapy Insight: sexual dysfunction in patients

767 with chronic kidney disease. *Nat. Clin. Pract. Nephrol.* 2007;3:200–207.

768 52. Davison JM, Bailey DJ. Pregnancy following renal transplantation. *J. Obstet. Gynaecol.*

769 *Res.* 2003;29:227–333.

770 53. Barua M, Hladunewich M, Keunen J *et al.* Successful pregnancies on nocturnal home

771 hemodialysis. *Clin. J. Am. Soc. Nephrol.* 2008;3:392–396.

772 54. van Eps C, Hawley C, Jeffries J *et al.* Changes in serum prolactin, sex hormones and

773 thyroid function with alternate nightly nocturnal home haemodialysis. *Nephrology (Carlton).*

774 2012;17:42–47.

775 55. Chronic kidney disease in adults: assessment and management | 1-recommendations |

776 Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/cg182/chapter/1-

777 Recommendations. Last accessed 26/09/2016

778 56. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic

779 Kidney Disease. http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO_BP_GL.pdf.

780 Last accessed 26/09/2016.

781 57. Gillon TER, Pels A, von Dadelszen P *et al.* Hypertensive disorders of pregnancy:a

782 systematic review of international clinical practice guidelines. *PLoS One* 2014;9:e113715.

783 58. Hypertension in pregnancy: diagnosis and management | Guidance and guidelines |

784 NICE. https://www.nice.org.uk/Guidance/CG107. Last accessed 26/09/2016.

785 59. Duley L, Henderson-Smart DJ, Meher S *et al.* Antiplatelet agents for preventing pre-

786 eclampsia and its complications. *Cochrane database Syst. Rev.* 2007:CD004659.

787 60. Stratta P, Canavese C, Quaglia M. Pregnancy in patients with kidney disease. *J. Nephrol.*

788 2006;19:135–143.

61. Ferrazzani S, Caruso A, De Carolis S *et al.* Proteinuria and outcome of 444 pregnancies complicated by hypertension. *Am. J. Obstet. Gynecol.* 1990;162:366–371.

62. Imbasciati E, Ponticelli C. Pregnancy and Renal Disease: Predictors for Fetal and Maternal Outcome. *Am. J. Nephrol.* 1991;11:353–362.

63. Smyth A, Oliveira GHM, Lahr BD *et al.* A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin. J. Am. Soc. Nephrol.* 2010;5:2060–2068.

64. Bramham K, Soh MC, Nelson-Piercy C. Pregnancy and renal outcomes in lupus nephritis:an update and guide to management. *Lupus* 2012;21:1271–1283.

65. Stanhope TJ, White WM, Moder KG *et al.* Obstetric Nephrology:Lupus and Lupus Nephritis in Pregnancy. *Clin. J. Am. Soc. Nephrol.* 2012;7:2089-2099.

66. Buyon JP, Kim MY, Guerra MM *et al.* Predictors of Pregnancy Outcomes in Patients With Lupus:A Cohort Study. *Ann. Intern. Med.* 2015;163:153–163.

67. Thornhill AR, deDie-Smulders CE, Geraedts JP *et al.* ESHRE PGD Consortium "Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)". *Hum. Reprod.* 2005;20:35–48.

68. De Rycke M, Georgiou I, Sermon K *et al.* PGD for autosomal dominant polycystic kidney disease type 1. *Mol. Hum. Reprod.* 2005;11:65–71.

69. Elsinga J, de Jong-Potjer LC, van der Pal-de Bruin KM *et al.* The effect of preconception counselling on lifestyle and other behaviour before and during pregnancy. *Womens. Health Issues* 2008;18:S117-125.

70. O'Higgins S, McGuire BE, Mustafa E *et al.* Barriers and facilitators to attending pre-pregnancy care services:the ATLANTIC-DIP experience. *Diabet. Med.* 2014;31:366–374.

71. Wiles KS, Bramham K, Vais A *et al.* Pre-pregnancy counselling for women with chronic

kidney disease: a retrospective analysis of nine years' experience. *BMC Nephrol.* 2015;16:28.

72. Agricola E, Pandolfi E, Gonfiantini M V *et al.* A cohort study of a tailored web intervention for preconception care. *BMC Med. Inform. Decis. Mak.* 2014;14:33.

73. Hamill LL, McCance DR, Deery M *et al.* Impact of a preconception counselling resource (DVD) on preconception folic acid intake in women with diabetes. *Proc. Nutr. Soc.* 2014;73:E64.

74. McKay DB, Josephson MA. Pregnancy in recipients of solid organs - effects on mother and child. *N. Engl. J. Med.* 2006;354:1281–1293.

75. Kim H, Jeong JC, Yang J *et al.* The optimal therapy of calcineurin inhibitors for pregnancy in kidney transplantation. *Clin. Transplant.* 2015;29:142–148.

76. Aktürk S, Çelebi ZK, Erdoğmuş Ş *et al.* Pregnancy After Kidney Transplantation:Outcomes, Tacrolimus Doses, and Trough Levels. *Transplant. Proc.* 2015;47:1442–1444.

77. Hebert MF, Zheng S, Hays K *et al.* Interpreting tacrolimus concentrations during pregnancy and postpartum. *Transplantation* 2013;95:908–915.

78. Ostensen M. Disease specific problems related to drug therapy in pregnancy. *Lupus* 2004;13:746–750.

79. Zheng S, Easterling TR, Hays K *et al.* Tacrolimus placental transfer at delivery and neonatal exposure through breast milk. *Br. J. Clin. Pharmacol.* 2013;76:988–996.

80. Slabiak-Blaz N, Adamczak M, Gut N *et al.* Administration of Cyclosporine A in Pregnant Rats - the Effect on Blood Pressure and on the Glomerular Number in Their Offspring. *Kidney Blood Press. Res.* 2015;40:413–423.

81. Armenti VT, Constantinescu S, Moritz MJ *et al.* Pregnancy after transplantation. *Transplant. Rev. (Orlando).* 2008;22:223–240.

82. Bramham K, Chusney G, Lee J *et al.* Breastfeeding and tacrolimus: serial monitoring in breast-fed and bottle-fed infants. *Clin. J. Am. Soc. Nephrol.* 2013;8:563–567.

83. McKay DB, Adams PL, Bumgardner GL *et al.* Reproduction and pregnancy in transplant recipients: current practices. *Prog. Transplant.* 2006;16:127–132.

84. Coscia LA, Constantinescu S, Davison JM *et al.* Immunosuppressive drugs and fetal outcome. *Best Pract. Res. Clin. Obstet. Gynaecol.* 2014;28:1174–1187.

85. Perez-Aytes A, Ledo A, Boso V *et al.* In utero exposure to mycophenolate mofetil:a characteristic phenotype? *Am. J. Med. Genet. A* 2008;146A:1–7.

86. Sifontis NM, Coscia LA, Constantinescu S *et al.* Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. *Transplantation* 2006;82:1698–1702.

87. Chu S-H, Liu K-L, Chiang Y-J *et al.* Sirolimus used during pregnancy in a living related renal transplant recipient:a case report. *Transplant. Proc.* 2008;40:2446–2448.

88. Guardia O, Rial MDC, Casadei D. Pregnancy under sirolimus-based immunosuppression. *Transplantation* 2006;81:636.

89. Framarino dei Malatesta M, Corona LE, De Luca L *et al.* Successful pregnancy in a living-related kidney transplant recipient who received sirolimus throughout the whole gestation. *Transplantation* 2011;91:e69-71.

90. Jankowska I, Oldakowska-Jedynak U, Jabiry-Zieniewicz Z *et al.* Absence of teratogenicity of sirolimus used during early pregnancy in a liver transplant recipient. *Transplant. Proc.* 2004;36:3232–3233.

91. Carta P, Caroti L, Zanazzi M. Pregnancy in a kidney transplant patient treated with everolimus. *Am. J. Kidney Dis.* 2012;60:329.

92. Margoles HR, Gomez-Lobo V, Veis JH *et al.* Successful maternal and fetal outcome in a

kidney transplant patient with everolimus exposure throughout pregnancy:a case report. *Transplant. Proc.* 2014;46:281–283.

93. Fiocchi R, D'Elia E, Vittori C *et al.* First Report of a Successful Pregnancy in an Everolimus-Treated Heart-Transplanted Patient:Neonatal Disappearance of Immunosuppressive Drugs. *Am. J. Transplant* 2016;16:1319-1322.

94. Carta P, Zanazzi M, Minetti EE. Unplanned pregnancies in kidney transplanted patients treated with everolimus: three case reports. *Transpl. Int.* 2015;28:370–372.

95. Veroux M, Corona D, Veroux P. Pregnancy under everolimus-based immunosuppression. *Transpl. Int.* 2011;24:e115-7.

96. Josephson MA, McKay DB. Pregnancy and kidney transplantation. *Semin. Nephrol.* 2011;31:100–110.

97. Kutzler HL, Ye X, Rochon C *et al.* Administration of Anti-thymocyte Globulin (Rabbit) to Treat a Severe, Mixed Rejection Episode in a Pregnant Renal Transplant Recipient. *Pharmacotherapy* 2016;36:e18-22.

98. Østensen M, Khamashta M, Lockshin M *et al.* Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res. Ther.* 2006;8:209.

99. Anderson GG, Rotchell Y, Kaiser DG. Placental transfer of methylprednisolone following maternal intravenous administration. *Am. J. Obstet. Gynecol.* 1981;140:699–701.

100. Mariotti V, Marconi A, Pardi G. Undesired effects of steroids during pregnancy. *J Matern Fetal Neonatal Med.* 2004;16suppl2:5-7.

101. Hyrich KL, Verstappen SMM. Biologic therapies and pregnancy:the story so far. *Rheumatology (Oxford).* 2014;53:1377–1385.

102. Izmirly PM, Kim MY, Llanos C *et al.* Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with

systemic lupus erythematosus exposed to hydroxychloroquine. *Ann. Rheum. Dis.* 2010;69:1827–1830.

103. Webster P, Wardle A, Bramham K *et al.* Tacrolimus is an effective treatment for lupus nephritis in pregnancy. *Lupus* 2014;23:1192–1196.

104. Nadeem S, Hashmat S, Defreitas MJ *et al.* Renin Angiotensin System Blocker Fetopathy:A Midwest Pediatric Nephrology Consortium Report. *J. Pediatr.* 2015;167:881–885.

105. Cooper WO, Hernandez-Diaz S, Arbogast PG *et al.* Major congenital malformations after first-trimester exposure to ACE inhibitors. *N. Engl. J. Med.* 2006;354:2443–2451.

106. Tabacova S, Little R, Tsong Y *et al.* Adverse pregnancy outcomes associated with maternal enalapril antihypertensive treatment. *Pharmacoepidemiol. Drug Saf.* 2003;12:633–646.

107. Velázquez-Armenta EY, Han JY, Choi JS *et al.* Angiotensin II receptor blockers in pregnancy: a case report and systematic review of the literature. *Hypertens. pregnancy* 2007;26:51–66.

108. Yakoob MY, Bateman BT, Ho E *et al.* The risk of congenital malformations associated with exposure to β-blockers early in pregnancy:a meta-analysis. *Hypertension* 2013;62:375–381.

109. Tranquilli AL, Giannubilo SR. Use and safety of calcium channel blockers in obstetrics. *Curr. Med. Chem.* 2009;16:3330–3340.

110. Valcyte® (valganciclovir hydrochloride) Patient Support. http://www.valcyte.com/patient. Last accessed 26/09/2016.

111. Yi W, Liu M, Cai H-D. Safety of lamivudine treatment for chronic hepatitis B in early pregnancy. *World J. Gastroenterol.* 2012;18:6645–6650.

112. Wang L, Kourtis AP, Ellington S *et al.* Safety of tenofovir during pregnancy for the mother and fetus:a systematic review. *Clin. Infect. Dis.* 2013;57:1773–1781.

113. Bramham K, Seed PT, Lightstone L *et al.* Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. *Kidney Int.* 2016;89:874–885.

Legends:

Table 1: Prepregnancy kidney function in patients with CKD with estimates of problems in pregnancy (fetal growth restriction, preeclampsia, preterm delivery, and significant kidney function loss in pregnancy [>25% SCr increment]), obstetric outcome, and loss of kidney function: The effect of altering cut-off between moderate and severe dysfunction from 2.8 mg/dL (≥250µmol/L) to 2.0 mg/dL (≥180µmol/L), respectively

Table 2: Hypertensive disorders of pregnancy

Table 3: Drug Safety in Pregnancy

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Table 1:

Renal Status (*dysfunction*)	Scr (mg/dL)	Problems in Pregnancy (%)	Successful Obstetric Outcome (%)	Compared to pre-pregnancy a permanent PP loss of kidney function (>25% increment in Scr) (%)	ESRF within 1 year PP (%)
Mild	≤1.4 (≤125µmol/L)	26	96	<2	-
Moderate	≥1.4 (≥125µmol/L)	50	90	25	3
Severe^{++}	≥2.8 (≥250µmol/L)	86	74	55	40
Mild	≤1.4 (≤125µmol/L)	26	96	<2	-
Moderate	≥1.4 (≥125µmol/L)	42	95	15	1
Severe^{++}	≥2.0 (≥180µmol/L)	79	78	50	38

Estimates are on the basis of a 26 year literature review (1984-2010) of pregnancies that attained ≥ 24-weeks gestation.
PP = post-partum; ESRF = end stage renal failure.
From Lindheimer and Davison NephSap

Table 2: Hypertensive Disorders of Pregnancy	Characteristics
	Preeclampsia is diagnosed in the setting of hypertension in association with thrombocytopenia, impaired liver function tests, the new development of renal insufficiency, pulmonary edema , or new-onset cerebral or visual disturbances
Chronic hypertension	Anti-hypertensive requirement before pregnancy or hypertension beginning before the 20th week of pregnancy or hypertension continuing for more than 12 weeks after delivery
Chronic hypertension with superimposed pre-eclampsia	Combination of the two
Gestational hypertension	BP elevation after 20 weeks of gestation in the absence of proteinuria, thrombocytopenia, impaired liver function, new onset of kidney dysfunction, pulmonary edema, or new cerebral or visual disturbances

Table 3:

	Safe	Not Safe	Safety Not Determined
Immunosuppressants	Tacrolimus Cyclosporin Azathioprine Corticosteroids Hydroxychloroquine	Cyclophosphamide Mycophenolate products Rituximab	Sirolimus Everolimus
Anti-Hypertensives	Labetalol Calcium Channel Antagonists Methyldopa Hydralazine Furosemide	ACE inhibitors Angiotensin Receptor Blockers Minoxidil	
Antibiotics Commonly Used in Immunosuppressed Patients	Aciclovir Valaciclovir Lamivudine Tenofovir Isoniazid Nystatin (topical)	Ganciclovir Valganciclovir Co-Trimoxazole Quinolones	

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