PART XV

GUEST LECTURE

Chairmen: V Andreucci
          D Verbeelen
PREGNANCY IN WOMEN WITH RENAL DISEASE AND RENAL TRANSPLANTATION


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Counselling women with chronic renal disease or a renal transplant about pregnancy (whether contemplated or in progress) is not easy and involves much more than simply giving a ‘yes’ or ‘no’ answer. Their expectation is higher than ever and their questions more searching: ‘Is pregnancy really advisable? Will it be complicated? Will I have a live and healthy baby? Will there be any long-term damage to my health?’

It is worrying that firmly held and opposing views have emerged which are based on inconclusive data. A clearer picture is emerging and a consensus is in sight. This review will focus on the problems encountered by renal disease and renal transplant patients during pregnancy and the effect pregnancy has on long-term prognosis.

Renal function and its clinical implications in normal pregnancy

Glomerular filtration rate (GFR) increases very early in pregnancy and as a result serum levels of creatinine and urea which average 72µmol/L and 4.5mmol/L respectively in non-pregnant women, decrease to mean values of 51µmol/L and 3.0mmol/L in gravidas. Caution is essential when gauging renal function from serum creatinine levels because an individual may lose up to 50 per cent of renal function and still have a serum creatinine of less than 130µmol/L and also remain symptom-free. Nevertheless, a helpful rule of thumb is that while values of creatinine of 75µmol/L and urea of 5.0mmol/L are acceptable in non-pregnant subjects, they are suspect in pregnancy. Serial assessment of renal function in pregnancy, however, should be based on the clearance of creatinine rather than on its serum concentration. Because urinary protein excretion increases during pregnancy, proteinuria should not be considered abnormal until it exceeds 300mg in 24 hours.

Renal dysfunction and its clinical implications in renal disease

Becoming pregnant and then sustaining a viable pregnancy depends more on the degree of functional impairment rather than on the specific renal disease present.
Nature gives a helping hand because fertility becomes blunted as renal function falls so that when non-pregnant serum creatinine and urea exceed 380\(\mu\)mol/L and 10mmol/L respectively, normal pregnancy is uncommon. There are exceptions, however, with successes in women who have moderate to severe disease, including some temporarily requiring or permanently receiving peritoneal or haemodialysis [1–3]. It should be remembered, though, that isolated cases can leave a vivid impression and affect thinking disproportionately if their outcome was successful. Cases ending in disaster are usually forgotten and/or unreported.

The prevailing opinion is that obstetric outcome and renal prognosis is related to the degree of renal insufficiency [4] (Table 1). The outlook also hinges on the balance between the effect the kidney disease could have on the pregnancy and the effect the pregnancy could have on that disease.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Plasma creatinine ((\mu)mol/L (mg/dl))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Preserved or mildly decreased renal function</td>
<td>&lt;125 (1.4)</td>
</tr>
<tr>
<td>Minimal hypertension</td>
<td></td>
</tr>
<tr>
<td>2. Moderate renal insufficiency</td>
<td>(\geq125) (1.4)</td>
</tr>
<tr>
<td>3. Severe renal insufficiency</td>
<td>(\geq250) (2.8)</td>
</tr>
</tbody>
</table>

**Outlook in women with preserved or mildly decreased renal function and minimal hypertension**

Women with normal or only mildly decreased renal function before conception usually have a successful obstetric outcome and pregnancy does not adversely affect the course of their disease [5–8]. While generally true for most patients, this statement has to be tempered somewhat in lupus nephropathy, and possibly in membranoproliferative glomerulonephritis, focal glomerulosclerosis and IgA nephropathy which appear more sensitive to intercurrent pregnancy. In addition, women with polyarteritis nodosa and scleroderma do poorly when pregnant. Where renal disease is detected for the first time during pregnancy (usually as proteinuria or hypertension, with a definitive biopsy diagnosis established retrospectively in the puerperium), it is surmized that renal function was relatively preserved before the pregnancy that brought an underlying mild lesion to clinical expression.

Most women show increments in GFR although these are less than those measured in healthy gravidas [6]. Increased proteinuria is the most common renal effect of pregnancy in women with underlying glomerular diseases, in whom it occurs in almost 50 per cent of pregnancies, often exceeding 3g in 24 hours, frequently leading to nephrotic oedema. It is rarely seen in women with chronic pyelonephritis. Better judgment on the timing of delivery, with preterm intervention if needed, has obviously improved perinatal mortality when compared to 20–30 years ago and currently over 90 per cent of pregnancies succeed. Still, perinatal mortality is moderately higher than in normal
women. The prevalence of hypertension, renal functional abnormalities and proteinuria, as well as their severity, are considerably lower inbetween pregnancies and during long-term follow-up. When renal failure does supervene it rarely bears any temporal relationship to pregnancy and simply reflects the inexorable course of that specific kidney disease.

These generalizations are endorsed by the most recent studies, where not only was a tissue diagnosis available but also sufficient data to evaluate long-term renal prognosis. In the study of Katz and colleagues [6] all women had normal or at most slightly impaired renal function (serum creatinine, 125 μmol/L) before conception. Proteinuria was present in nearly half of all pregnancies and hypertension in 20 per cent, but both were mild in most cases (Figure 1).

![Figure 1](image)

**Figure 1.** The course of renal disease in 89 women during pregnancy and post-partum (left side) and in 80 of those women who were followed-up after pregnancy (right side). Numbers within the bars are individual pregnancies (on the left) and individual women (on the right)

FX = function; ESRD = end-stage renal disease [7]

Similar conclusions were reached in other recent studies [9-15] (Table II). For instance, Surian and co-workers who surveyed 122 pregnancies in 86 women, with the most common diagnoses of IgA nephropathy and Alport’s syndrome, found that more than 50 per cent of the gestations were uneventful [15]. Twenty-four pregnancies were complicated by hypertension (reversible in 13 cases in which it was attributed to superimposed pre-eclampsia), and in 10 women there was deterioration of renal function (defined as an increase of 50 per cent or more in serum creatinine), but it abated after delivery in six of them. Of the four pregnancies that led to worsening of kidney function, two were in women with membranoproliferative glomerulonephritis and one each with amyloidosis and Alport’s syndrome. Unfortunately, no data on renal function before conception were available, but from the unusually high incidence (41%) of renal abnormalities detected for the first time during pregnancy (usually as proteinuria or hypertension), it can be surmised that kidney function was
<table>
<thead>
<tr>
<th>Patients/ Pregnancies</th>
<th>During pregnancy t BP ↓ RF</th>
<th>Perinatal loss t BP ↓ RF</th>
<th>Long-term t BP ↓ RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz et al (1980)</td>
<td>23% 16% 9% 1% 6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barcelo &amp; Lopez (1984)</td>
<td>27% 10% 5% 6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surian et al (1984)</td>
<td>20% 8% 14% 9% 3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Jungers et al (1984)</td>
<td>33% 7% 7% 17% 6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>**Hou et al (1984)</td>
<td>58% 21% 16% 18% 25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>**Imbasciati et al (1984)</td>
<td>66% 26% 13% 40% 26%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP = blood pressure; RF = renal function
non-pregnant $P_{cr} \geq 125 \mu$mol/L (1.4mg/dl) in a *few patients/in **all patients
[7,9,11–13,15]

relatively preserved before the pregnancy. It was concluded that in most gravidas, hypertension influenced the obstetric complication rate, but pregnancy did not modify the natural history of glomerular disease, although women with membranoproliferative glomerulonephritis have a higher propensity to experience renal function deterioration and women with IgA nephropathy tend to develop persistent hypertension during and after pregnancy.

Another large series of patients with primary glomerular disease is that of Jungers and co-workers, who retrospectively analysed data from 122 patients (7 of whom had moderate renal dysfunction) having 240 pregnancies [13]. Fetal mortality was significantly higher (34%) in the 80 pregnancies complicated by hypertension than in the 160 normotensive pregnancies (21%). Where hypertension was present prior to conception or developed early in pregnancy losses were much greater (64%) than when developed only in the third trimester (12%). In patients in whom hypertension was not treated or could not be adequately controlled, no livebirths were obtained. Furthermore, fetal losses were higher in the presence of nephrotic syndrome, the duration rather than the intensity of which, was the most important factor. Renal deterioration occurred in 17 pregnancies with fetal losses significantly higher if this developed early in pregnancy (82%) as opposed to in the third trimester (4%). The highest rates of renal deterioration were seen in patients with membranoproliferative glomerulonephritis and IgA nephropathy.

**Outlook in women with moderate renal insufficiency**

Prognosis is more guarded where renal function is moderately impaired before pregnancy (serum creatinine $\geq 125 \mu$mol/L), but it is difficult to convincingly settle this issue in these women, mainly because conclusive evidence is still unavailable. The influence of the level of kidney function before or when first seen in pregnancy has been specifically assessed by Bear [16,17]. No immediate loss of renal function could be detected in 29 patients whose serum creatinine
concentrations were less than 133μmol/L, and although uraemia did occur in five women, it was concluded that in each case it was not hastened by pregnancy but developed as a gradual consequence of the underlying kidney lesion. In contrast, four of eight patients whose initial serum creatinine exceeded 142μmol/L experienced a significant further increase in blood creatinine during pregnancy, which was complicated in virtually every case. Indeed, four patients in this group progressed to end-stage renal failure within 18 months of delivery. Bear, and others since, [13] have emphasized that uncontrolled hypertension during pregnancy is a most crucial factor where overall deterioration occurs. His personal recommendation was that pregnancy is best avoided in women who have lost 50 per cent of their renal function.

Kincaid-Smith and her colleagues [18,19] recorded a high incidence of renal morbidity in women with moderate renal impairment in early pregnancy and five of 11 developed serious deterioration of renal function during pregnancy, which culminated in terminal renal failure within several months. Because of this experience and the fact that deterioration was apparently also seen in an occasional patient with stable renal function, these workers have in general adopted a rather pessimistic approach to pregnancy in women with underlying renal disease.

New data are now appearing as a result of a surge of interest in this topic. Hou and co-workers have analysed 24 pregnancies (excluding first trimester abortions) in 22 women with moderate renal insufficiency (serum creatinine >125μmol/L) and are more optimistic [11]. In 14 gravidas, renal function remained stable or declined to a degree consistent with the natural history of their disease, whereas in seven women whose baseline serum creatinine levels ranged between 150 and 240μmol/L, pregnancy was accompanied by a decline in kidney function considered greater than expected from the natural course of their specific renal lesions. In this study GFR, (albeit estimated from serum creatinine) did not rise as it does in healthy women or those with kidney disease but preserved function. Development or worsening of hypertension to moderately severe levels was also common and dictated a decision for delivery. This was not always linked to a fall in renal function. The authors concluded that pregnancy in women with moderate renal insufficiency might cause a decline in renal function but in most instances it did not and more important fetal salvage was much higher than previously documented.

Thus, in the presence of moderate renal insufficiency, the chance for a successful pregnancy is good. This represents a marked improvement in fetal prognosis from that described a decade ago, and is due to advances in perinatal care. Currently, obstetricians have a greater reliance placed on judicious and deliberate preterm delivery and the skills of the neonatologists are such that 80 per cent of infants of 1000g survive (Table III). Some women, however, do suffer significant renal functional deterioration during pregnancy that may not improve after delivery, thus accelerating the downhill course of the underlying disease.
<table>
<thead>
<tr>
<th>Renal Disease</th>
<th>1950s</th>
<th>1960s</th>
<th>1970s</th>
<th>1980s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm delivery</td>
<td>8%</td>
<td>10%</td>
<td>19%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Mild</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>18%</td>
<td>15%</td>
<td>7%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>15%</td>
<td>21%</td>
<td>40%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>58%</td>
<td>45%</td>
<td>23%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Estimate based on 27 studies (1954–1984) including 1902 pregnancies in 1311 women. (SLE not included) [5–31]

**Outlook in women with severe renal insufficiency**

The majority of women with severe renal insufficiency have amenorrhea or anovulatory menstrual cycles [32]. The likelihood of conceiving, let alone having a normal and successful pregnancy and delivery, is therefore small. Data on such patients are very scarce and it is difficult to evaluate whether pregnancy has a detrimental effect on their disease, but as renal function is already severely compromised this issue could be considered to be largely irrelevant [4]. Suffice it to say that pregnancy in patients with advanced renal failure is likely to have a serious impact on their health, which together with the uncertain (but very small) chance of a successful obstetric outcome, must be taken into account when counselling such women. Really this group of patients should never take additional health risks, and the aim should be to preserve what little renal function remains and/or achieve renal rehabilitation via a dialysis and transplant programme. Only after successful transplantation should the question of pregnancy be reopened if appropriate.

**Pre-conception counselling**

If the question is bluntly asked ‘Is a pregnancy advisable?’ then it would seem that it is probably best restricted to women whose pre-conception serum creatinine concentrations are 180μmol/L or less and who have a diastolic blood pressure of 90mmHg or less. As already mentioned, some are more strict and recommend that pregnancy should not be undertaken when serum creatinine exceeds 133μmol/L [16,17]. Whatever level is chosen, it must be remembered that degrees of impairment that do not cause symptoms or appear to disrupt homeostasis in non-pregnant individuals can certainly jeopardize pregnancy. As a broad guideline, a woman with chronic renal disease wishing to have a family should not wait too long because renal function will in any case diminish with age.
Management during pregnancy

Clinicians do not always have the occasion to counsel women with chronic renal disease prior to conception. A patient with suspected or known renal disease could present already pregnant and then the question has to be asked, (particularly if there are problems in early pregnancy) ‘Should the pregnancy continue? The simpler the guidelines the better, and several factors should be taken into account.

Renal function If renal function deteriorates significantly at any stage of pregnancy and a reversible cause cannot be found (urinary tract infection, subtle dehydration or electrolyte imbalance, occasionally precipitated by inadvertent diuretic therapy) the pregnancy should be ended by elective delivery. Near term, a 15–20 per cent decrement in function, which affects blood creatinine minimally, is acceptable [1]. In contrast when proteinuria occurs but blood pressure is normal and renal function preserved, the pregnancy can be allowed to continue.

Blood pressure Most of the specific risks of hypertension appear to be mediated through superimposed pre-eclampsia [33]. There is still controversy about the incidence of pre-eclampsia in those women who have pre-existing renal disease, mainly because a clinical diagnosis cannot be made with certainty as hypertension and proteinuria may be manifestations of the underlying disease. Whereas treatment of mild hypertension (diastolic blood pressure ≈95mmHg in the second trimester of ≈105mmHg or less in the third) is not necessary in normal gravidas there is a view emerging that it is prudent to treat hypertension in pregnant women with underlying renal disease more aggressively than with hypertension alone as it may help to preserve function. Of course, more severe hypertension should be treated in the interests of maternal well-being as well as possibly allowing the pregnancy to continue so that further fetal maturation occurs before delivery.

Fetal monitoring and judging the time to deliver Fetal surveillance is needed because kidney disease can be associated with intrauterine growth retardation and when complications do arise the judicious moment for intervention is influenced by fetal status. The application of current technology should minimize both intrauterine fetal death caused by inappropriately prolonging the pregnancy and neonatal mortality from the hazards of prematurity. Advances in neonatology have been such that regardless of gestational age 80 per cent of babies at 1000g and >95 per cent at 1500g survive better in a neonatal intensive care unit than in a hostile intrauterine environment. Delivery before term may be necessary if there are signs of fetal growth retardation, if there is impending intrauterine death, if kidney function deteriorates substantially, or if uncontrollable hypertension and/or superimposed pre-eclampsia supervenes.
Special problems with specific renal diseases

As mentioned earlier, the crux of the matter, be it counselling, clinical assessment or predicting obstetric outcome depends on the degree of renal functional

<table>
<thead>
<tr>
<th>Renal disease</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Controversial; prognosis is most favourable if disease in satisfactory remission prior to conception.Steroid dosage should be increased post-partum</td>
</tr>
<tr>
<td>Chronic pyelonephritis (infectious tubulointerstitial disease)</td>
<td>Bacteriuria in pregnancy may lead to exacerbation</td>
</tr>
<tr>
<td>Urolithiasis</td>
<td>Ureteral dilatation and stasis do not seem to affect natural history but infections can be more frequent</td>
</tr>
<tr>
<td>Permanent urinary diversion</td>
<td>Depending on original reason for surgery there may be other malformations of the urogenital tract. Urinary tract infection common during pregnancy and renal function may undergo reversible decrease. No significant obstructive problem but caesar- ean section might be necessary for abnormal presentation</td>
</tr>
<tr>
<td>Chronic glomerulonephritis and non-infectious tubulointerstitial disease</td>
<td>One view is that glomerulonephritis is adversely affected by the coagulation changes of pregnancy. Urinary tract infections may occur more frequently. Usually no adverse effect in the absence of hypertension</td>
</tr>
<tr>
<td>Periarteritis nodosa</td>
<td>Fetal prognosis is poor. Maternal death often occurs. Therapeutic abortion seems to be relatively safe</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>If onset during pregnancy then there can be rapid overall deterioration. Reactivation of quiescent scleroderma can occur post-partum</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>No adverse effect on the renal lesion. Increased frequency of infections, oedema and/or pre-eclampsia</td>
</tr>
<tr>
<td>Polycystic disease</td>
<td>Functional impairment and hypertension usually minimal in child-bearing years</td>
</tr>
<tr>
<td>After nephrectomy, solitary and pelvic kidneys</td>
<td>Pregnancy well tolerated. Might be associated with other malformations of urogenital tract. Dystocia rarely occurs with a pelvic kidney</td>
</tr>
</tbody>
</table>
impairment rather than on the specific renal disease itself. This is not to say, however, that particular renal diseases do not have important problems peculiar to each of them, some of which are summarized in Table IV. Further detailed discussion can be found elsewhere [34]. Nevertheless specific mention will be made of systemic lupus erythematosus (SLE) because it is a relatively common disease which occurs mainly in women of childbearing age.

Systemic lupus erythematosus

The widespread disturbance of the immune system, the multiple organ involvement and the complex clinical picture in SLE, along with the complicated immunology of pregnancy, make it a complex issue [35]. With regard to the effects of pregnancy on SLE, transient improvements, no change and relapses have all been reported. Other controversies centre around the significance of lupus appearing for the first time ever during pregnancy, its masquerading and/or misdiagnosis as pre-eclampsia, its tendency to relapse in the puerperium, and whether or not steroids should be prescribed or their dosage increased at this time.

A consensus of opinion is now emerging on the basis of several recent studies [34–41] (Table V). Hayslett and Lynn [26] analysed 65 pregnancies in 47 patients with lupus nephropathy in a retrospective study and concluded that the

<table>
<thead>
<tr>
<th>TABLE V. SLE and pregnancy: disease status and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies</td>
</tr>
<tr>
<td>--------------</td>
</tr>
</tbody>
</table>
| Hayslett & Lynn  
(1980)  
65          | 10                    | 12/55 (24%)                               | 3/24 Active 8/22 (22%)             |
| Fine et al    
(1981)  
52          | 11                    | 14/41 (34%)                               | 1/8 Remission 10/22 Active 4/11 (37%) |
| Jungers et al  
(1982)  
104         | 9                     | 16/95 (17%)                               | 0/11 Active 13/72 (18%)           |
| Imbasciati et al  
(1984)  
26          | 2                     | 8/24 (33%)                               | 1/8 Active 6/13 (25%)             |

(References [36–39])
course during pregnancy and after delivery correlated better with the activity of the disease in the six months preceding conception than with the specific type of renal SLE lesion [36]. The likelihood of a successful pregnancy was higher if SLE was in remission during this period; nevertheless, one-third of such gravidas (10 women) experienced a clinical exacerbation, including relapse of the nephropathy in the form of nephrotic syndrome or renal insufficiency. Importantly, in eight of these patients observed for more than three months after delivery, there was complete or partial remission of the exacerbation. The course of pregnancy was more problematical in those in whom SLE first appeared during pregnancy and in those with active disease at conception, but even in these groups most women improved after delivery.

Fine and colleagues assessed 39 patients with SLE [37]. Interestingly, these women did not conceive if there was even a moderate degree of renal impairment. During 52 pregnancies two-thirds had minimal or no renal functional abnormality and one-third experienced mild renal impairment only. No measurable deterioration of renal function could be detected in 40 of the 52 pregnancies, and in seven others there was a transient decline that was reversible. In the remaining five patients, kidney function further deteriorated and remained depressed during the first year of follow-up, with one patient dying two months after delivery.

Jungers and colleagues have assessed 36 SLE patients during 104 pregnancies and in most the pregnancy actually preceded the onset of disease [38]. In the group with pre-pregnancy SLE (26 pregnancies), clinical exacerbation was considerably more frequent if the disease was active at the time of conception than if it was not (66% vs 9%), but renal deterioration was rare and just about equal in the two subgroups (1 of 15 and 1 of 11 respectively). In contrast, where SLE first appeared during pregnancy or post-partum, three of nine pregnancies were complicated by nephrotic syndrome and a substantial increase in serum creatinine. Altogether, in the 36 pregnancies where SLE had antedated the pregnancy or occurred during it (and all had normal kidney function at conception), renal deterioration occurred in five. In three patients it was reversed by high-dose steroid therapy, but in two women, the nephropathy progressed to renal failure requiring dialysis.

Imbasciati and his colleagues have analysed data from 26 pregnancies in 19 patients with biopsy-diagnosed lupus nephropathy [39]. The nephropathy ran a variable course which could not always be predicted either from the renal biopsy or from the activity of SLE before conception. Although most of the gravidas did well, with either no change in renal function or only modest deterioration, three patients experienced moderate worsening of renal function, which persisted in one and was reversed in two others with post-partum steroids. More alarming, however, was the occurrence of acute renal failure after delivery in four gravidas, three of whom apparently experienced the onset of SLE during pregnancy. Two of these women recovered, but the other two died in renal failure of disseminated intravascular coagulation and sepsis.

The significance of lupus serum factors There is good evidence of the placental transmission of lupus serum factors, including the so-called LE-anticoagulant
[42–45]. This latter factor was first described in patients with SLE but it has since been observed in patients with other conditions and even in patients without any identifiable disorder. Intrauterine fetal death, in mid as well as late pregnancy, is common in women with circulating LE-anticoagulant and their placentae may show extensive thrombotic and arteriosclerotic changes [46]. Treatment with steroids and aspirin in low dosage may lead to successful pregnancies and therefore it is important to screen for LE-anticoagulant in all women with SLE (to identify this particular cohort), and also in women with a history of recurrent intrauterine fetal deaths or thrombotic episodes [44,45].

**Congenital heart block** There is an increased incidence of congenital cardiac anomalies in the babies of congenital heart block women with SLE and other maternal connective-tissue disease, even when maternal pathology is dormant. This appears to be related to the placental transmission of a maternal antibody to soluble tissue ribonucleoprotein, anti-Ro(SS-A), which is detectable in almost all cases of isolated congenital complete heart block [47]. The prevalence of anti-Ro(SS-A) in patients with SLE is 25–30 per cent where it may also have other effects, particularly recurrent abortion. Paradoxically, the mother's heart is usually unaffected, even though her antibody titres are higher than in the fetus. Immunofluorescence techniques have revealed that maternal autoantibody deposition initiates an immunologically based inflammatory reaction which is probably responsible for the congenital heart block as well as for endocardial fibroelastosis and probably certain other kinds of congenital heart disease [48]. Interestingly, maternal lupus may not become apparent clinically or serologically for many years after the birth of a baby with heart block [49].

**Counselling the patient** Patients with SLE often suffer from extrarenal manifestations of the disease and/or from complications of treatment [50]. A few will die as a result of renal failure. Thus any factors that might possibly hasten the appearance of additional problems cannot be dismissed lightly.

Decisions regarding disease activity and the potential effects of pregnancy must form an integral part of pre-pregnancy counselling for each couple. Obviously, they can be told that the majority of pregnancies succeed, especially if the maternal disease is in sustained, complete clinical remission for at least six months prior to conception. Indeed, this applies even if the patient had severe pathological changes in her original renal biopsy and heavy proteinuria in the early stages of her disease. But it should also be explained to patients that continued signs of disease activity and/or increasing renal dysfunction do reduce the likelihood of an uncomplicated pregnancy.

**Renal disease and pregnancy: concluding remarks**

In patients with chronic renal disease all advice must take into account the balance between pregnancy outcome and the impact that pregnancy might have on the disease in the long-term. The crucial determinants are the functional status of the kidneys at conception, the presence or absence of hypertension, and the nature of the renal lesion. A patient will achieve a successful outcome
provided her renal dysfunction is minimal. If dysfunction is moderate there is still a fair chance that pregnancy will succeed, but the risks are much greater than in normal pregnancy.

Hypertension during pregnancy is probably the most important factor in determining fetal outcome. These statements have to be tempered somewhat in certain nephropathies that appear to be more problematical during pregnancy, especially collagen disorders, and possibly reflux nephropathy, focal glomerulosclerosis, IgA nephropathy and membranoproliferative glomerulonephritis. When there is severe renal impairment attempts at pregnancy or its continuation if already underway are not recommended.

As for long-term impact, pregnancy does not adversely affect the natural history of the underlying renal lesion if kidney dysfunction is minimal and hypertension is absent at conception — again with the exception of the collagen disorders. The appearance of renal dysfunction during pregnancy or its worsening, if already present, may be predictive of the further development of renal failure. The prospects, classified according to the degree of renal impairment are given in Table VI.

<table>
<thead>
<tr>
<th>Will there be........?</th>
<th>Severity of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>A complicated pregnancy</td>
<td>22%</td>
</tr>
<tr>
<td>A live and healthy baby</td>
<td>95%</td>
</tr>
<tr>
<td>Any long-term harm</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Based on data from 15 studies (1973–1984) [5–19]

Let there be no doubt, there are controversies [51,52]. As mentioned already, the prevailing opinion is that with contemporary standards of antenatal care pregnancy does not usually affect remote renal prognosis and that fetal prognosis is only moderately, but acceptably, worse than in healthy women. The other view, whilst agreeing that antenatal renal deterioration usually abates or reverses post-partum, emphasizes that pregnancy can trigger an irreversible decline in renal function. What is needed therefore are more prospective studies where kidney function can be assessed before, during and after pregnancy in sufficient numbers of women in all disease categories.

In due course we must look afresh at longer term prognosis and why pregnancy might aggravate disease. This is because a process that is receiving much attention at present is ‘hyperfiltration sclerosis’, which is said to occur in the residual (intact) glomeruli in kidneys of patients with moderate renal insufficiency and in the single kidney situation, which when sustained causes progressive loss of renal function, and might lessen renal lifespan. Although no specific evidence for a deleterious effect in pregnancy is available, these considerations cannot be ignored because any gravida, healthy or with renal disease experiences
many months of physiological hyperfiltration as part of the overall maternal adaptation in pregnancy. If, therefore, the augmented GFR of pregnancy is sustained sufficiently long enough to cause glomerular damage then this is one maternal physiological change in pregnancy which would be maladaptive. Similarly, elevated blood pressure may if sustained, relentlessly contribute to further deterioration long after any primary injury is over. The little evidence that is available at present with regard to pregnancy, tends to argue against hyperfiltration sclerosis. An investigation of glomerular function and morphology showed no persistent abnormality in rats which successfully completed five consecutive cycles of pregnancy and lactation (a considerable time span in the life of the rat) when compared to age-matched virgin controls [53]. Some of our own present work (JMD) indicates that this may also be the case in humans. This is clearly an area for further study.

**Pregnancy and renal transplantation**

After a woman has had a renal transplant her renal and endocrine function rapidly return to normal and sexual activity usually resumes [32,54]. About one in 50 women of childbearing age with a functioning renal transplant becomes pregnant. Of all the conceptions 40 per cent do not exceed the initial trimester due to spontaneous or therapeutic abortions and a small but increased incidence of ectopic pregnancy has been reported [55]. Of the pregnancies that continue past the first trimester 90 per cent end successfully. Over 1500 pregnancies are on record in women with a renal allograft, but of course, many pregnancies, successful and unsuccessful, go unreported [55,56]. Interestingly, there is a report of a transplant performed with the clinicians unaware that the recipient was 16 weeks pregnant and the fact that mother, baby and kidney did not come to harm does not negate the importance of contraception counselling in all renal failure patients and excluding the possibility of pregnancy prior to transplantation [57].

**Pre-conception counselling**

The return of fertility and the possibility of conception in transplanted women of childbearing age makes appropriate counselling mandatory. Contraceptive advice should be routine and couples who want a child should be encouraged to discuss all the implications right down to the harsh realities of maternal survival prospects. All involved must appreciate the possibility that a patient may not live to participate in the long-term care of her child.

Each centre formulates its own specific guidelines. Most advise, somewhat anecdotally, that it is best to wait 18 months to two years post-transplant. In fact, this has turned out to be good advice because by then the patient will certainly have recovered from the major surgery and its sequelae, graft function will have stabilized, immunosuppression will be at maintenance levels (minimizing potential teratogenic and suppressive effects) and the risks of low birth weight or small-for-dates babies will be minimal. A suitable set of comprehensive guidelines is given here, bearing in mind that failure to meet any of the criteria listed is
only a relative contraindication \( [55,58] \): (a) Good general health for two years after transplantation, (b) Stature compatible with good obstetric outcome, (c) No proteinuria, (d) No significant hypertension, (e) No evidence of graft rejection, (f) No evidence of pelvicycelycal distention on a recent intravenous urogram, (g) Stable renal function – plasma creatinine of 180\( \mu \)mol/L or less (preferably 130\( \mu \)mol/L or less), (h) Drug therapy reduced to maintenance levels; prednisone, 15mg/day or less and azathioprine, 2mg/kg body weight/day or less. (Safe doses of Cyclosporin A have not yet been established because of its limited clinical use \([59]\).)

**Management during pregnancy**

The pregnant renal transplant patient is a high-risk patient. Routine antenatal care should be hospital-based and be supplemented with attention to renal function surveillance, blood pressure control, bone disease, anaemia, the detection of any sort of infection and assessment of fetal wellbeing. Serial immunological surveillance, as yet in its infancy and of unknown value, has also been used to assess progress in pregnancy \([60]\).

**Graft rejection** Immunosuppressive therapy is usually maintained at pregnancy levels, but adjustments may be needed if there are decreases in the maternal leucocyte or platelet counts. When maternal leucocyte counts are kept within the physiological limits for normal pregnancy, the neonate is usually born with a normal blood count \([61]\). Azathioprine liver toxicity has been reported during pregnancy and has responded to dose reduction. The most sensitive method of monitoring the effects of altering the effects of azathioprine dosage is the measurement of red cell 6-thioguanine nucleotide (6-TG nucleotide), which is a metabolite of both azathioprine and 6-mercaptopurine, and is perhaps the best index of bioavailability \([62]\).

Several reports suggest that serious rejection episodes occur in nine per cent of pregnant renal allograft recipients, where pregnancy is beyond the second trimester \([55]\). This incidence of rejection is in fact no greater than that expected for non-pregnant allograft recipients but it might be considered high because it has always been assumed that the privileged immunological state of pregnancy would benefit the transplant. Furthermore, there are reports of reduction or cessation of immunosuppressive therapy during pregnancy without rejection episodes \([61,63]\).

Unfortunately no factors serve to consistently predict which patients will develop rejection during pregnancy and there is little information as to whether pregnancy influences the course of subclinical chronic rejection, a problem present in most recipients \([64]\).

Difficulties can arise in distinguishing rejection from acute pyelonephritis, recurrent glomerulopathy and possibly severe pre-eclampsia. Renal biopsy (which can be safely undertaken during pregnancy) is often necessary for a definitive diagnosis. Ultrasonography nowadays can be very helpful – alterations in the echogenicity of the renal parenchyma and the presence of an indistinct corticomedullary boundary are indicative of rejection \([65]\).
There have been at least 15 ‘successful’ pregnancies reported to the pharmaceutical company that supplies Cyclosporin A but so far there are only a few published reports of (non-complicated) pregnancies in patients taking this drug [59,66]. Cyclosporin A is supposedly more effective than conventional immunosuppression but evaluations are urgently needed in gravids because there are numerous adverse effects attributed to this drug in non-pregnant transplant recipients including renal and hepatic toxicity, tremor, convulsions and neoplasia [67].

**Renal function** The better the renal function before pregnancy the better the increment during pregnancy and the more satisfactory is the obstetric outcome [68]. Permanent impairment of renal function can occur during pregnancy, especially where it is already compromised prior to conception. Even in patients with satisfactory renal function before pregnancy there may be a decline in GFR as well as the appearance of significant proteinuria during the third trimester, but these are usually transient and normal function returns post-partum (Figures 2 and 3).

**Hypertension** There is a 30 per cent chance of developing ‘pre-eclampsia’ but since the diagnosis is usually made by clinical criteria, it may be incorrect. As mentioned previously, in the absence of a renal biopsy it may be difficult to

![Diagram](image-url)

Figure 2. Serial 24 hour creatinine clearance in six women with renal transplants. Measurements from 10 healthy women (mean±SD) are shown by upper line and shaded area. (Davison, unpublished data)
Figure 3. Serial 24 hour total protein excretion during 10 pregnancies in eight women with renal transplants (mean±SD). Protein excretion for 10 healthy women studied similarly (mean±SD) are shown by the last line and shaded area [68].

distinguish pre-eclampsia from rejection, acute pyelonephritis and even recurrent glomerulopathy. Serum uric acid levels and 24-hour urinary protein excretion are often well above the norms for pregnancy in normotensive pregnant allograft recipients. Thus elevated values do not necessarily signify pre-eclampsia or herald its onset. Moreover, although many of the hypertensive syndromes occurring in pregnancy transplant recipients are quite severe, there is only one report of a patient in whom the condition progressed rapidly to eclampsia [69]. Incidentally, her subsequent pregnancy was normotensive and uneventful [70].

Fetal monitoring and judging the time to deliver. The factors for patients with chronic renal disease are equally applicable (see Renal dysfunction etc section). Timing depends on balancing the risks of intrauterine fetal jeopardy against neonatal morbidity and mortality, bearing in mind at all times the mother’s wellbeing.

The transplanted kidney very rarely produces mechanical dystocia during labour and it does not sustain apparent mechanical injury during vaginal delivery. Caesarean section is usually only necessary for purely obstetric reasons. Regardless of the route of delivery steroids must be augmented at this time. Prophylactic antibiotics should be used for any surgical procedure (however trivial), as for example an episiotomy.
Neonatal problems

There are hazards for the neonate [55]. Pre-term delivery occurs in 50 per cent and intrauterine growth retardation in at least 20 per cent. Although there are no frequent or predominant congenital abnormalities, one or more complications occur in about 35 per cent of offspring, including respiratory distress syndrome, leucopenia, thrombocytopenia, adrenocortical insufficiency, cytomegalic virus and other infections as well as development of HBsAg carrier state.

Infectious hepatitis Renal transplant recipients may have been exposed to multiple transfusions as well as haemodialysis and some may carry the hepatitis B virus. Whereas women developing acute hepatitis in late pregnancy or within two months after delivery often transmit HBsAg to their offspring, the risk to children of asymptomatic carriers is much lower, and antigenicity is most likely to occur in infants whose mothers were also HBsAg positive [71].

When HBsAg is transmitted to the baby, it invariably disappears within a few weeks after birth, only to be found later in life if active infection ever develops. This suggests that many HBsAg-positive neonates have been infected (i.e. with their mother's blood or vaginal secretions) at delivery and this maternally acquired antigen is cleared before a fresh infection is contracted (alternatively, it may 'incubate' outside of the blood system). Further evidence of perinatal infection is that most cord blood specimens are HBsAg negative or have very low HBsAg titres, even among those infants who become HBsAg carriers [71,72].

Without prophylaxis, some infants of HBsAg-positive mothers become carriers within two to three months of birth, an interval that again suggests that infection first occurred during labour or delivery. Furthermore, if infection occurred during pregnancy, immunoprophylaxis initiated at birth would be unlikely to be of value in preventing acquisition of the carrier state by the infant. However, hepatitis B immune globulin (HBIG) or hepatitis B virus vaccine (HBVV) given within a few hours of birth is highly effective in reducing the HBsAg carrier state in 50–70 per cent of infants, but not if administration is delayed beyond 48 hours [71–74]. Recently it has been shown that HBIG and HBVV combined is a highly effective way of preventing perinatal transmission of HBsAg infection, with over 90 per cent of infants born to HBsAg-positive carrier mothers protected, a much better rate than either HBIG or HBVV alone [71]. Most of the remaining 10 per cent who become carriers, despite this combined therapy, are presumed to have had in utero infections, which were already established at birth.

Breast feeding There are substantial benefits to breast feeding. It has been argued that the baby has been exposed to azathioprine and its metabolites throughout pregnancy and that their concentrations in mothers' milk is minimal, and therefore, breast feeding should be allowed [75,76]. As yet, little is known about the quantities of azathioprine and its metabolites in breast milk and what levels are trivial or substantial from a biological point of view [75]. Until these problems are resolved, breast feeding should not be encouraged.
Long-term paediatric assessment

Azathioprine can cause transient gaps and breaks in the chromosomes of lymphocytes, defects which disappear spontaneously in five to 32 months but such anomalies may not be as temporary in tissues not yet studied [55]. The consequences could be the eventual development of malignancies in the affected offspring or abnormalities in the next generation. There are some disturbing observations from animal studies: for instance, fertility problems affect the female offspring of mice that have received low doses of 6-mercaptopurine, the major metabolite of azathioprine (equivalent to 3mg/kg) [77]. These offspring subsequently prove to be sterile or, if they conceive, have smaller litters and more dead fetuses than do dams that had not been exposed to the 3mg. Thus exposure in utero may not effect otherwise normal females until they embark upon their reproductive careers.

Follow-up after pregnancy

Renal outlook Long-term impact, both in terms of renal prognosis and patient wellbeing, are difficult to assess. The majority experience, as reported in the literature, suggests that to wait two to three years after transplantation before becoming pregnant is safe and pregnancy does not seem to cause any irreversible decline in renal function [55,56]. Based on a comparison of very small groups of renal cadaver transplant recipients (those who became pregnant and those who did not), a recent study concluded that pregnancy had no effect on graft function or survival [78]. Considerably more data are needed in this area.

Gynaecological considerations Another factor related to long-term immunosuppression (usually with azathioprine and steroids) is the thirty-five times increased risk of developing malignancy. This is probably due to loss of immune surveillance, chronic immunosuppression allowing tumour proliferation and prolonged antigenic stimulation of the reticuloendothelial system. The genital tract is an important site for cancer and there are reports of cervical change ranging from cellular atypia to invasive squamous cell carcinoma as well as carcinoma of the vulva in young patients [19]. Regular pelvic examination and cervical cytology are essential in all of these women. Lastly, unusual malignancies have been reported and include reactivation of latent choriocarcinoma [80] and transmission of metastases from choriocarcinoma with a cadaver kidney [81].

Contraception counselling Oral contraceptives can produce subtle changes in the immune system but this is not necessarily a contraindication to their use. Some specifically advise against them, however, because of the possibility of causing or aggravating hypertension or further increasing the incidence of thromboembolism. If oral contraceptives are prescribed, therefore, careful and frequent follow-up is needed.

An intrauterine contraceptive device (IUCD) may aggravate menstrual problems, which in turn may confuse the signs and symptoms of abnormalities of early pregnancy. The increased risk of pelvic infection associated with the use
of an IUCD makes this method worrisome in an immunosuppressed patient and in any case it has been suggested that the efficacy of these devices is reduced by immunosuppressive and anti-inflammatory agents, possibly due to a modification of the leucocyte response [82]. Nevertheless, many patients request this method and careful counselling and follow-up are essential.

Renal transplantation and pregnancy: concluding remarks

This review is far from complete but has indicated that in the absence of severe maternal problems and with careful management during pregnancy, women with renal transplants can achieve successful obstetric outcome. If further advances are to be made in obstetric and neonatal care then multicentre co-operation must be strengthened. Special emphasis should be placed on the improvement of pre-pregnancy assessment criteria, the study of the significance of hypertension and proteinuria in the third trimester, the assessment of long-term renal prognosis and the organization of adequate long-term follow-up of the offspring.

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