



## Pregnancy in Chronic Kidney Disease and Kidney Transplantation

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1 **Pregnancy in Chronic Kidney Disease and Kidney Transplantation**

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14 **RUNNING HEADLINE:** Pregnancy in CKD & Kidney Transplantation

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3 25 **ABSTRACT**  
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5 26 Chronic kidney disease (CKD) affects up to 6% of women of childbearing age in high income  
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7 27 countries, and is estimated to affect 3% of pregnant women. Advanced renal dysfunction,  
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9 28 proteinuria, hypertension and poorly controlled underlying primary renal disease are all  
10  
11 29 significant risks for adverse maternal, fetal and renal outcomes. In order to achieve the best  
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14 30 outcomes it is therefore of paramount importance that these pregnancies are planned,  
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17 31 where possible, to allow the opportunity to counsel women and their partners in advance  
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19 32 and to optimize these risks. These pregnancies should be deemed high risk and they require  
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21 33 close antenatal monitoring from an expert multidisciplinary team.  
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24 34 We discuss the effect of pregnancy on CKD, and also current guidelines and literature with  
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26 35 specific reference to transplantation, autoimmune disease and medication use in  
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28 36 pregnancy. We also discuss the benefits of pre-pregnancy counselling and give practical  
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30 37 recommendations to advise pregnant women with renal disease.  
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3 49 **THE IMPACT OF KIDNEY FUNCTION ON PREGNANCY OUTCOME**  
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5 50 CKD stage and outcomes  
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7 51 The pregnancies of most normotensive women with mild or even moderate renal  
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9 52 dysfunction succeed, but are prone to more complications than those of gravidas with  
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11 53 normal renal function. However, pregnancy is much more hazardous when kidney  
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13 54 dysfunction is advanced. Women with advanced chronic kidney disease (CKD) have a lower  
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15 55 likelihood of conceiving because of the decreased fertility associated with the hormonal  
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17 56 changes of worsening kidney function and ESRD.<sup>1</sup> When they do conceive, advanced CKD  
18  
19 57 predisposes to intrauterine growth restriction and preterm delivery,<sup>2</sup> and pregnancy has  
20  
21 58 been blamed for hastening the rate of decline of kidney function, increasing proteinuria,  
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23 59 and hypertension.<sup>3</sup> Such views however are based on insufficient data. Thus the level of  
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25 60 kidney function/dysfunction and its effect on pregnancy remains a debated area.  
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33 62 An evolving state of understanding  
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36 63 Currently there is controversy reflecting the swinging pendulum of attitudes related to  
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38 64 pregnancy in women with CKD, as well as the evolution of how the nephrology community  
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40 65 assesses renal function. In 1975, an anonymously authored Lancet editorial noted that  
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42 66 physicians in the past preferred avoiding pregnancy in women with any degree of CKD by  
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44 67 noting: "Children of women with renal disease used to be born dangerously or not at all -  
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46 68 not at all if their doctors had their way".<sup>4</sup> The editorial took the then provocative stance  
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48 69 that as most pregnancies succeed in the setting of mild kidney dysfunction, this attitude  
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50 70 should be changed. Davison and Lindheimer<sup>5</sup> noted in 2010 that studies in the decades  
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52 71 after the Lancet editorial led to a better understanding of outcomes for pregnancy in  
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54 72 women with kidney dysfunction. Observational studies indicated that outcomes depended  
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3 73 on the degree of renal insufficiency pre-pregnancy, and the presence or absence of  
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5 74 hypertension.<sup>6</sup> Based on these parameters, women were grouped into three categories:  
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8 75 mild, moderate, or severe dysfunction. Normotensive women with preserved or mildly  
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10 76 decreased but stable kidney function (defined as a serum creatinine (SCr) of  $\leq 1.4$  mg/dL) did  
11  
12 77 well with over 95% live births, 75% of which were appropriate size for gestational age.  
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15 78 However, prognosis worsened with moderate dysfunction (SCr  $\geq 1.4$  mg/dL-2.8 mg/dL) and  
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17 79 more so with severe impairment (SCr level  $\geq 2.8$  mg/dL).<sup>7</sup> These estimates were based on a  
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19  
20 80 26-year literature review (1984-2010), as well as personal patient files by John Davison,  
21  
22 81 most recently published in a NephSAP editorial by Drs Lindheimer and Davison, in the issue  
23  
24 82 devoted to renal disease and hypertension in pregnancy (reproduced with permission in  
25  
26 83 Table 1).<sup>8</sup>

#### 28 29 30 31 85 Creatinine vs eGFR

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33 86 In 2002 the Kidney Disease Outcomes Quality Initiative (KDOQI) released a new chronic  
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35 87 kidney disease (CKD) classification designating five categories based on estimated  
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37 88 glomerular filtration rate (eGFR).<sup>9</sup> Ignoring the question of whether this classification system  
38  
39 89 over-diagnosed kidney disease and dysfunction in some, the eGFR based system provided  
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41 90 another filter through which to consider pregnancy outcomes. Piccoli and colleagues<sup>10</sup> used  
42  
43 91 the classification and looked at pregnancy outcomes in 504 pregnancies in women with CKD  
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45 92 compared with 836 low-risk pregnancies in women without CKD. They considered whether  
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47 93 hypertension, proteinuria ( $> 1$  gram/day), systemic disease, or CKD stage at baseline  
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49 94 affected pregnancies. Outcomes assessed were: cesarean section, preterm delivery, early  
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51 95 preterm delivery, small for gestational age, need for neonatal intensive care unit, new onset  
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53 96 of hypertension, new onset/doubling of proteinuria, CKD stage shift, and a combined  
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3 97 outcome. The majority of patients in the study were classified as CKD stage 1. The authors  
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5 98 concluded that adverse outcomes increased with increasing stage of CKD, including  
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7 99 surprisingly stage 1, even in the absence of hypertension, baseline proteinuria, and systemic  
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10 100 diseases. The eGFR was calculated based on the Cockcroft–Gault, Modification of Diet in  
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12 101 Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)  
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14 102 formulas. As CKD-EPI and MDRD have been found to underestimate GFR in pregnancy<sup>11,12</sup>  
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16  
17 103 and Cockcroft-Gault has been demonstrated to both underestimate and overestimate GFR  
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19 104 in hypertensive pregnant women,<sup>13</sup> it is possible that some of the patients in Piccoli’s study  
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21 105 had lower GFRs than the group in which they were classified. Some of the individuals  
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23 106 reported to have CKD stage 1, could therefore have had a higher stage. While Piccoli *et al*’s  
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26 107 findings were primarily in women with mild and moderate dysfunction Imbasciati *et al*  
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28 108 studied 49 women with preconception stage 3 to 5 CKD observed for a mean of 39 months  
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30 109 after delivery. In the latter study only individuals with both GFR less than 40 ml/min/1.73m<sup>2</sup>  
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33 110 and greater than 1 gram of proteinuria per day were noted to have poor fetal outcomes and  
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35 111 accelerated kidney function loss.<sup>14</sup> A meta-analysis by Zhang *et al* of 23 studies that included  
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37 112 1514 pregnancies with CKD found no significant difference in renal outcomes in pregnant  
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39 113 women with CKD compared with non-pregnant women with CKD. The study did however  
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41 114 find that adverse pregnancy outcomes, including preeclampsia, premature births, SGA/low  
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43 115 birth weight, cesarean section, stillbirth, fetal death, and neonatal death, were increased in  
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46 116 women with CKD compared to those without. The conclusions that can be drawn from the  
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48 117 meta-analysis must be put into context because the literature review focused on patients  
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50 118 with CKD stages 1-3, thus excluding those with stage 4 or 5 who are most vulnerable for  
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53 119 progression of disease.<sup>15</sup>  
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3 120 In their review and recent editorial Lindheimer and Davison<sup>5,8</sup> underscore that most eGFR  
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5 121 formulae correlate poorly with measured GFR in pregnant women, and that obstetricians  
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7 122 familiar with absolute values of creatinine may be unfamiliar with the nephrology  
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9 123 community's CKD system . However, despite the seeming differences between those who  
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11 124 are considering pregnancy outcomes through an eGFR based CKD stages filter, and those  
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13 125 who are more comfortable with the serum creatinine based assessment, proponents of  
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15 126 both agree that degree of kidney function plays an important role in outcome. Neither  
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17 127 group advocates returning to the pre-1975 mindset of avoiding pregnancy in women with  
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19 128 mild kidney dysfunction, however defined.  
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27 130 Additional contributing factors

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29 131 Whilst clearly important, kidney function alone does not uniformly predict pregnancy  
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31 132 outcomes. There are likely to be additional contributing factors to pregnancy outcomes,  
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33 133 such as active systemic disease or endothelial injury. For example certain specific diseases  
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35 134 such as Systemic Lupus Erythematosus (SLE) may exert a greater adverse effect on the  
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37 135 pregnancy making it impossible to isolate the role of kidney function per se on outcomes.<sup>16</sup>  
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39 136 Similarly kidney transplantation does not present a pristine model to look at kidney function  
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41 137 alone because of the effects of immunosuppression.  
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48 139 Kidney transplantation and outcome

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50 140 A national UK cohort study demonstrated that most pregnancies after renal transplantation  
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52 141 are successful, although the risks of pre-eclampsia still remain higher than controls<sup>17</sup> and  
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54 142 this higher risk of pre-eclampsia affects even those with good GFRs.<sup>18</sup> Patients should be  
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56 143 counselled of this accordingly and the other precautions discussed in the pre-pregnancy  
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3 144 counselling section, initiated. How does the connection between kidney function and  
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5 145 pregnancy outcomes relate to pregnancy outcomes in kidney transplant recipients? Similar  
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8 146 to findings in advanced kidney failure, transplant patients appear to have a lower pregnancy  
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10 147 rate than the general public.<sup>19</sup> Registry, cohort, and meta-analysis studies demonstrate that  
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12 148 pregnancies in transplant recipients, which are more likely to be complicated by  
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15 149 hypertension, are at greater risk for prematurity, small for gestational age, cesarean  
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17 150 sections, the diagnosis of preeclampsia and perinatal mortality.<sup>17,18,20</sup> Of note while  
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19 151 pregnancy and renal function outcomes in transplant recipients have been studied based on  
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21 152 creatinine levels, we could locate no assessments based on the CKD staging system. In  
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23 153 transplant recipients, there are the additional factors of immunosuppression medications.  
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26 154 These factors make it hard to isolate and define the kidney function effect on pregnancy in  
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28 155 this group. Long term follow-up of transplant recipients with and without a history of  
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30 156 pregnancy supports the idea that pregnancy does not worsen long term outcomes.<sup>21</sup>  
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33 157 However, there may be subsets of transplant patients in whom pregnancy accelerates renal  
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35 158 function decline. Data from the UK Pregnancy registry indicate that women with kidney  
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37 159 allografts whose pre-pregnancy SCr is greater than 150 $\mu$ mol/L (approximately 1.7 mg/dL)  
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39 160 have an increased serum creatinine after pregnancy, suggesting that the pregnancy itself  
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41 161 may negatively affect graft function.<sup>22</sup> Despite limitations of available data in the transplant  
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43 162 recipient, guidelines advise that amongst other factors, the basis for determining reasonable  
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46 163 timing for pregnancy is the presence of adequate and stable graft function (arbitrarily set as  
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48 164 a SCr<1.5 mg/dL).<sup>23</sup> The American Society of Transplantation recommends that prior to  
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50 165 pregnancy there should be no rejection for one year, adequate and stable graft function, no  
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52 166 acute infections, and stable immunosuppression dosing.<sup>24</sup> Pregnancy should be delayed  
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55 167 until at least one year after renal transplantation<sup>25</sup> as postponement is associated with  
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3 168 better outcomes.<sup>26</sup> A recent study by Rose et al that examined allograft outcome and  
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5 169 pregnancy timing in the first 3 post-transplant years of Medicare insured kidney transplant  
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7 170 recipients suggests that pregnancy in the first 2 post-transplant years is associated with  
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9 171 increased allograft loss compared with waiting an additional year.<sup>27</sup> Beyond optimal post-  
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11 172 transplant pregnancy timing, there are many other unanswered questions about pregnancy  
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13 173 in transplant recipients including the optimal pre-pregnancy kidney function and whether  
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15 174 having pre-existent donor specific antibodies affects pregnancy outcomes, or the  
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17 175 transplanted kidney. This last consideration is of particular concern given the usual pre-  
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19 176 pregnancy modification of immunosuppression, with discontinuation of mycophenolic acid  
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21 177 formulations.

#### 22 178 Kidney donors

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27 179 Pregnancy in kidney donors may be the perfect model in which to consider the role of  
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29 180 kidney function. Donors are intensively medically screened and only allowed to donate a  
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31 181 kidney if healthy. Their post-donation level of kidney function is approximately 75-80% of  
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33 182 normal.<sup>28</sup> They do not have systemic disease and their remaining kidney, though  
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35 183 hypertrophied and hyperfiltering, is normal. Three studies have found that post-donation  
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37 184 pregnancies may be at increased risk for complications. Garg et al performed a population  
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39 185 study and found a significantly higher incidence of gestational hypertension or preeclampsia  
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41 186 in donors compared with matched non-donors.<sup>29</sup> Ibrahim et al's survey of previous kidney  
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43 187 donors documented subjects reporting significant increases in diagnosed preeclampsia,  
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45 188 hypertension, and gestational diabetes in pregnancies after donation compared with  
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47 189 before.<sup>30</sup> Reisaeter et al found more pre-eclampsia diagnosed in women after donation  
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49 190 compared with pregnancies before.<sup>31</sup>

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3 192 Kidney function impact  
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5 193 Taken together the studies, case series, and registries indicate that kidney function alone  
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7 194 plays a role in pregnancy outcomes, though usually limited unless kidney dysfunction is  
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9 195 moderate and proteinuria is present. Whether pregnancy in women with CKD changes the  
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11 196 course of their kidney disease, is less clear. Kidney donors aside, patients with CKD (with or  
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13 197 without kidney transplants) have other factors that may independently influence pregnancy  
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15 198 outcomes, be it underlying disease, medications, proteinuria, or hypertension.  
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## 21 200 **BLOOD PRESSURE**

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24 201 Hypertension during pregnancy is an increasingly recognized problem, and one that has led  
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26 202 to the creation of several management guidelines.<sup>32-35</sup> Using hospital discharge data from  
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28 203 the Nationwide Inpatient sample (NIS) part of the Healthcare Cost and Utilization Project, a  
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30 204 2012 population-based study examined 56,494,634 deliveries between 1995 and 2008.  
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32 205 During this period the prevalence of primary and secondary hypertension increased from  
33  
34 206 0.9% to 1.52% and 0.07% to 0.24% respectively.<sup>36</sup> Hypertension during pregnancy can be  
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36 207 broken down into four types as outlined in Table 2: pre-eclampsia / eclampsia, chronic  
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38 208 hypertension, chronic hypertension with superimposed pre-eclampsia, and gestational  
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40 209 hypertension.<sup>32</sup> Management of hypertension during pregnancy differs from that in non-  
41  
42 210 pregnant states. Blood pressure goals are more permissive during gestation. However the  
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44 211 American College of Obstetricians and Gynecology (ACOG) recommends that if there is  
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46 212 evidence of end organ damage, treatment goals should be as rigid as in the non-pregnant  
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48 213 state.<sup>32</sup>  
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3 215 The reasoning behind why management in the pregnant and non-pregnant state differs is  
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5 216 several-fold including that pregnancy is a time limited event in which the benefits of  
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7 217 treatment are not easily realized, and treatment exposes the fetus to medications which  
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9 218 may affect intrauterine programming and may lead to reduced utero-placental blood flow  
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11 219 with compromised fetal circulation.<sup>37,38</sup> Whether or not blood pressure management should  
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13 220 differ in pregnancy from non-pregnant states is a point of current debate. Those who  
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15 221 advocate that the 2 should not differ note that hypertension during pregnancy is not as  
16  
17 222 benign as once thought. Hypertension during pregnancy has been associated with an  
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19 223 increased risk for acute kidney injury (AKI), pulmonary edema, need for ventilator support,  
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21 224 and cerebrovascular complications.<sup>39,40</sup> There is also now evidence that a hypertensive  
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23 225 pregnancy is associated with later-in-life left ventricular hypertrophy.<sup>41</sup> An  
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25 226 echocardiography study of pregnant and non-pregnant women who were normotensive or  
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27 227 had essential hypertension suggested that pregnancy and hypertension have synergistic  
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29 228 effects in causing myocardial hypertrophy.<sup>42</sup> This latter study indicates that cardiac changes  
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31 229 may be seen not only years after delivery, but during the pregnancy too.

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33 230 The debate over whether or not blood pressure goals in pregnant women with hypertension  
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35 231 should be relaxed or stringent and the ACOG guidelines are timely as the Tight Control of  
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37 232 Hypertension in Pregnancy Study (CHIPS) recently demonstrated that pregnancy outcomes  
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39 233 and maternal complications were not significantly different in pregnant women whose  
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41 234 hypertension was controlled more or less tightly.<sup>43</sup> However this debate is not germane to  
42  
43 235 CKD because CKD is a form of end organ damage and the CHIPS trial excluded individuals  
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45 236 with renal dysfunction. Consequently we suggest that such patients should be treated  
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47 237 more aggressively, that is in a manner similar to the non-pregnant state i.e. aiming for tight  
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49 238 control.

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3 239 Fetal and maternal outcomes for pregnant women with CKD are markedly worse in the  
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5 240 presence of hypertension. Bateman *et al* observed odds ratios of stillbirth, poor fetal  
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7 241 growth, and spontaneous delivery <37 weeks gestation to be 7.29, 7.49 and 8.60 compared  
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10 242 with 1.74, 2.29 and 2.25 respectively in women with CKD plus hypertension compared with  
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12 243 those with CKD alone.<sup>36</sup> Maternal complications were also markedly increased in women  
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14 244 with CKD who had chronic hypertension compared with those with CKD but without chronic  
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17 245 hypertension. For example, preeclampsia and AKI odds ratios were 27.87 and 253.4  
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19 246 compared with 3.28 and 62.4 respectively. Whether or not blood pressure control in  
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21 247 women with CKD and chronic hypertension would reduce these risks has not been studied.  
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23 248 The United Kingdom's National Institute of Health and Clinical Excellence (NICE) clinical  
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25 249 guidelines recommend keeping BP lower than 140/90 mmHg in pregnant women with  
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27 250 target-organ damage, including CKD.<sup>37</sup> However, the evidence behind this blood pressure  
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29 251 goal is scant at best.

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

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## 260 **PRE-PREGNANCY COUNSELLING**

261 The value of pre-pregnancy counselling has been recognized in women with diabetes for  
262 several decades.<sup>46</sup> Pre-pregnancy counselling in women with chronic kidney disease offers

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2  
3 263 the opportunity to minimize disease activity, optimize blood pressure control and  
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5 264 proteinuria, alter teratogenic medications and also to educate couples about potential fetal  
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7 265 and maternal adverse events that may occur during pregnancy and the puerperium in this  
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10 266 high risk group. It also allows discussion of the inheritance of genetic disorders of the kidney  
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12 267 including cystic diseases, metabolic diseases and glomerular basement membrane  
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14 268 disorders. The confidential enquiries into maternal deaths in the UK endorses that pre-  
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16 269 pregnancy counselling should be routinely commissioned and offered to women with pre-  
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18 270 existing medical illnesses in view of the morbidity and mortality triggered by these  
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20 271 diseases.<sup>47</sup> The advice given is clearly dependent on underlying renal disease, baseline renal  
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22 272 function, proteinuria and blood pressure at conception and this should be delivered in a  
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24 273 patient focused, individualised manner. Women with chronic kidney disease should be  
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26 274 counselled prior to pregnancy of the increasing risk of maternal and fetal complications as  
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28 275 GFR declines. These risks include fetal growth restriction, pre-term birth, pre-eclampsia,  
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30 276 fetal death and deterioration of maternal renal function / disease flare.<sup>48</sup>  
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### 38 278 **Fertility**

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40 279 Women may need to be advised that advanced chronic kidney disease impairs fertility.<sup>49</sup>  
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42 280 This is due to a multitude of reasons, although these are poorly characterized in the  
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44 281 literature. Hyperprolactinemia is common in patients with CKD, due to reduced renal  
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46 282 clearance and increased production from suppression of dopaminergic activity, and this  
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48 283 inhibits gonadotropin secretion. This manifests as amenorrhea in women.<sup>50,51</sup> Levels of  
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50 284 leutinising hormone and follicle stimulating hormone are also elevated in CKD, although the  
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52 285 physiological surge in LH usually seen during the mid-cycle of healthy women is not seen in  
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54 286 those with CKD, and this can lead to anovulation.<sup>51</sup> These hypothalamic-pituitary axis  
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3 287 dysfunctions, in combination with the psychological impact of CKD causing depression and  
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5 288 reduced libido, can significantly reduce the chances of conception. However, fertility can be  
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7 289 restored after renal transplantation.<sup>52</sup> As pregnancy outcomes are progressively poorer with  
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10 290 advancing chronic kidney disease, younger women who want to become pregnant are often  
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12 291 advised to be transplanted first. If this is not possible, nocturnal haemodialysis may restore  
13  
14 292 menses and improve the chances of pregnancy.<sup>53,54</sup>  
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### 19 294 **Optimization Before Pregnancy**

21 295 Blood pressure should be optimized before pregnancy. Both KDIGO and UK National  
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23 296 Institute for Health and Care Excellence (NICE) recommend that adults with CKD, without  
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26 297 proteinuria should aim for a blood pressure below 140/90mmHg. NICE recommend that  
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28 298 those with CKD who have diabetes or those with proteinuria (ACR >70mg/mmol) aim for a  
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31 299 blood pressure below 130/80mmHg. KDIGO also recommend this level for patients with an  
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33 300 ACR >30mg/mmol.<sup>55,56</sup> These targets should be achieved prior to conception with drugs  
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36 301 that are safe to continue during pregnancy (summarized in table 3). ACE inhibitors and  
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38 302 angiotensin receptor blockers should be stopped prior to pregnancy or as early as possible  
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41 303 after discovering pregnancy. A recent systematic review of the management of hypertensive  
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43 304 disorders in pregnancy recommends the preventative use of low dose aspirin to reduce pre-  
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45 305 eclampsia, and in severe hypertension.<sup>57</sup> UK NICE guidelines also advocate the use of  
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47 306 aspirin from 12 weeks of gestation in women at high risk to reduce the incidence of pre-  
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49 307 eclampsia.<sup>58</sup> Such risk factors include chronic kidney disease and autoimmune diseases such  
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51 308 as systemic lupus erythematosus. This is based on a Cochrane review of 59 trials.<sup>59</sup>  
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54 309 Proteinuria may occur in 30% of women who do not have proteinuria before pregnancy,<sup>60</sup>  
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57 310 and may confer poorer fetomaternal outcomes<sup>61,62</sup>. Proteinuria should therefore, where  
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3 311 possible, be controlled during pre-pregnancy counselling, and the main way to achieve this  
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5 312 is through optimizing treatment of baseline renal disease and blood pressure control.  
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7  
8 313 Women with proteinuria should be counselled about the potential requirement for  
9  
10 314 thromboprophylaxis during pregnancy.

11  
12 315 . Systemic lupus erythematosus (SLE) affects women of child bearing age without affecting  
13  
14  
15 316 fertility and so pregnancy is not uncommon. A meta-analysis of 2751 women with SLE  
16  
17 317 showed that those with active lupus nephritis (LN) had an increased risk of maternal  
18  
19 318 hypertensive disorders and premature birth.<sup>63</sup> Disease flare, high initial creatinine and  
20  
21 319 proteinuria at conception are predictive of worse outcomes. In addition, flares may cause a  
22  
23 320 decline in renal function and accelerate progression to end-stage renal disease. Pregnancy  
24  
25 321 should be planned and drugs altered accordingly prior to pregnancy, including stopping /  
26  
27 322 substituting mycophenolic acid products. A minimum six month period of disease  
28  
29 323 quiescence prior to pregnancy is therefore recommended.<sup>64,65</sup> The PROMISSE (Predictors of  
30  
31 324 Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic  
32  
33 325 Lupus Erythematosus) study, a large prospective cohort study including 385 patients,  
34  
35 326 recently demonstrated that 81% of pregnancies in women with inactive or stable  
36  
37 327 mild/moderate disease were uncomplicated.<sup>66</sup> Features indicating a higher risk for adverse  
38  
39 328 pregnancy outcomes, included a positive lupus anticoagulant, antihypertensive use, a low  
40  
41 329 platelet count, Hispanic or non-white ethnicity, and a physician's global assessment score  
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43 330 >1; and those women without these generally had favourable outcomes.  
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### 51 332 **Pre-implantation diagnosis**

52  
53 333 It is important to discuss the option of preimplantation genetic diagnosis (PGD) with women  
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55 334 whose CKD is secondary to a genetically inherited cause. Recent advances in techniques  
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3 335 used for in vitro-fertilisation allow removal of one or two cells at the eight cell stage of  
4  
5 336 blastocyst formation.<sup>67</sup> These blastomeres can then be analysed for the mutations  
6  
7 337 responsible for conditions such as Alports Syndrome or Adult Polycystic Kidney Disease.<sup>68</sup>  
8  
9  
10 338 Although there are limited data, initial reports suggest PGD is associated with similar  
11  
12 339 success in pregnancy outcome when compared with routine IVF.  
13  
14  
15 340  
16  
17 341 Pre-pregnancy counselling improves knowledge and changes behavior prior to pregnancy<sup>69</sup>  
18  
19 342 which may help to reduce adverse events. The optimum way of offering pre-conception  
20  
21 343 counselling has not been established. Patients with diabetes agreed that being informed of  
22  
23 344 the risks prior to pregnancy is crucial, but existing childcare and work commitments  
24  
25 345 prevented attendance to such services. They also stressed that the positive aspects of  
26  
27 346 having children should be discussed rather than only medical complications.<sup>70</sup> In a  
28  
29 347 retrospective analysis of 179 women with chronic kidney disease undergoing pre-pregnancy  
30  
31 348 counselling in a large single centre, consultations included the multi-disciplinary team of a  
32  
33 349 consultant obstetric physician, obstetrician and nephrologist.<sup>71</sup> These women had an  
34  
35 350 overwhelmingly positive experience, with approximately 90% finding the clinic informative,  
36  
37 351 with understandable information and helpful in deciding about pursuing pregnancy.  
38  
39 352 However, 17% found the process intimidating, but this may prove difficult to abrogate in  
40  
41 353 such a highly emotive situation. Clearly the inclusion of midwives, general practitioners,  
42  
43 354 counsellors, psychologists and clinical geneticists when required, may prove an extremely  
44  
45 355 useful addition to this team. Electronic media including the internet and DVDs have also  
46  
47 356 proven beneficial.<sup>72,73</sup>  
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## 358 MEDICATIONS



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3 359 Women with CKD including those with a kidney transplant are prescribed different types of  
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5 360 medications that have the potential to adversely affect the pregnancy outcomes. These  
6  
7 361 include immunosuppressive, anti-hypertensive and anti-viral medications. Each is important  
8  
9 362 for the mother's overall health, but their effects on the pregnant woman and her developing  
10  
11 363 fetus have been a concern for many practitioners. The major classes of medications used in  
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13 364 women with CKD and in transplant recipients and their known effects on the mother and  
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15 365 her offspring will be described below. See table 3.  
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367 **Immunosuppressants:**

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

375  
376 There are no guidelines about dosing of immunosuppressant medications during pregnancy,  
377 but several studies have provided recommendations. Kim *et al* recently reported on blood  
378 levels of calcineurin inhibitors during gestation in 88 pregnancies from 75 transplant  
379 recipients.<sup>75</sup> In 80 cases the serum creatinine was decreased by an average of 0.14mg/dl  
380 during pregnancy and returned to pre-pregnancy levels after delivery. Tacrolimus blood  
381 trough levels decreased during the second trimester (from 5.8 ±2.8 ng/ml) to 4.2  
382 ±1.8ng/ml). Likewise, cyclosporine levels decreased during the second trimester from 125.1

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3 383  $\pm 65.1$  ng/ml to  $75.4 \pm 35$  ng/ml. The recommendations of this study were to increase  
4  
5 384 calcineurin inhibitor dose by approximately 20-25% during gestation to maintain optimal  
6  
7 385 drug levels. Aktürk also reported on the pharmacokinetics of tacrolimus during pregnancy  
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9  
10 386 and recommended calcineurin inhibitor dosing is significantly increased in order to maintain  
11  
12 387 adequate trough levels during pregnancy.<sup>76</sup> Women should be informed that tacrolimus  
13  
14 388 levels need to be closely monitored in pregnancy. It is highly bound to plasma protein and  
15  
16 389 erythrocytes, with complicated pharmacokinetics that are even further altered by normal  
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18 390 physiological changes in pregnancy such as anaemia, hypoalbuminaemia and increased  
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20 391 creatinine clearance. Maintaining whole blood tacrolimus levels after conception risks  
21  
22 392 toxicity but no dose change may incur under-treatment. Unbound trough concentrations  
23  
24 393 may be the most appropriate level to monitor during pregnancy,<sup>77</sup> but these are technically  
25  
26 394 challenging to measure in routine practice.  
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28 395 Immunosuppressive medications cross the maternal-placental-fetal interface<sup>74,78</sup> and  
29  
30 396 therefore there are always concerns about their effect on fetal development. The fetal liver,  
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32 397 which is interposed between the umbilical vein and fetal inferior vena cava, filters the  
33  
34 398 pharmacologic agents that pass through the placenta, including immunosuppressants.  
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36 399 Calcineurin inhibitors are well-known to cross the placenta and enter the fetal circulation.<sup>74</sup>  
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38 400 Zheng et al recently reported on tacrolimus concentrations in maternal and umbilical cord  
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40 401 blood at delivery in eight transplant recipients and found that umbilical cord venous blood  
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42 402 concentrations were 71% that of maternal concentrations. The lower fetal blood  
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44 403 concentrations were proposed to be caused by the active transport of tacrolimus from the  
45  
46 404 fetus toward the mother by placental P-glycoprotein.<sup>79</sup> Whether in utero exposure to  
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48 405 tacrolimus has adverse effects on fetal development however is not known. In animal  
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50 406 studies it was recently shown that rats treated with cyclosporine (CSA) during pregnancy  
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3 407 experienced impaired kidney development, suggesting a predisposition to chronic kidney  
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5 408 disease and hypertension in adult life.<sup>80</sup> Despite this, tacrolimus is deemed safe in  
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7 409 pregnancy<sup>81</sup> and breastfeeding.<sup>82</sup>  
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10 410 Corticosteroids pass through the placenta, but most of the maternal dose undergoes  
11  
12 411 placental metabolism<sup>74</sup> and therefore the fetus is generally protected from adverse effects  
13  
14 412 of corticosteroids. While adverse effects associated with in utero exposure to  
15  
16 413 corticosteroids are rare, there have though been sporadic reports of adrenal suppression in  
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18 414 newborns of pregnant transplant recipients particularly when the corticosteroids dose was  
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20 415 high.  
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26 417 Azathioprine also passes into the fetal circulation, but the fetus lacks inosinate  
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28 418 pyrophosphorylase, which is required for the conversion of azathioprine to its active  
29  
30 419 metabolite 6-mercaptopurine.<sup>74</sup> Therefore, concerns about the use of azathioprine in  
31  
32 420 pregnancy have been less than for other immunosuppressive.<sup>83</sup> Indeed, mycophenolic acid  
33  
34 421 products are routinely substituted for azathioprine before and during pregnancy.<sup>23</sup>  
35  
36 422 Substantial data have shown that mycophenolic acid products are associated with an  
37  
38 423 increased incidence of spontaneous abortion and a distinct pattern of birth defects.<sup>84</sup> The  
39  
40 424 spectrum of mycophenolate embryopathy includes ocular anomalies, corpus callosum  
41  
42 425 agenesis, heart defects, kidney malformations, diaphragmatic hernia and skeletal  
43  
44 426 deformities.<sup>85</sup> Numerous reports of mycophenolate-associated malformations led the FDA  
45  
46 427 to issue a black box warning on its use during pregnancy.  
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50 428 Less is known about the effects of sirolimus in pregnancy. Sifontis reported on seven  
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52 429 pregnancies with sirolimus exposure in seven pregnancies.<sup>86</sup> In three there were  
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54 430 miscarriages and four resulted in live births. No malformations were observed but sirolimus  
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3 431 was switched to azathioprine during the first trimester in one case and in another the  
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5 432 immunosuppressive regimen was switched from mycophenolate to sirolimus at 24 weeks. In  
6  
7 433 the latter case the infant was born with features typical of mycophenolate embryopathy.  
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9 434 There are several reports of sirolimus exposure during the whole pregnancy, without  
10  
11 435 apparent adverse effects on the fetus.<sup>87-90</sup>  
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13 436 Recently there have been several reports about pregnancy in transplant recipients taking  
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15 437 the mTOR inhibitor everolimus during their pregnancy.<sup>91,92</sup> One report of an unplanned  
16  
17 438 pregnancy in a heart transplant recipient described a normal baby without obvious  
18  
19 439 congenital defects. The fetus was exposed to everolimus as concentrations were similar in  
20  
21 440 maternal and neonatal umbilical blood, and fetal blood levels were detected for 5 days after  
22  
23 441 birth. In contrast CsA levels, which were also detected in umbilical blood, disappeared  
24  
25 442 within 2 days of delivery in fetal blood.<sup>93</sup> Other reports have been published recently  
26  
27 443 describing exposure to everolimus during pregnancies in kidney transplant recipients  
28  
29 444 without apparent congenital malformations.<sup>94,95</sup> Although the few reports of unremarkable  
30  
31 445 pregnancies with the use of mTOR inhibitors are encouraging, additional data are needed to  
32  
33 446 confirm their safe use during pregnancy.  
34  
35 447 Treatment of rejection with corticosteroids is the mainstay during pregnancy and is  
36  
37 448 generally considered safe to the fetus.<sup>96</sup> Recently Kutzler et al reported on the safe use of  
38  
39 449 anti-thymocyte globulin (ATG) to successfully treat a pregnant renal transplant recipient  
40  
41 450 with mixed acute cellular rejection and antibody-mediated rejection.<sup>97</sup> The patient was also  
42  
43 451 treated with high-dose corticosteroids, intravenous immunoglobulin and plasmapheresis in  
44  
45 452 addition to ATG; and she gave birth to a healthy baby boy. The safety of rejection treatment  
46  
47 453 with ATG or other monoclonal or polyclonal antibodies has not been evaluated in clinical  
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3 454 trials in pregnant transplant recipients and only scattered case reports are available. There  
4  
5 455 are no data on the long term impact on the exposed children's immune repertoire.  
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7 456 Management of lupus nephritis (LN) and other causes of autoimmune glomerulonephritides  
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10 457 in pregnancy remains challenging due to limited safe therapeutic options.  
11  
12 458 Cyclophosphamide and mycophenolate mofetil are teratogenic, and are generally to be  
13  
14 459 avoided in pregnancy, although can be considered from the third trimester.<sup>98</sup> Steroids are  
15  
16 460 often used in pregnancy as they are not associated with congenital abnormalities<sup>99</sup> but can  
17  
18 461 cause premature rupture of membranes, preterm delivery, maternal sepsis and gestational  
19  
20 462 diabetes.<sup>100</sup> Data on Rituximab use in pregnancy are limited but it does cross the placenta  
21  
22 463 and lymphopaenia has been reported in new born children.<sup>101</sup> Hydroxychloroquine and  
23  
24 464 azathioprine are safe in pregnancy and should be considered in treatment regimens prior to  
25  
26 465 conception, along with aspirin. Hydroxychloroquine (HCQ) reduces the risk cardiac  
27  
28 466 manifestations of neonatal lupus in anti-Ro-positive mothers and is actively recommended  
29  
30 467 in women with LN before and during pregnancy.<sup>102</sup> Tacrolimus may be a useful alternative  
31  
32 468 or adjunctive therapy for LN flare during pregnancy.<sup>103</sup>  
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#### 41 **Anti-Hypertensives:**

42  
43 471 Adverse effects of renin angiotensin system (RAS) blockade have been shown for some time,  
44  
45 472 and ACE inhibitors and angiotensin receptor blockers are teratogenic.<sup>104-107</sup> In a recent  
46  
47 473 retrospective study performed through the Midwest Pediatric Nephrology Consortium, RAS  
48  
49 474 blocker fetopathy was identified and confirmed to depend on the timing of exposure, with  
50  
51 475 the most severe renal manifestations occurring with exposure after the first trimester.<sup>104</sup>  
52  
53 476 Beta blockers are commonly used during pregnancy and recent meta-analyses showed that  
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55 477 first-trimester oral beta-blocker exposure was associated with no increase in major  
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3 478 congenital anomalies, but examination of organ-specific malformations revealed increased  
4  
5 479 odds of cardiovascular defects, cleft lip/palate, and neural tube defects.<sup>108</sup> There is  
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8 480 significant heterogeneity in the reports and thus it is not clear at this time whether beta-  
9  
10 481 blockers are associated with these defects. Calcium channel blockers have recently been  
11  
12 482 used in the management of hypertensive disorders of pregnancy and preterm labor.  
13  
14 483 Teratogenicity with calcium channel blockers has been shown in animals, but no cases have  
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16  
17 484 yet been reported in humans and at this time are reported to be safe for use in pregnancy-  
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19 485 associated hypertension.<sup>109</sup>

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24 487 ***Antivirals:***

25  
26 488 Several antivirals have been used during pregnancy. The most commonly used antiviral  
27  
28 489 agents target CMV infection. All of these have fetal toxicity. Valganciclovir should not be  
29  
30 490 used as animal studies have revealed it can cause embryoletality, fetotoxicity,  
31  
32 491 teratogenicity, and mutagenicity. Valganciclovir may cause impaired fertility in both males  
33  
34 492 and females.<sup>110</sup> If CMV prophylaxis is required, valaciclovir is considered safe though  
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36 493 possibly less effective. Lamivudine and tenofovir are safe for Hepatitis B prophylaxis.<sup>111, 112</sup>

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45 496 **CONCLUSIONS**

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47 497 Pregnancy in women with CKD and kidney transplant should be planned, considered high  
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49 498 risk, and ideally managed by an expert multidisciplinary team. The best outcomes are likely  
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51 499 seen where there has been careful pre-pregnancy evaluation and planning, and close  
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53 500 monitoring during antenatal care. The outcomes for women and babies continue to improve  
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3 501 but we still need better biomarkers e.g. placental growth factor (PIGF) to identify those  
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5 502 women at higher risk of developing superimposed pre-eclampsia.<sup>113</sup>  
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#### 11 **DISCLOSURES**

12 505 **Michelle A. Josephson is member of the Mycophenolate Pregnancy Registry Advisory**

13  
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15 506 **Committee**

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49 Legends:  
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51 Table 1: Prepregnancy kidney function in patients with CKD with estimates of problems in  
52 pregnancy (fetal growth restriction, preeclampsia, preterm delivery, and significant kidney  
53 function loss in pregnancy [ $>25\%$  SCr increment]), obstetric outcome, and loss of kidney  
54 function: The effect of altering cut-off between moderate and severe dysfunction from 2.8  
55 mg/dL ( $\geq 250\mu\text{mol/L}$ ) to 2.0 mg/dL ( $\geq 180\mu\text{mol/L}$ ), respectively  
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3 793 Table 2: Hypertensive disorders of pregnancy

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6 796 Table 3: Drug Safety in Pregnancy

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3 **1 Pregnancy in Chronic Kidney Disease and Kidney Transplantation**  
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14 **RUNNING HEADLINE:** Pregnancy in CKD & Kidney Transplantation  
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25 **ABSTRACT**

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

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

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## 49 THE IMPACT OF KIDNEY FUNCTION IN AND OF ITSELF ON PREGNANCY OUTCOME

### 50 CKD ~~degreestage~~ and outcomes

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

### 62 An evolving state of understanding

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

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3 73 on the degree of renal insufficiency pre-pregnancy, and the presence or absence of  
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5 74 hypertension.<sup>6</sup> Based on these parameters, women were grouped into three categories:  
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8 75 mild, moderate, or severe dysfunction. Normotensive women with preserved or mildly  
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10 76 decreased but stable kidney function (defined as a serum creatinine (SCr) of  $\leq 1.4$  mg/dL) did  
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12 77 well with over 95% live births, 75% of which were appropriate size for gestational age.  
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14 78 However, prognosis worsened with moderate dysfunction (SCr  $\geq 1.4$  mg/dL-2.8 mg/dL) and  
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17 79 more so with severe impairment (SCr level  $\geq 2.8$  mg/dL).<sup>7</sup> [These estimates were based on a](#)  
18  
19  
20 80 [26-year literature review \(1984-2010\), as well as personal patient files by John Davison,](#)  
21  
22 81 [most recently published in a NephSAP editorial by Drs Lindheimer and Davison, in the issue](#)  
23  
24 82 [devoted to renal disease and hypertension in pregnancy \(reproduced with permission in](#)  
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26  
27 83 [Table 1\).](#)<sup>8</sup> [See Table 1.](#)

#### 84 85 [Creatinine vs eGFR](#)

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



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3 97 outcome. The majority of patients in the study were classified as CKD stage 1. [The authors](#)  
4  
5 98 [concluded that adverse outcomes increased with increasing stage of CKD, including](#)  
6  
7 99 [surprisingly stage 1, even in the absence of hypertension, baseline proteinuria, and systemic](#)  
8  
9  
10 100 [diseases.](#) ~~The study analysis had sufficient data to confirm that adverse outcomes increased~~  
11  
12 101 ~~with increasing stage of CKD, including surprisingly stage 1, even in the absence of~~  
13  
14 102 ~~hypertension, baseline proteinuria, and systemic diseases.~~ [The eGFR was calculated based](#)  
15  
16 103 [on the Cockcroft-Gault, Modification of Diet in Renal Disease \(MDRD\), and Chronic Kidney](#)  
17  
18 104 [Disease Epidemiology Collaboration \(CKD-EPI\) formulas. As CKD-EPI and MDRD have been](#)  
19  
20 105 [found to underestimate GFR in pregnancy<sup>11,12</sup> and Cockcroft-Gault has been demonstrated](#)  
21  
22 106 [to both underestimate and overestimate GFR in hypertensive pregnant women,<sup>13</sup> it is](#)  
23  
24 107 [possible that some of the patients in Piccoli's study had lower GFRs than the group in which](#)  
25  
26 108 [they were classified. Some of the individuals reported to have CKD stage 1, could therefore](#)  
27  
28 109 [have had a higher stage.](#) While Piccoli *et al's* findings were primarily in women with mild and  
29  
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32  
33 110 moderate dysfunction Imbasciati et al studied 49 women with preconception stage 3 to 5  
34  
35 111 CKD observed for a mean of 39 months after delivery. In the latter study only individuals  
36  
37 112 with both GFR less than 40 ml/min/1.73m<sup>2</sup> and greater than 1 gram of proteinuria per day  
38  
39 113 were noted to have poor fetal outcomes and accelerated kidney function loss.<sup>14</sup> A meta-  
40  
41 114 analysis by Zhang et al of 23 studies that included 1514 pregnancies with CKD found no  
42  
43 115 significant difference in renal outcomes in pregnant women with CKD compared with non-  
44  
45 116 pregnant women with CKD. The study did however find that adverse pregnancy outcomes,  
46  
47 117 including preeclampsia, premature births, SGA/low birth weight, cesarean section, stillbirth,  
48  
49 118 fetal death, and neonatal death, were increased in women with CKD compared to those  
50  
51 119 without. [The conclusions that can be drawn from the meta-analysis must be put into](#)  
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3 120 | [context because the literature review focused on patients with CKD stages 1-3, thus](#)  
4  
5 121 | [excluding those with stage 4 or 5 who are most vulnerable for progression of disease.](#)<sup>15</sup>  
6  
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8 122 | In their review and recent editorial Lindheimer and Davison<sup>5,8</sup> underscore that most eGFR  
9  
10 123 | formulae correlate poorly with measured GFR in pregnant women, and that obstetricians  
11  
12 124 | familiar with absolute values of creatinine may be unfamiliar with the nephrology  
13  
14 125 | community's CKD system . However, despite the seeming differences between those who  
15  
16 126 | are considering pregnancy outcomes through an eGFR based CKD stages filter, and those  
17  
18 127 | who are more comfortable with the serum creatinine based assessment, proponents of  
19  
20 128 | both agree that degree of kidney function plays an important role in outcome. Neither  
21  
22 129 | group advocates returning to the pre-1975 mindset of avoiding pregnancy in women with  
23  
24 130 | mild kidney dysfunction, however defined.  
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30  
31 132 | [Additional contributing factors](#)  
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34 133 | Whilst clearly important, kidney function alone does not uniformly predict pregnancy  
35  
36 134 | outcomes. [There are likely to be additional contributing factors to pregnancy outcomes,](#)  
37  
38 135 | [such as active systemic disease or endothelial injury. For example c](#)Certain specific diseases  
39  
40 136 | such as Systemic Lupus Erythematosus (SLE) may exert a greater adverse effect on the  
41  
42 137 | pregnancy making it impossible to isolate the role of kidney function per se on outcomes.<sup>16</sup>  
43  
44 138 | Similarly kidney transplantation does not present a pristine model to look at kidney function  
45  
46 139 | alone because of the effects of immunosuppression.  
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52 141 | [Kidney transplantation and outcome](#)  
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54  
55 142 | [A national UK cohort study demonstrated that most pregnancies after renal transplantation](#)  
56  
57 143 | [are successful, although the risks of pre-eclampsia still remain higher than controls](#)<sup>17</sup> [and](#)  
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3 144 [this higher risk of pre-eclampsia affects even those with good GFRs.](#)<sup>18</sup> [Patients should be](#)  
4  
5 145 [counselled of this accordingly and the other precautions discussed in the pre-pregnancy](#)  
6  
7 146 [counselling section, initiated.](#) How does the connection between kidney function and  
8  
9 147 pregnancy outcomes relate to pregnancy outcomes in kidney transplant recipients? Similar  
10  
11 148 to findings in advanced kidney failure, transplant patients appear to have a lower [fertility](#)  
12  
13 149 [pregnancy](#) rate than the general public.<sup>19</sup> Registry, cohort, and meta-analysis studies  
14  
15 150 demonstrate that pregnancies in transplant recipients, which are more likely to be  
16  
17 151 complicated by hypertension, are at greater risk for prematurity, small for gestational age,  
18  
19 152 cesarean sections, the diagnosis of preeclampsia and perinatal mortality.<sup>17,18,20</sup> Of note  
20  
21 153 while pregnancy and renal function outcomes in transplant recipients have been studied  
22  
23 154 based on creatinine levels, we could locate no assessments based on the CKD staging  
24  
25 155 system. In transplant recipients, there are the additional factors of immunosuppression  
26  
27 156 [medications](#). These factors make it hard to isolate and define the kidney function effect on  
28  
29 157 pregnancy in this group. Long term follow-up of transplant recipients with and without a  
30  
31 158 history of pregnancy supports the idea that pregnancy does not worsen long term  
32  
33 159 outcomes.<sup>21</sup>  
34  
35 160 [However, there may be subsets of transplant patients in whom pregnancy accelerates renal](#)  
36  
37 161 [function decline.](#)~~However, there may be subsets of transplant patients in whom it does.~~  
38  
39 162 Data from the UK Pregnancy registry indicate that women with kidney allografts whose pre-  
40  
41 163 pregnancy SCr is greater than 150 $\mu$ mol/L (approximately 1.7 mg/dL) have an increased  
42  
43 164 serum creatinine after pregnancy, suggesting that the pregnancy itself may negatively affect  
44  
45 165 graft function.<sup>22</sup> Despite limitations of available data in the transplant recipient, guidelines  
46  
47 166 advise that amongst other factors, the basis for determining reasonable timing for  
48  
49 167 pregnancy is the presence of adequate and stable graft function (arbitrarily set as a SCr<1.5  
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3 168 | mg/dL).<sup>23</sup> [The American Society of Transplantation recommends that prior to pregnancy](#)  
4  
5 169 | [there should be no rejection for one year, adequate and stable graft function, no acute](#)  
6  
7 170 | [infections, and stable immunosuppression dosing.](#)<sup>24</sup> [Pregnancy should be delayed until at](#)  
8  
9 171 | [least one year after renal transplantation](#)<sup>25</sup> [as postponement is associated with better](#)  
10  
11 172 | [outcomes.](#)<sup>26</sup> [A recent study by Rose et al that examined allograft outcome and pregnancy](#)  
12  
13 173 | [timing in the first 3 post-transplant years of Medicare insured kidney transplant recipients](#)  
14  
15 174 | [suggests that pregnancy in the first 2 post-transplant years is associated with increased](#)  
16  
17 175 | [allograft loss compared with waiting an additional year.](#)<sup>27</sup> [Beyond optimal post-transplant](#)  
18  
19 176 | [pregnancy timing,](#) there are many [other](#) unanswered questions about pregnancy in  
20  
21 177 | transplant recipients including the optimal pre-pregnancy kidney function and whether  
22  
23 178 | having pre-existent donor specific antibodies affects pregnancy outcomes, or the  
24  
25 179 | transplanted kidney. This last consideration is of particular concern given the usual pre-  
26  
27 180 | pregnancy modification of immunosuppression, with discontinuation of mycophenolic acid  
28  
29 181 | formulations.

### 182 183 [Kidney donors](#)

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

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2  
3 192 al's survey of previous kidney donors documented subjects reporting significant increases in  
4  
5 193 diagnosed preeclampsia, hypertension, and gestational diabetes in pregnancies after  
6  
7 194 donation compared with before.<sup>30</sup> Reisaeter et al found more pre-eclampsia diagnosed in  
8  
9 195 women after donation compared with pregnancies before.<sup>31</sup>  
10  
11  
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196

### 197 [Kidney function impact](#)

17 198 Taken together the studies, case series, and registries indicate that kidney function alone  
18  
19 199 plays a role in pregnancy outcomes, though usually limited unless kidney dysfunction is  
20  
21 200 moderate and proteinuria is present. Whether pregnancy in women with CKD changes the  
22  
23 201 course of their kidney disease, is less clear. Kidney donors aside, patients with CKD (with or  
24  
25 202 without kidney transplants) have other factors that may independently influence pregnancy  
26  
27 203 outcomes, be it underlying disease, medications, proteinuria, or hypertension.  
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### 205 **BLOOD PRESSURE**

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35  
36 206 ~~Using hospital discharge data from the Nationwide Inpatient sample (NIS) part of the~~  
37  
38 207 ~~Healthcare Cost and Utilization Project, a 2012 population based study examined~~  
39  
40 208 ~~56,494,634 deliveries between 1995 and 2008. During this period the prevalence of primary~~  
41  
42 209 ~~and secondary hypertension increased from 0.9% to 1.52% and 0.07% to 0.24%~~  
43  
44 210 ~~respectively.~~<sup>25</sup> Hypertension during pregnancy is an increasingly recognized problem, and  
45  
46 211 one that has led to the creation of several management guidelines.<sup>32-35</sup> [Using hospital](#)  
47  
48 212 [discharge data from the Nationwide Inpatient sample \(NIS\) part of the Healthcare Cost and](#)  
49  
50 213 [Utilization Project, a 2012 population-based study examined 56,494,634 deliveries between](#)  
51  
52 214 [1995 and 2008. During this period the prevalence of primary and secondary hypertension](#)  
53  
54 215 [increased from 0.9% to 1.52% and 0.07% to 0.24% respectively.](#)<sup>36</sup> Hypertension during  
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3 216 pregnancy can be broken down into four types as outlined in Table 2: pre-eclampsia /  
4  
5 217 eclampsia, chronic hypertension, chronic hypertension with superimposed pre-eclampsia,  
6  
7 218 and gestational hypertension.<sup>32</sup> ~~Women who require antihypertensive medications before~~  
8  
9  
10 219 ~~pregnancy or whose hypertension begins before the 20<sup>th</sup> week of pregnancy, or whose~~  
11  
12 220 ~~hypertension continues for more than 12 weeks following delivery are defined as having~~  
13  
14 221 ~~chronic hypertension. By contrast gestational hypertension is diagnosed when blood~~  
15  
16 222 ~~pressure elevation occurs after the 20<sup>th</sup> week of pregnancy in the absence of proteinuria or~~  
17  
18 223 ~~thrombocytopenia, impaired liver function, new onset of kidney dysfunction, pulmonary~~  
19  
20 224 ~~edema, or new cerebral or visual disturbances.~~<sup>30</sup> Management of hypertension during  
21  
22 225 pregnancy differs from that in non-pregnant states. Blood pressure goals are more  
23  
24 226 permissive during gestation. ~~Furthermore, there are substantial differences as to when to~~  
25  
26 227 ~~start pharmacological therapy between the American College of Obstetrics and Gynecology~~  
27  
28 228 ~~(ACOG) and several other National and International guidelines.~~<sup>31</sup> ~~The report of the~~  
29  
30 229 ~~American College of Obstetricians and Gynecologists' Task Force on Hypertension in~~  
31  
32 230 ~~Pregnancy recommends "For women with chronic hypertension and BP less than 160 mm~~  
33  
34 231 ~~Hg systolic or 105 mm Hg diastolic that they not be treated with pharmacologic~~  
35  
36 232 ~~antihypertensive therapy." However, for those women who have chronic hypertension and~~  
37  
38 233 ~~are already treated with antihypertensive medications, the target range is 120-160 mm Hg~~  
39  
40 234 ~~systolic and 80-105 mm Hg diastolic." However the American College of Obstetricians and~~  
41  
42 235 ~~Gynecology (ACOG) They also recommend~~<sup>32</sup> that if there is evidence of end organ damage,  
43  
44 236 treatment goals should be as rigid as in the non-pregnant state.  
45  
46 237  
47  
48 238 The reasoning behind why management in the pregnant and non-pregnant state differs is  
49  
50 239 several-fold including that. ~~This includes at least in part that as~~ pregnancy is a time limited  
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3 240 event in which, the benefits of treatment are not easily realized~~appreciated during the~~  
4  
5 241 time. ~~Another guiding principal behind the more relaxed blood pressure thresholds is that~~  
6  
7 242 and medication treatment exposes ~~not only the mother, but also~~ the fetus to medications  
8  
9 243 which may affect intrauterine programming and may lead to reduced utero-placental blood  
10  
11 244 flow with compromised fetal circulation.<sup>37,38</sup> Whether or not blood pressure management  
12  
13 245 should differ in pregnancy from non-pregnant ~~these 2~~ states is a point of current debate.  
14  
15 246 Those who advocate that the 2 should not differ ~~lower thresholds for treatment~~ note that  
16  
17 247 hypertension during pregnancy is not as benign as once thought. Hypertension during  
18  
19 248 pregnancy has been associated with an increased risk for acute kidney injury (AKI),  
20  
21 249 pulmonary edema, need for ventilator support, and cerebrovascular complications.<sup>39,40</sup>  
22  
23 250 There is also now evidence that a hypertensive pregnancy is associated with later-in-life left  
24  
25 251 ventricular hypertrophy.<sup>41</sup> An echocardiography study of pregnant and non-pregnant  
26  
27 252 women who were normotensive or had essential hypertension suggested that pregnancy  
28  
29 253 and hypertension have synergistic effects in causing myocardial hypertrophy.<sup>42</sup> This latter  
30  
31 254 study indicates that cardiac changes may be seen not only years after delivery, but during  
32  
33 255 the pregnancy too.  
34  
35 256 The debate over whether or not blood pressure goals in pregnant women with hypertension  
36  
37 257 should be relaxed or stringent and the ACOG guidelines are timely as the Tight Control of  
38  
39 258 Hypertension in Pregnancy Study (CHIPS) recently demonstrated that pregnancy outcomes  
40  
41 259 and maternal complications were not significantly different in pregnant women whose  
42  
43 260 hypertension was controlled more or less tightly.<sup>43</sup> ~~However this debate is~~ ~~but are~~ not  
44  
45 261 germane to CKD. ~~This is~~ because CKD *is* a form of end organ damage and the CHIPS trial  
46  
47 262 excluded individuals with renal dysfunction. ~~and~~ Consequently we suggest that such  
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3 263 patients should be treated more aggressively, that is in a manner similar to the non-  
4  
5 264 pregnant state i.e. aiming for tight control.  
6

7  
8 265 Fetal and maternal outcomes for pregnant women with CKD are markedly worse in the  
9  
10 266 presence of hypertension. Bateman *et al* observed odds ratios of stillbirth, poor fetal  
11  
12 267 growth, and spontaneous delivery <37 weeks gestation to be 7.29, 7.49 and 8.60 compared  
13  
14 268 with 1.74, 2.29 and 2.25 respectively in women with CKD plus hypertension compared with  
15  
16 269 those with CKD alone.<sup>36</sup> Maternal complications were also markedly increased in women  
17  
18 270 with CKD who had chronic hypertension compared with those with CKD but without chronic  
19  
20 271 hypertension. For example, preeclampsia and AKI odds ratios were 27.87 and 253.4  
21  
22 272 compared with 3.28 and 62.4 respectively. Whether or not blood pressure control in  
23  
24 273 women with CKD and chronic hypertension would reduce these risks has not been studied.  
25  
26

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28  
29 274 ~~Nevertheless, the treatment goals for blood pressure during pregnancy in the setting of CKD~~  
30  
31 275 ~~are lower.~~ The United Kingdom's National Institute of Health and Clinical Excellence (NICE)  
32  
33 276 clinical guidelines recommend keeping BP lower than 140/90 mmHg in pregnant women  
34  
35 277 with target-organ damage, including CKD.<sup>37</sup> However, the evidence behind this blood  
36  
37 278 pressure goal is scant at best.  
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41 279  
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43 280 The optimal blood pressure target for pregnant women with CKD and hypertension remains  
44  
45 281 an unanswered question and important knowledge gap. Identifying that target is becoming  
46  
47 282 increasingly important as the prevalence of CKD in pregnant women has increased from a  
48  
49 283 range of 0.1% to 1% in the past to an estimated current prevalence of around 3%,<sup>44</sup> with  
50  
51 284 recent literature suggesting that up to 6% of women of child-bearing age in high income  
52  
53 285 countries are affected by CKD.<sup>45</sup>  
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## 287 PRE-PREGNANCY COUNSELLING

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

## 304 Fertility

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

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3 311 leutinising hormone and follicle stimulating hormone are also elevated in CKD, although the  
4  
5 312 physiological surge in LH usually seen during the mid-cycle of healthy women is not seen in  
6  
7 313 those with CKD, and this can lead to anovulation.<sup>51</sup> These hypothalamic-pituitary axis  
8  
9 314 dysfunctions, in combination with the psychological impact of CKD causing depression and  
10  
11 315 reduced libido, can significantly reduce the chances of conception. However, fertility can be  
12  
13 316 restored after renal transplantation.<sup>52</sup> As pregnancy outcomes are progressively poorer with  
14  
15 317 advancing chronic kidney disease, younger women who want to become pregnant are often  
16  
17 318 advised to be transplanted first. If this is not possible, nocturnal haemodialysis may restore  
18  
19 319 menses and improve the chances of pregnancy.<sup>53,54</sup>  
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### 321 **Optimization Before Pregnancy**

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29 322 Blood pressure should be optimized before pregnancy. Both KDIGO and UK National  
30  
31 323 Institute for Health and Care Excellence (NICE) recommend that adults with CKD, without  
32  
33 324 proteinuria should aim for a blood pressure below 140/90mmHg. NICE recommend that  
34  
35 325 those with CKD who have diabetes or those with proteinuria (ACR >70mg/mmol) aim for a  
36  
37 326 blood pressure below 130/80mmHg. KDIGO also recommend this level for patients with an  
38  
39 327 ACR >30mg/mmol.<sup>55,56</sup> These targets should be achieved prior to conception with drugs  
40  
41 328 that are safe to continue during pregnancy (summarized in table 3). ACE inhibitors and  
42  
43 329 angiotensin receptor blockers should be stopped prior to pregnancy or as early as possible  
44  
45 330 after discovering pregnancy. A recent systematic review of the management of hypertensive  
46  
47 331 disorders in pregnancy recommends the preventative use of low dose aspirin to reduce pre-  
48  
49 332 eclampsia, and in severe hypertension.<sup>57</sup> UK NICE guidelines also advocate the use of  
50  
51 333 aspirin from 12 weeks of gestation in women at high risk to reduce the incidence of pre-  
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3 334 eclampsia.<sup>58</sup> Such risk factors include chronic kidney disease and autoimmune diseases such  
4  
5 335 as systemic lupus erythematosus. This is based on a Cochrane review of 59 trials.<sup>59</sup>  
6  
7 336 Proteinuria may occur in 30% of women who do not have proteinuria before pregnancy,<sup>60</sup>  
8  
9  
10 337 and may confer poorer feto-maternal outcomes<sup>61,62</sup>. Proteinuria should therefore, where  
11  
12 338 possible, be controlled during pre-pregnancy counselling, and the main way to achieve this  
13  
14 339 is through optimizing treatment of baseline renal disease and blood pressure control.  
15  
16 340 Women with proteinuria should be counselled about the potential requirement for  
17  
18 341 thromboprophylaxis during pregnancy.  
19  
20  
21 342 There are a number of clinical practice guidelines for the management of hypertensive  
22  
23 343 disorders of pregnancy worldwide. A recent systematic review showed that there is good  
24  
25 344 inter guideline consistency for the definitions of chronic hypertension, proteinuria and  
26  
27 345 gestational hypertension. Also consistent were the preventative use of low dose aspirin to  
28  
29 346 reduce pre eclampsia, and in severe hypertension.<sup>52</sup> Prior to conception, women should be  
30  
31 347 educated about the symptoms of pre eclampsia. ACE inhibitors and angiotensin receptor  
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33 348 blockers should be stopped prior to pregnancy or as early as possible after discovering  
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35 349 pregnancy.  
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38 350 UK NICE guidelines advocate the use of aspirin from 12 weeks of gestation in women at high  
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41 351 risk to reduce the incidence of pre eclampsia.<sup>53</sup> Such risk factors include chronic kidney  
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43 352 disease and autoimmune diseases such as systemic lupus erythematosus. This is based on a  
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45 353 Cochrane review of 59 trials.<sup>54</sup>  
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47  
48 354 Systemic lupus erythematosus (SLE) affects women of child bearing age without affecting  
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51 355 fertility and so pregnancy is not uncommon. A meta-analysis of 2751 women with SLE  
52  
53 356 showed that those with active lupus nephritis (LN) had an increased risk of maternal  
54  
55 357 hypertensive disorders and premature birth.<sup>63</sup> Disease flare, high initial creatinine and  
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3 358 proteinuria at conception are predictive of worse outcomes. In addition, flares may cause a  
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5 359 decline in renal function and accelerate progression to end-stage renal disease. Pregnancy  
6  
7 360 should be planned and drugs altered accordingly prior to pregnancy, including stopping /  
8  
9 361 substituting mycophenolic acid products. A minimum six month period of disease  
10  
11 362 quiescence prior to pregnancy is therefore recommended.<sup>64,65</sup> The PROMISSE (Predictors of  
12  
13 363 Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic  
14  
15 364 Lupus Erythematosus) study, a large prospective cohort study including 385 patients,  
16  
17 365 recently demonstrated that 81% of pregnancies in women with inactive or stable  
18  
19 366 mild/moderate disease were uncomplicated.<sup>66</sup> Features indicating a higher risk for adverse  
20  
21 367 pregnancy outcomes, included a positive lupus anticoagulant, antihypertensive use, a low  
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23 368 platelet count, Hispanic or non-white ethnicity, and a physician's global assessment score  
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25 369 >1; and those women without these generally had favourable outcomes.  
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27 370 Women with chronic kidney disease should be counselled prior to pregnancy of the  
28  
29 371 increasing risk of maternal and fetal complications as GFR declines. These risks include fetal  
30  
31 372 growth restriction, pre-term birth, pre-eclampsia, fetal death and deterioration of maternal  
32  
33 373 renal function / disease flare.<sup>56</sup> Advanced chronic kidney disease impairs fertility<sup>88</sup> which can  
34  
35 374 be restored after renal transplantation.<sup>89</sup> As pregnancy outcomes are progressively poorer  
36  
37 375 with advancing chronic kidney disease, younger women who want to become pregnant are  
38  
39 376 often advised to be transplanted first. A national UK cohort study demonstrated that most  
40  
41 377 pregnancies after renal transplantation are successful, although the risks of pre-eclampsia  
42  
43 378 still remain higher than controls<sup>45</sup> and this higher risk of pre-eclampsia is even in those with  
44  
45 379 good GFRs.<sup>47</sup> Patients should be counselled of this accordingly and the other precautions  
46  
47 380 discussed here initiated. Pregnancy should be delayed until one year after renal  
48  
49 381 transplantation<sup>90</sup> as postponement is associated with better outcomes.<sup>91</sup> The American  
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3 382 Society of Transplantation recommend that prior to pregnancy there should be no rejection  
4  
5 383 for one year, adequate and stable graft function, no acute infections, and stable  
6  
7 384 immunosuppression dosing.<sup>92</sup>  
8  
9

### 10 **Pre-implantation diagnosis**

11  
12 386 It is important to discuss the option of preimplantation genetic diagnosis (PGD) with women  
13  
14 387 whose CKD is secondary to a genetically inherited cause. Recent advances in techniques  
15  
16 388 used for in vitro-fertilisation allow removal of one or two cells at the eight cell stage of  
17  
18 389 blastocyst formation.<sup>67</sup> These blastomeres can then be analysed for the mutations  
19  
20 390 responsible for conditions such as Alports Syndrome or Adult Polycystic Kidney Disease.<sup>68</sup>  
21  
22 391 Although there are limited data, initial reports suggest PGD is associated with similar  
23  
24 392 success in pregnancy outcome when compared with routine IVF.  
25  
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30  
31 394 Pre-pregnancy counselling improves knowledge and changes behavior prior to pregnancy<sup>69</sup>  
32  
33 395 which may help to reduce adverse events. The optimum way of offering pre-conception  
34  
35 396 counselling has not been established. Patients with diabetes agreed that being informed of  
36  
37 397 the risks prior to pregnancy is crucial, but existing childcare and work commitments  
38  
39 398 prevented attendance to such services. They also stressed that the positive aspects of  
40  
41 399 having children should be discussed rather than only medical complications.<sup>70</sup> In a  
42  
43 400 retrospective analysis of 179 women with chronic kidney disease undergoing pre-pregnancy  
44  
45 401 counselling in a large single centre, consultations included the multi-disciplinary team of a  
46  
47 402 consultant obstetric physician, obstetrician and nephrologist.<sup>71</sup> These women had an  
48  
49 403 overwhelmingly positive experience, with approximately 90% finding the clinic informative,  
50  
51 404 with understandable information and helpful in deciding about pursuing pregnancy.  
52  
53 405 However, 17% found the process intimidating, but this may prove difficult to abrogate in  
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3 406 such a highly emotive situation. Clearly the inclusion of midwives, general practitioners,  
4  
5 407 counsellors, psychologists and clinical geneticists when required, may prove an extremely  
6  
7 408 useful addition to this team. Electronic media including the internet and DVDs have also  
8  
9  
10 409 proven beneficial.<sup>72,73</sup>  
11

410

411 **MEDICATIONS**

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16  
17 412 Women with CKD including those with a kidney transplant are prescribed different types of  
18  
19 413 medications that have the potential to adversely affect the pregnancy outcomes. These  
20  
21 414 include immunosuppressive, anti-hypertensive and anti-viral medications. Each is important  
22  
23 415 for the mother's overall health, but their effects on the pregnant woman and her developing  
24  
25 416 fetus have been a concern for many practitioners. The major classes of medications used in  
26  
27 417 women with CKD and in transplant recipients and their known effects on the mother and  
28  
29 418 her offspring will be described below. See table [32](#).  
30  
31  
32

419

420 **Immunosuppressants:**

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35  
36  
37 421 ~~These are routinely required by women with renal transplants and often in women with~~  
38  
39 422 ~~various systemic diseases affecting the kidney as well as those with primary~~  
40  
41 423 ~~glomerulonephritis. The mother must maintain adequate immunosuppressive drug levels~~  
42  
43 424 ~~during her pregnancy, otherwise she risks rejection of her allograft or a flare of her~~  
44  
45 425 ~~underlying disease.~~ Maintaining adequate immunosuppressive drug levels can be a  
46  
47 426 challenge because drug levels change dramatically during gestation, primarily due to  
48  
49 427 changes in blood volume and placental metabolism. Due to a natural increase in glomerular  
50  
51 428 filtration rate, small changes in renal function can indicate significant rejection in pregnant  
52  
53 429 transplant recipients<sup>74</sup> and close monitoring of renal function and drug levels is important. It  
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3 430 is important to closely monitor drug levels throughout all phases of gestation and  
4  
5 431 collaboration with the transplant center is mandatory during and immediately after the  
6  
7 432 pregnancy.  
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10 433

11  
12 434 There are no guidelines about dosing of immunosuppressant medications during pregnancy,  
13  
14 435 but several studies have provided recommendations. Kim *et al* recently reported on blood  
15  
16 436 levels of calcineurin inhibitors during gestation in 88 pregnancies from 75 transplant  
17  
18 437 recipients.<sup>75</sup> In 80 cases the serum creatinine was decreased by an average of 0.14mg/dl  
19  
20 438 during pregnancy and returned to pre-pregnancy levels after delivery. Tacrolimus blood  
21  
22 439 trough levels decreased during the second trimester (from 5.8  $\pm$ 2.8 ng/ml) to 4.2  
23  
24 440  $\pm$ 1.8ng/ml). Likewise, cyclosporine levels decreased during the second trimester from 125.1  
25  
26 441  $\pm$ 65.1 ng/ml to 75.4  $\pm$ 35 ng/ml. The recommendations of this study were to increase  
27  
28 442 calcineurin inhibitor dose by approximately 20-25% during gestation to maintain optimal  
29  
30 443 drug levels. Aktürk also reported on the pharmacokinetics of tacrolimus during pregnancy  
31  
32 444 and recommended calcineurin inhibitor dosing is significantly increased in order to maintain  
33  
34 445 adequate trough levels during pregnancy.<sup>76</sup> Women should be informed that tacrolimus  
35  
36 446 levels need to be closely monitored in pregnancy. It is highly bound to plasma protein and  
37  
38 447 erythrocytes, with complicated pharmacokinetics that are even further altered by normal  
39  
40 448 physiological changes in pregnancy such as anaemia, hypoalbuminaemia and increased  
41  
42 449 creatinine clearance. Maintaining whole blood tacrolimus levels after conception risks  
43  
44 450 toxicity but no dose change may incur under-treatment. Unbound trough concentrations  
45  
46 451 may be the most appropriate level to monitor during pregnancy,<sup>77</sup> but these are technically  
47  
48 452 challenging to measure in routine practice.  
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3 453 Immunosuppressive medications cross the maternal-placental-fetal interface<sup>74,78</sup> and  
4  
5 454 therefore there are always concerns about their effect on fetal development. The fetal liver,  
6  
7 455 which is interposed between the umbilical vein and fetal inferior vena cava, filters the  
8  
9 456 pharmacologic agents that pass through the placenta, including immunosuppressants.  
10  
11 457 Calcineurin inhibitors are well-known to cross the placenta and enter the fetal circulation.<sup>74</sup>  
12  
13 458 Zheng et al recently reported on tacrolimus concentrations in maternal and umbilical cord  
14  
15 459 blood at delivery in eight transplant recipients and found that umbilical cord venous blood  
16  
17 460 concentrations were 71% that of maternal concentrations. The lower fetal blood  
18  
19 461 concentrations were proposed to be caused by the active transport of tacrolimus from the  
20  
21 462 fetus toward the mother by placental P-glycoprotein.<sup>79</sup> Whether in utero exposure to  
22  
23 463 tacrolimus has adverse effects on fetal development however is not known. In animal  
24  
25 464 studies it was recently shown that rats treated with cyclosporine (CSA) during pregnancy  
26  
27 465 experienced impaired kidney development, suggesting a predisposition to chronic kidney  
28  
29 466 disease and hypertension in adult life.<sup>80</sup> Despite this, tacrolimus is deemed safe in  
30  
31 467 pregnancy<sup>81</sup> and breastfeeding.<sup>82</sup>  
32  
33 468 Corticosteroids pass through the placenta, but most of the maternal dose undergoes  
34  
35 469 placental metabolism<sup>74</sup> and therefore the fetus is generally protected from adverse effects  
36  
37 470 of corticosteroids. While adverse effects associated with in utero exposure to  
38  
39 471 corticosteroids are rare, there have though been sporadic reports of adrenal suppression in  
40  
41 472 newborns of pregnant transplant recipients- [particularly when the corticosteroids dose was](#)  
42  
43 473 [high.](#)  
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45 474  
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55 475 Azathioprine also passes into the fetal circulation, but the fetus lacks inosinate  
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57 476 pyrophosphorylase, which is required for the conversion of azathioprine to its active  
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1  
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3 477 metabolite 6-mercaptopurine.<sup>74</sup> Therefore, concerns about the use of azathioprine in  
4  
5 478 pregnancy have been less than for other immunosuppressive.<sup>83</sup> Indeed, mycophenolic acid  
6  
7 479 products are routinely substituted for azathioprine before and during pregnancy.<sup>23</sup>  
8  
9  
10 480 Substantial data have shown that mycophenolic acid products are associated with an  
11  
12 481 increased incidence of spontaneous abortion and a distinct pattern of birth defects.<sup>84</sup> The  
13  
14 482 spectrum of mycophenolate embryopathy includes ocular anomalies, corpus callosum  
15  
16 483 agenesis, heart defects, kidney malformations, diaphragmatic hernia and skeletal  
17  
18 484 deformities.<sup>85</sup> Numerous reports of mycophenolate-associated malformations led the FDA  
19  
20  
21 485 to issue a black box warning on its use during pregnancy.  
22

23  
24 486 Less is known about the effects of sirolimus in pregnancy. Sifontis reported on seven  
25  
26 487 pregnancies with sirolimus exposure in seven pregnancies.<sup>86</sup> In three there were  
27  
28 488 miscarriages and four resulted in live births. No malformations were observed but sirolimus  
29  
30 489 was switched to azathioprine during the first trimester in one case and in another the  
31  
32 490 immunosuppressive regimen was switched from mycophenolate to sirolimus at 24 weeks. In  
33  
34 491 the latter case the infant was born with features typical of mycophenolate embryopathy.  
35  
36 492 There are several reports ~~were~~ of sirolimus exposure during the whole pregnancy, without  
37  
38 493 apparent adverse effects on the fetus.<sup>87-90</sup>  
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41  
42  
43 494 Recently there have been several reports about pregnancy in transplant recipients taking  
44  
45 495 the mTOR inhibitor everolimus during their pregnancy.<sup>91,92</sup> One report of an unplanned  
46  
47 496 pregnancy in a heart transplant recipient described a normal baby without obvious  
48  
49 497 congenital defects. The fetus was exposed to everolimus as concentrations were similar in  
50  
51 498 maternal and neonatal umbilical blood, and fetal blood levels were detected for 5 days after  
52  
53 499 birth. In contrast CsA levels, which were also detected in umbilical blood, disappeared  
54  
55 500 within 2 days of delivery in fetal blood.<sup>93</sup> Other reports have been published recently  
56  
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59  
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3 501 describing exposure to everolimus during pregnancies in kidney transplant recipients  
4  
5 502 without apparent congenital malformations.<sup>94,95</sup> Although the few reports of unremarkable  
6  
7 503 pregnancies with the use of mTOR inhibitors are encouraging, additional data are needed to  
8  
9 504 confirm their safe use during pregnancy.

10  
11 505 Treatment of rejection with corticosteroids is the mainstay during pregnancy and is  
12  
13 506 generally considered safe to the fetus.<sup>96</sup> Recently Kutzler et al reported on the safe use of  
14  
15 507 anti-thymocyte globulin (ATG) to successfully treat a pregnant renal transplant recipient  
16  
17 508 with mixed acute cellular rejection and antibody-mediated rejection.<sup>97</sup> The patient was also  
18  
19 509 treated with high-dose corticosteroids, intravenous immunoglobulin and plasmapheresis in  
20  
21 510 addition to ATG; and she gave birth to a healthy baby boy. The safety of rejection treatment  
22  
23 511 with ATG or other monoclonal or polyclonal antibodies has not been evaluated in clinical  
24  
25 512 trials in pregnant transplant recipients and only scattered case reports are available. There  
26  
27 513 are no data on the long term impact on the exposed children's immune repertoire.

28  
29 514 Management of lupus nephritis (LN) and other causes of autoimmune glomerulonephritides  
30  
31 515 in pregnancy remains challenging due to limited safe therapeutic options.

32  
33 516 Cyclophosphamide and mycophenolate mofetil are teratogenic, and are generally to be  
34  
35 517 avoided in pregnancy, although can be considered from the third trimester.<sup>98</sup> Steroids are  
36  
37 518 often used in pregnancy as they are not associated with congenital abnormalities<sup>99</sup> but can  
38  
39 519 cause premature rupture of membranes, preterm delivery, maternal sepsis and gestational  
40  
41 520 diabetes.<sup>100</sup> Data on Rituximab use in pregnancy are limited but it does cross the placenta  
42  
43 521 and lymphopaenia has been reported in new born children.<sup>101</sup> Hydroxychloroquine and  
44  
45 522 azathioprine are safe in pregnancy and should be considered in treatment regimens prior to  
46  
47 523 conception, along with aspirin. Hydroxychloroquine (HCQ) reduces the risk cardiac  
48  
49 524 manifestations of neonatal lupus in anti-Ro-positive mothers and is actively recommended  
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3 525 in women with LN before and during pregnancy.<sup>102</sup> Tacrolimus may be a useful alternative  
4  
5 526 or adjunctive therapy for LN flare during pregnancy.<sup>103</sup>  
6  
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8 527  
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10 528 ***Anti-Hypertensives:***

11  
12 529 Adverse effects of renin angiotensin system (RAS) blockade have been shown for some time,  
13  
14 530 and ACE inhibitors and angiotensin receptor blockers are teratogenic.<sup>104–107</sup> In a recent  
15  
16  
17 531 retrospective study performed through the Midwest Pediatric Nephrology Consortium, RAS  
18  
19 532 blocker fetopathy was identified and confirmed to depend on the timing of exposure, with  
20  
21 533 the most severe renal manifestations occurring with exposure after the first trimester.<sup>104</sup>  
22  
23  
24 534 Beta blockers are commonly used during pregnancy and recent meta-analyses showed that  
25  
26 535 first-trimester oral beta-blocker exposure was associated with no increase in major  
27  
28 536 congenital anomalies, but examination of organ-specific malformations revealed increased  
29  
30 537 odds of cardiovascular defects, cleft lip/palate, and neural tube defects.<sup>108</sup> There is  
31  
32 538 significant heterogeneity in the reports and thus it is not clear at this time whether beta-  
33  
34 539 blockers are associated with these defects. Calcium channel blockers have recently been  
35  
36 540 used in the management of hypertensive disorders of pregnancy and preterm labor.  
37  
38 541 Teratogenicity with calcium channel blockers has been shown in animals, but no cases have  
39  
40 542 yet been reported in humans and at this time are reported to be safe for use in pregnancy-  
41  
42 543 associated hypertension.<sup>109</sup>  
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48 544

49 545 ***Antivirals:***

50  
51  
52 546 Several antivirals have been used during pregnancy. The most commonly used antiviral  
53  
54 547 agents target CMV infection. All of these have fetal toxicity. Valganciclovir should not be  
55  
56 548 used as animal studies have revealed it can cause embryoletality, fetotoxicity,  
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3 549 teratogenicity, and mutagenicity. Valganciclovir may cause impaired fertility in both males  
4  
5 550 and females.<sup>110</sup> If CMV prophylaxis is required, valaciclovir is considered safe though  
6  
7  
8 551 possibly less effective. Lamivudine and tenofovir are safe for Hepatitis B prophylaxis.<sup>111, 112</sup>  
9

10 552

### 11 12 553 ~~PRE-PREGNANCY COUNSELLING~~

13  
14 554 ~~The value of pre-pregnancy counselling has been recognised in women with diabetes for~~  
15  
16  
17 555 ~~several decades.<sup>78</sup> Pre-pregnancy counselling in women with chronic kidney disease offers~~  
18  
19  
20 556 ~~the opportunity to minimise disease activity, optimise blood pressure control and~~  
21  
22 557 ~~proteinuria, alter teratogenic medications and also to educate couples about potential fetal~~  
23  
24 558 ~~and maternal adverse events that may occur during pregnancy and the puerperium in this~~  
25  
26  
27 559 ~~high risk group. It also allows discussion of the inheritance of genetic disorders of the kidney~~  
28  
29 560 ~~including cystic diseases, metabolic diseases and glomerular basement membrane~~  
30  
31 561 ~~disorders. The confidential enquiries into maternal deaths in the UK endorses that pre-~~  
32  
33  
34 562 ~~pregnancy counselling should be routinely commissioned and offered to women with pre-~~  
35  
36 563 ~~existing medical illnesses in view of the morbidity and mortality triggered by these~~  
37  
38  
39 564 ~~diseases.<sup>79</sup> The advice given is clearly dependent on underlying renal disease, baseline renal~~  
40  
41 565 ~~function, proteinuria and blood pressure at conception and this should be delivered in a~~  
42  
43 566 ~~patient focused, individualised manner.~~

44  
45 567 ~~There are a number of clinical practice guidelines for the management of hypertensive~~  
46  
47  
48 568 ~~disorders of pregnancy worldwide. A recent systematic review showed that there is good~~  
49  
50  
51 569 ~~inter guideline consistency for the definitions of chronic hypertension, proteinuria and~~  
52  
53 570 ~~gestational hypertension. Also consistent were the preventative use of low dose aspirin to~~  
54  
55 571 ~~reduce pre-eclampsia, and in severe hypertension.<sup>80</sup> Prior to conception, women should be~~  
56

57 572 ~~educated about the symptoms of pre-eclampsia. ACE inhibitors and angiotensin receptor~~  
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3 573 ~~blockers should be stopped prior to pregnancy or as early as possible after discovering~~  
4  
5 574 ~~pregnancy.~~

6  
7  
8 575 ~~UK NICE guidelines advocate the use of aspirin from 12 weeks of gestation in women at high~~  
9  
10 576 ~~risk to reduce the incidence of pre-eclampsia.<sup>84</sup> Such risk factors include chronic kidney~~  
11  
12 577 ~~disease and autoimmune diseases such as systemic lupus erythematosus. This is based on a~~  
13  
14  
15 578 ~~Cochrane review of 59 trials.<sup>82</sup>~~

16  
17 579 ~~Systemic lupus erythematosus (SLE) affects women of child bearing age without affecting~~  
18  
19 580 ~~fertility and so pregnancy is not uncommon. A meta-analysis of 2751 women with SLE~~  
20  
21 581 ~~showed that those with active lupus nephritis (LN) had an increased risk of maternal~~  
22  
23 582 ~~hypertensive disorders and premature birth.<sup>82</sup> Disease flare, high initial creatinine and~~  
24  
25 583 ~~proteinuria at conception are predictive of worse outcomes. In addition, flares may cause a~~  
26  
27 584 ~~decline in renal function and accelerate progression to end stage renal disease. Pregnancy~~  
28  
29 585 ~~should be planned and drugs altered accordingly prior to pregnancy, including stopping /~~  
30  
31 586 ~~substituting mycophenolic acid products. A minimum six month period of disease~~  
32  
33 587 ~~quiescence prior to pregnancy is therefore recommended.<sup>84,85</sup> The PROMISSE (Predictors of~~  
34  
35 588 ~~Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic~~  
36  
37 589 ~~Lupus Erythematosus) study, a large prospective cohort study including 385 patients,~~  
38  
39 590 ~~recently demonstrated that 81% of pregnancies in women with inactive or stable~~  
40  
41 591 ~~mild/moderate disease were uncomplicated.<sup>86</sup> Features indicating a higher risk for adverse~~  
42  
43 592 ~~pregnancy outcomes, included a positive lupus anticoagulant, antihypertensive use, a low~~  
44  
45 593 ~~platelet count, Hispanic or non white ethnicity, and a physician's global assessment score~~  
46  
47 594 ~~>1, and those women without these generally had favourable outcomes.~~

48  
49 595 ~~Women with chronic kidney disease should be counselled prior to pregnancy of the~~  
50  
51 596 ~~increasing risk of maternal and fetal complications as GFR declines. These risks include fetal~~  
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3 597 ~~growth restriction, pre-term birth, pre-eclampsia, fetal death and deterioration of maternal~~  
4  
5 598 ~~renal function / disease flare.<sup>87</sup> Advanced chronic kidney disease impairs fertility<sup>88</sup> which can~~  
6  
7  
8 599 ~~be restored after renal transplantation.<sup>89</sup> As pregnancy outcomes are progressively poorer~~  
9  
10 600 ~~with advancing chronic kidney disease, younger women who want to become pregnant are~~  
11  
12 601 ~~often advised to be transplanted first. A national UK cohort study demonstrated that most~~  
13  
14 602 ~~pregnancies after renal transplantation are successful, although the risks of pre-eclampsia~~  
15  
16 603 ~~still remain higher than controls<sup>45</sup> and this higher risk of pre-eclampsia is even in those with~~  
17  
18 604 ~~good GFRs.<sup>47</sup> Patients should be counselled of this accordingly and the other precautions~~  
19  
20 605 ~~discussed here initiated. Pregnancy should be delayed until one year after renal~~  
21  
22 606 ~~transplantation<sup>90</sup> as postponement is associated with better outcomes.<sup>91</sup> The American~~  
23  
24  
25  
26 607 ~~Society of Transplantation recommend that prior to pregnancy there should be no rejection~~  
27  
28 608 ~~for one year, adequate and stable graft function, no acute infections, and stable~~  
29  
30 609 ~~immunosuppression dosing.<sup>92</sup>~~  
31  
32  
33 610 ~~Pre-pregnancy counselling improves knowledge and changes behavior prior to pregnancy<sup>93</sup>~~  
34  
35 611 ~~which may help to reduce adverse events. The optimum way of offering pre-conception~~  
36  
37 612 ~~counselling has not been established. Patients with diabetes agreed that being informed of~~  
38  
39 613 ~~the risks prior to pregnancy is crucial, but existing childcare and work commitments~~  
40  
41 614 ~~prevented attendance to such services. They also stressed that the positive aspects of~~  
42  
43 615 ~~having children should be discussed rather than only medical complications.<sup>94</sup> In a~~  
44  
45  
46 616 ~~retrospective analysis of 179 women with chronic kidney disease undergoing pre-pregnancy~~  
47  
48 617 ~~counselling in a large single centre, consultations included the multi-disciplinary team of a~~  
49  
50 618 ~~consultant obstetric physician, obstetrician and nephrologist.<sup>95</sup> These women had an~~  
51  
52 619 ~~overwhelmingly positive experience, with approximately 90% finding the clinic informative,~~  
53  
54 620 ~~with understandable information and helpful in deciding about pursuing pregnancy.~~  
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3 621 ~~However, 17% found the process intimidating, but this may prove difficult to abrogate in~~  
4  
5 622 ~~such a highly emotive situation. Clearly the inclusion of midwives, general practitioners,~~  
6  
7 623 ~~counsellors, psychologists and clinical geneticists when required, may prove an extremely~~  
8  
9  
10 624 ~~useful addition to this team. Electronic media including the internet and DVDs have also~~  
11  
12 625 ~~proven beneficial.~~<sup>96,97</sup>  
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## 627 CONCLUSIONS

628 Pregnancy in women with CKD and kidney transplant should be planned, considered high  
629 risk, and ideally managed by an expert multidisciplinary team. The best outcomes are [likely](#)  
630 seen where there has been careful pre-pregnancy evaluation and planning, and close  
631 monitoring during antenatal care. The outcomes for women and babies continue to improve  
632 but we still need better biomarkers e.g. placental growth factor (PIGF) to identify those  
633 women at higher risk of developing superimposed pre-eclampsia.<sup>113</sup>  
634

634

## 635 DISCLOSURES

636 **Michelle A. Josephson is member of the Mycophenolate Pregnancy Registry Advisory**  
637 **Committee**  
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916 Legends:

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918 Table 1: Prepregnancy kidney function in patients with CKD with estimates of problems in  
919 pregnancy (fetal growth restriction, preeclampsia, preterm delivery, and significant kidney  
920 function loss in pregnancy [ $>25\%$  SCr increment]), obstetric outcome, and loss of kidney  
921 function: The effect of altering cut-off between moderate and severe dysfunction from 2.8  
922 mg/dL ( $\geq 250\mu\text{mol/L}$ ) to 2.0 mg/dL ( $\geq 180\mu\text{mol/L}$ ), respectively  
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924 Table 2: Hypertensive disorders of pregnancy

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927 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 (%)
<i>Mild</i>	≤1.4 (≤125μmol/L)	26	96	<2	-
<i>Moderate</i>	≥1.4 (≥125μmol/L)	50	90	25	3
<i>Severe</i> <sup>++</sup>	≥2.8 (≥250μmol/L)	86	74	55	40
<i>Mild</i>	≤1.4 (≤125μmol/L)	26	96	<2	-
<i>Moderate</i>	≥1.4 (≥125μmol/L)	42	95	15	1
<i>Severe</i> <sup>++</sup>	≥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 20 <sup>th</sup> 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
<b>Immunosuppressants</b>	Tacrolimus Cyclosporin Azathioprine Corticosteroids Hydroxychloroquine	Cyclophosphamide Mycophenolate products Rituximab	Sirolimus Everolimus
<b>Anti-Hypertensives</b>	Labetalol Calcium Channel Antagonists Methyldopa Hydralazine Furosemide	ACE inhibitors Angiotensin Receptor Blockers Minoxidil	
<b>Antibiotics Commonly Used in Immunosuppressed Patients</b>	Aciclovir Valaciclovir Lamivudine Tenofovir Isoniazid Nystatin (topical)	Ganciclovir Valganciclovir Co-Trimoxazole Quinolones	



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The publication information where the figure will be used is as follows:

<b>Title of article/publication</b>	Pregnancy in Chronic Kidney Disease and Kidney Transplantation
<b>Authors</b>	Webster P, Lightstone L, McKay DB, Josephson MA
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