Pregnancy and Renal Failure
The Case for Application of Dosage Guidelines

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Abstract

Pregnancies in women with renal disease, undergoing dialysis treatment or with kidney transplants are increasingly observed. Serious problems with drug dose adjustment may arise in pregnant women with renal impairment. This review gives a practical overview on the risks of drug use during gestation, the recommended drugs of choice (e.g. methyldopa, cyclosporin), and provides some proposals for dosage adjustments in pregnant women with renal impairment.

In normal pregnancy, the glomerular filtration rate and plasma volume in-
crease, whereas plasma protein binding and liver function may be impaired. An increase in dosage is needed for cyclosporin and for methadone because of increased hepatic clearance. The dosage of erythropoetin must be increased because of lower potency in pregnant women. Little more is known on the impact of gestation on drug dose, since pharmacokinetic studies are rarely done in pregnant women.

The dosages of magnesium, lithium and morphine must be reduced in renal impairment. Dose adjustment to renal function is critical and is essential for anti-infective agents (e.g. ceftazidime, ganciclovir). Basing drug dose on estimated creatinine clearance might be the most practical solution in pregnant women with renal impairment.

1. Drug Therapy and Pregnancy

Toxicological and epidemiological interest is increasingly focusing on pregnancy. However, dosage guidelines and clearance predictions in pregnant women are hard to obtain. Only occasionally are drug kinetics in pregnancy investigated. Out of 1203 published articles on pharmacokinetics and pregnancy, only 61 reported relevant parameters. Pregnancy is an exclusion criterion for most pharmacokinetic studies. Usually pregnant women are supposed to be healthy, they do not take drugs, and need no such information. After the thalidomide tragedy, any drug use in pregnancy is generally discouraged. However, 75 to 99% of women take drugs during pregnancy.

In normal pregnancy there is a physiological increase in glomerular filtration rate (GFR) of approximately 25%. This might require a higher dose of ampicillin, cefazolin, cefuroxime, and cephradine (ceftridine) in women without kidney diseases. Plasma volume expands by approximately 50%, and total body water increases by 8 litres. Larger water volume and higher pregnancy weight might make higher dosage mandatory in critical situations. In contrast, a decrease in plasma protein binding and in metabolic capacity of the liver can be assumed. Hepatic albumin synthesis decreases by approximately 20% in midpregnancy. These physiological changes do not usually pose many problems with drug dosages. However, any kidney disease and renal impairment will influence drug elimination and distribution in pregnant women, making drug dose adjustment an important consideration in treating pregnant women.

Decreased plasma binding leads to a larger estimate for the volume of distribution, since total drug concentrations in plasma decrease. Because absolute free drug concentration remains constant, paradoxically, dosage must not be increased in drugs with larger volume because of impaired plasma binding. However, for therapeutic drug monitoring, lower target concentrations must be considered to be therapeutic in such conditions with a decreased plasma binding (e.g. for phenytoin, carbamazepine).

Higher doses of cyclosporin and methadone are required because of increased hepatic clearance. Thiamazole (methimazole) and pancuronium bromide have a shorter elimination half-life and more rapid clearance in pregnant women. Methadone is another rare example where a pharmacokinetic study is published in pregnant women. Contrary to our expectations, methadone elimination is more rapid (half-life 19 vs 30 hours), and oral clearance is higher (148 vs 96 ml/min) compared with non-pregnant volunteers. Methadone dosage must be further increased in pregnancy since bioavailability decreases as a result of increased hepatic clearance with higher presystemic extraction. Furosemide kinetics have been investigated in pregnant women and were not different from normal published values (elimination half-life of 1.2 to 2.0 hours and a clearance of 153 ml/min).
2. Pregnancy in Women with Renal Disease

It is no longer necessary to recommend to women with renal disease that they not become pregnant. Successful pregnancy outcomes can be achieved in 89 to 98% of women with renal disease, diabetes mellitus or kidney transplants with proper prenatal care. In recent years the number of pregnant women with renal disease, undergoing dialysis-treatment or with kidney transplants has increased. In addition, as a result of routine measurements a renal disease eventually may become apparent during pregnancy.

2.1. Pregnancy and Renal Disease

Any renal disease can occur in pregnant women, such as rapidly progressive glomerulonephritis. However, except for lupus nephritis, this is a very rare event. A pre-existing glomerulonephritis such as minimal-change lesions usually do not progress during pregnancy, and deterioration is rare as shown for immunoglobulin (Ig)A nephritis. Pregnancy can lead to further impairment of renal function mainly in kidney diseases with proteinuria. There is a physiological reflux in pregnancy that can lead to hydronephrosis and obstructive nephropathy. Because of this physiological reflux, patients with interstitial nephritis or juvenile reflux nephropathy can deteriorate. However, the gestational age was shorter (33 vs 37 weeks) and pregnancy loss was more common in women with pre-existing renal disease (14/43 versus 3/43) who were prospectively compared with pregnancy in women without renal disease.

2.2. Pregnancy and Dialysis

Pregnancy is a rare event in women on long term dialysis and only occurs during the first few years when residual renal function is preserved. A successful pregnancy has been reported in approximately 90 dialysis patients worldwide, and of these, 25 were on continuous peritoneal dialysis. Pregnancy led to childbirth in only 50% of 141 patients on dialysis; perinatal death occurred in 12%, premature delivery in 48%, and delivery by caesarean section was needed in 66%. Polyhydramnios, preeclampsia, high blood pressure, anaemia, low birth weight, and growth retardation are reported mainly in women with systemic lupus erythematosus (SLE) or diabetes mellitus. The risks for the mother are fever, volume overload and overhydration. A high protein diet (> 1.5 g/kg bodyweight) and an intensified dialysis regimen (6 times a week) are recommended.

2.3. Pregnancy after Kidney Transplantation

In approximately 1600 women with kidney transplants a total of 2309 pregnancies are reported world-wide. There is no special malformation associated with pregnancy in kidney transplant patients. Favourable signs for a successful pregnancy are stable kidney function, an interval since transplantation of 2 years and more, normal blood pressure, and low dose prednisone with 7.5 mg/day rather than 10 mg/day. The main risks are pre-eclampsia (29%), infections (22%), anaemia, caesarean section, intrauterine growth retardation, low birth weight (<2500g), and deterioration of kidney transplant function. Spontaneous or therapeutic abortion is reported in about 30%. Antihypertensive medication is required in 56%. Frequent complications are bacterial infections of the urinary tract, vaginal mycosis, toxoplasmosis, and cytomegalovirus and herpesvirus infections. Breast feeding is discouraged in this patient group, for example, while taking cyclosporin; the newborn might be exposed to higher cyclosporin concentrations through breast milk than the fetus through the placenta.

The risk of impaired transplant function is increased in patients with elevated creatinine levels and in those with a renal obstruction. Usually the transplant function stays stable during pregnancy, a rejection episode during or within 3 months after pregnancy occurs in only 11%, and loss of transplant within 2 years after pregnancy in 9%. One successful pregnancy has been reported in a woman receiving a kidney transplant.
with ganciclovir and antithymocyte globulin treatment one week after conception.\textsuperscript{[36]}

3. Guideline Objectives and Methods

For all drugs where clinical end-points (e.g. blood glucose levels in diabetes mellitus) or drug concentration monitoring are established, the frequency of monitoring should be intensified during gestation (e.g. cyclosporin, tacrolimus, mycophenolate mofetil, vancomycin, lithium, phenytoin, anti-Xa heparin). Pregnancy in women with renal impairment poses three problems: (i) progress in renal disease; (ii) teratotoxicity and embryotoxicity, along with (iii) inadequate information on dose adjustment.

Renal impairment is assumed in all patients with a serum creatinine levels of $\geq 120 \mu$mol/L (1.4 mg/dl), and in those on dialysis.\textsuperscript{[30]} This is a population where dosage adjustment is needed and the pharmacokinetic knowledge is scarce. Therefore, we completed a literature search on the keywords pregnancy, renal impairment, dialysis, transplantation and drug dose adjustment, and respective drugs in Medline and PubMed. On the basis of our clinical experience and counselling practice in this field, we provide an overview on the drugs of choice or the alternatives we have (table I), and on the dosage proposals we can make (table II).

3.1 Dose Adjustment to Renal Function

Drug dose adjustment to renal function is most important for the anti-infective drugs (table II). The dosage of magnesium must be reduced and adjusted to renal function because the half-life of 4 hours increases in renal impairment since 90 percent of magnesium dose is eliminated by the kidneys.\textsuperscript{[67]} Morphine and methadone are required by women with addiction.\textsuperscript{[107,115]} The dosage of morphine must be reduced in patients with renal failure because the active M-6-G metabolite accumulates when the half-life increases from 4 to 31 hours.

GFR as the main determinant of renal function is most reliably measured by ioxelox clearance in pregnant women.\textsuperscript{[114]} Practically, the creatinine clearance (CL\textsubscript{CR}) works as the best suited non-

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Drug} & \textbf{Recommendation} \\
\hline
\textbf{Antimicrobials} & \\
Aminoglycosides (gentamicin, netilmicin)\textsuperscript{[38]} & No \\
Amoxycillin\textsuperscript{[39]} & Yes \\
Amphotericin B\textsuperscript{[40]} & Yes \\
Azithromycin\textsuperscript{[41]} & Yes \\
Cephalosporins\textsuperscript{[39,42]} & Yes \\
cefuroxime\textsuperscript{[3]} & Yes \\
Clindamycin\textsuperscript{[41]} & Yes \\
Cotrimoxazole\textsuperscript{[43]} & No \\
Erythromycin\textsuperscript{[20,42]} & Yes \\
Fluconazole (short course)\textsuperscript{[44,46]} & Yes \\
Furazidine (flrazolidine)\textsuperscript{[47]} & Yes \\
Itraconazole\textsuperscript{[48]} & Yes \\
Mefloquine\textsuperscript{[49]} & Yes \\
Metronidazole\textsuperscript{[42,45]} & Yes \\
Oxacillin\textsuperscript{[42,50]} & Yes \\
Penicillins\textsuperscript{[39,42]} & Yes \\
Quinolones\textsuperscript{[39,52,53]} & No \\
Rifampicin & No \\
Sulfadoxine\textsuperscript{[51]} & Yes \\
Tetracylines\textsuperscript{[39,42]} & No \\
Thallium\textsuperscript{[54]} & No \\
Trimethoprim\textsuperscript{[43]} & No \\
Vancomycin (2nd/3rd trimester)\textsuperscript{[56]} & Yes \\
\hline
\textbf{Antiviral drugs} & \\
Delavirdine mesylate\textsuperscript{[56]} & No \\
Didanosine\textsuperscript{[56]} & Yes \\
Efavirenz\textsuperscript{[56]} & No \\
Ganciclovir\textsuperscript{[36]} & Yes \\
Lamivudine\textsuperscript{[57]} & Yes \\
Nelfinavir\textsuperscript{[56]} & Yes \\
Nevirapine\textsuperscript{[56]} & Yes \\
Ritonavir\textsuperscript{[56]} & Yes \\
Saquinavir\textsuperscript{[56]} & Yes \\
Zalcitabine\textsuperscript{[56]} & No \\
Zidovudine (long term)\textsuperscript{[56]} & No \\
Zidovudine (peripartum)\textsuperscript{[56,61]} & Yes \\
\hline
\textbf{Antihypertensives} & \\
ACE inhibitors\textsuperscript{[36,62]} & No \\
AT\textsubscript{1} receptor antagonists\textsuperscript{[63]} & No \\
$\beta$-Blockers & ? \\
\hline
\end{tabular}
\caption{Drugs that are allowed (yes), not allowed (no) or controversial (?) in pregnancy. Most of the drugs stated as not allowed should be avoided during the 1st trimester. ACE inhibitors and NSAIDs should not be given in the 3rd trimester. The category ‘allowed’ is used since no scientific consensus on the various classification systems yet exists, and global warnings can also do harm.\textsuperscript{[37]} Where available, the nontoxic alternative drug should be given during gestation.}
\end{table}
invasive estimate to adjust drug dose to renal impairment. The CL-CR can be derived even for pregnant women by the well-certified Cockcroft & Gault formula where the actual pregnancy body-weight is taken into account.[116] Thus, in pregnant women with renal impairment, the drug dosage can be adjusted to estimated CLCR as a measure for renal function and GFR. Renal failure with a GFR < 5 ml/min corresponds to functional anuria (anuric). Drug elimination, whether more or less, specifically depends on renal function, that is, the correlation between drug clearance (CL) and estimated GFR. 

### Other drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Allowance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomifene</td>
<td>No</td>
</tr>
<tr>
<td>Coffein</td>
<td>No</td>
</tr>
<tr>
<td>Cox-2 inhibitors</td>
<td>No</td>
</tr>
<tr>
<td>Desmopressin, vasopressin</td>
<td>Yes</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Yes</td>
</tr>
<tr>
<td>Encaidine</td>
<td>Yes</td>
</tr>
<tr>
<td>Flecaainde</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Yes</td>
</tr>
<tr>
<td>Gilbenclamide (glyburide) [avoid in renal impairment]</td>
<td>No</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (pravastatin, atorvastatin)</td>
<td>No</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>No</td>
</tr>
<tr>
<td>Insulin</td>
<td>Yes</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>Yes</td>
</tr>
<tr>
<td>Iron</td>
<td>Yes</td>
</tr>
<tr>
<td>Isotretinoin (Vitamin A acid)</td>
<td>No</td>
</tr>
<tr>
<td>Lithium</td>
<td>?</td>
</tr>
<tr>
<td>Metformin</td>
<td>No</td>
</tr>
<tr>
<td>Methadone</td>
<td>Yes</td>
</tr>
<tr>
<td>Morphine</td>
<td>Yes</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Yes</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Yes</td>
</tr>
<tr>
<td>Pyridoxine (vitamin B6)</td>
<td>Yes</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Yes</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Yes</td>
</tr>
<tr>
<td>Theophylline</td>
<td>No</td>
</tr>
<tr>
<td>Thiamazole (methimazole)</td>
<td>Yes</td>
</tr>
<tr>
<td>Thiamazole (methimazole) [2nd trimester?]</td>
<td>?</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>Yes</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**AT1** = angiotensin AT1 receptor; **Cox** = cyclo-oxygenase; **IV** = intravenous; **LMWH** = low molecular weight heparin; **no** = not allowed/avoid; **NSAIDs** = non-steroidal anti-inflammatories; **yes** = allowed; ? indicates controversial.
CLCR is linear.\textsuperscript{[117]} The intercept corresponds to the drug clearance with anuria (CLanur) and the slope $(a)$ indicates the dependence on renal function.

$$\text{CL} = \text{CL}_{\text{anur}} + a \times \text{CL}_{\text{CR}}$$

The half-life gives the best estimate of the effect of renal impairment on pharmacokinetics. The half-life provides an indication for the fraction that the dose should be reduced by or for the extension of the administration interval, or for both. The half-life is a direct determinant for the duration time of drug effect. Since individual variability for the volume of distribution is much less than for half-life or for clearance, the volume can be considered to be relatively constant ($V_d = \text{const.}$). Accordingly, there is an inverse proportionality between half-life ($t_{1/2}$) and drug clearance (CL). The fundamental pharmacokinetic correlation tells us that the half-life increases for example by a factor of 10 if the clearance reciprocally decreases to a fraction of 10%.

$$t_{1/2} = 0.693 \frac{V_d}{\text{CL}}.$$

At present, two dose adjustment rules exist, namely (i) the proportional dose reduction rule of Luzius Dettli, and (ii) the half-dosage rule of Calvin Kunin. The dose (D) and the administration interval (τ) variably can be adjusted to the estimated or calculated individual half-life ($t_{1/2}$) or to drug clearance (CL).

1. **Proportional dose reduction rule**\textsuperscript{[117]}

$$\frac{D}{\tau}_{\text{indiv}} = \left(\frac{D}{\tau}_{\text{norm}} \times \frac{\text{CL}_{\text{indiv}}}{\text{CL}_{\text{norm}}} \right)$$

2. **Half-dosage rule**\textsuperscript{[118]}

$$D_{\text{indiv}} = \frac{1}{2} \times D_{\text{start}} / t_{1/2} \text{ indiv}$$

The target concentration approach of Nicholas Holford,\textsuperscript{[119]} will need computer-based systems to be realised in clinical practice since where the target concentration is not established, it must be estimated or calculated.\textsuperscript{[119]} It is our experience that dose reductions in proportion to the drug clearance (Dettli-rule) will probably lead to insufficiently low dosages as, for example, for amoxicillin (table II). The amoxicillin half-life increases from 1.2 to 12 hours (i.e. clearance decrease by a factor of 10). The dose reduction from normal 1000mg to only 100mg every 8 hours might be subtherapeutic. Thus, for amoxicillin, we recommend giving one half of the loading dose every estimated half-life (Kunin-rule), that is 500mg every 12 hours (table II). The respective half-life values could also be used to adjust the dosage according to the Dettli rule.

The dose after haemodialysis ($D_{\text{HD}}$) comprises the dose off dialysis ($D_{\text{anur}}$) and the dose supplementing the dialysis effect ($D_{\text{suppl}}$).

$$D_{\text{HD}} = D_{\text{anur}} + D_{\text{suppl}}$$

Our proposed dose reductions are mainly calculated by using the Kunin-rule and half-life values (table II). The half-life values are derived from our pharmacokinetic database NEPharm.\textsuperscript{[120]} At present the NEPharm database contains 34,351 primary extracted values for 2,526 drugs with 14,295 pharmacokinetic parameters statistically synthesised from 4,318 primary publications.

Our proposals give the maximum dosages made for the most severe clinical conditions where underdosage might be even more deleterious than overdosage. This is particularly so for intensive care patients requiring renal replacement therapy who might be exposed to an increased risk of insufficient dosage resulting from precautionary dose reductions.\textsuperscript{[121]} The higher dosages might also be justified because the volume of distribution will increase during pregnancy mainly for water-soluble drugs, which are also the drugs where elimination is dependant on renal function. Dosage proposals are given for the extremes of normal and functional anuric renal function. By interpolation between the extremes the individual dose must be adjusted to the estimated fraction of remaining renal function.

## 4. Renal Disease in Pregnancy

Any acute renal failure might make haemodialysis mandatory during pregnancy. Daily haemodialysis regimens will be required to remove volume overload and to obtain near-normal serum urea (<20 mmol/L) and creatinine levels (<400...
µmol/L) as also required in pregnant patients on long-term dialysis. Besides diabetes mellitus, diabetes insipidus, and the anti-phospholipid syndromes, two serious renal diseases can occur during and immediately after pregnancy - the haemolytic uraemic syndrome and lupus nephritis.[122-124]

4.1 Haemolytic Uraemic Syndrome

The haemolytic uraemic syndrome must be treated by infusion of fresh frozen plasma and by plasma exchange as in nonpregnant patients. Immediate delivery is the rule but continuation of pregnancy until term can be achieved.[125]

4.2 Lupus Nephritis

During pregnancy, SLE can flare in 65% of affected women and it can have a first manifestation in pregnant women.[126] There is a predominant Th2 cell imbalance during pregnancy leading to the tolerance of the conception.[127] The elevated Th2 cytokines [interleukin (IL)-6 and IL-10] might induce lupus-antibody production with an exacerbation of SLE.[128] Anti-Ro (SS-A) antibodies that cross the placenta, can produce a neonatal lupus with AV-block, haemolysis and cytopenia in the child.[129]

In all women with a known diagnosis of SLE, prophylactic therapy with corticosteroids should be considered during pregnancy. However, corticosteroids frequently cannot prevent a lupus flare in pregnancy.[126] If there is active SLE in pregnancy, cyclophosphamide should be avoided except when there is a vital indication for the mother (see section 5.4). Use of chloroquine and hydroxychloroquine is controversial. Because of the very long elimination half-life of hydroxychloroquine from maternal tissues (weeks to months), discontinuing the drug would not eliminate foetal exposure, but jeopardise the pregnancy from a lupus flare.[74] Pregnancies have been reported in women who received hydroxychloroquine without any unfavourable sequelae.[71] From published reports of foetal exposure to either chloroquine or hydroxychloroquine, one source cited a rate of 4.5% which is within the expected 3 to 6% incidence of congenital malformations in a nonexposed population.[9]

In women with a transplant and underlying SLE, pregnancy outcome is not worse than in other kidney transplant patients.[130] Cyclosporin as a monotherapy is not advisable in patients with SLE, since cyclosporin induces only Th1 suppression favouring a shift to Th2 predominance and disease activity might be enhanced by Th2 predominance, such as in untreated SLE.[126]

It is most important to note that a severe manifestation of SLE during pregnancy can be treated with high dose intravenous immunoglobulins.[131,132] The dose of intravenous immunoglobulins must be high with 80g intravenously twice daily on 2 consecutive days every 4 weeks.[75,133] These exogenous immunoglobulins compete with the pathological immunoglobulins for the FcRn receptor responsible for immunoglobulin regeneration[134] and induce expression of the inhibitory FcγRIIB receptor.[135] Plasmapheresis is also well tolerated and effective in patients with the anticoagulant syndrome.[136]

4.3 Antiphospholipid Syndrome

Whether primary or secondary to SLE, the thrombophilia and hypercoagulopathy associated with antiphospholipid syndrome and circulating anticardiolipin antibody presents a big problem in pregnant patients. Spontaneous abortion usually results. Anticoagulation with heparin is necessary even in patients without a history of thrombosis[79] and high dose intravenous immunoglobulins are recommended.[131] However, the value of corticosteroids is debated.

4.4 Diabetes Mellitus

Pregnancy in women with diabetic nephropathy may be associated with the need for a caesarean section in 78%, with high blood pressure in 60%, preeclampsia in 41%, premature delivery in 22%, retarded fetal growth in 15%, and malformations in 8%. End-stage renal failure develops in 17% and 5% of these women die.[137]
Table II. Dosage proposals for anti-infective and antiviral drugs in patients with renal failure. Some recommendations are based only on our previous work and clinical experience.[112-114]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (h)</th>
<th>Dstart (mg)</th>
<th>Normal kidney functiona</th>
<th>Renal Impairmentb</th>
<th>Renal Failurec (dialysis status) where ( D_{HD} = D_{nond} + D_{suppl} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>A</td>
<td>MD (mg)</td>
<td>AI (h)</td>
<td>MD (mg)</td>
</tr>
<tr>
<td>Penicillins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1.2</td>
<td>12</td>
<td>1000</td>
<td>8</td>
<td>1000</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid</td>
<td>1.2</td>
<td>12</td>
<td>1000</td>
<td>8</td>
<td>1000</td>
</tr>
<tr>
<td>Subbactam</td>
<td>1</td>
<td>6.6</td>
<td>1000</td>
<td>8</td>
<td>1000</td>
</tr>
<tr>
<td>Acicillin</td>
<td>0.8</td>
<td>6.5</td>
<td>5000</td>
<td>8</td>
<td>5000</td>
</tr>
<tr>
<td>Dicloxacillin (PO)</td>
<td>0.8</td>
<td>2.3</td>
<td>1000</td>
<td>6</td>
<td>1000</td>
</tr>
<tr>
<td>Flucloracillin</td>
<td>0.8</td>
<td>3</td>
<td>1000</td>
<td>8</td>
<td>1000</td>
</tr>
<tr>
<td>Metzlocillin</td>
<td>1</td>
<td>9.7</td>
<td>4000</td>
<td>8</td>
<td>4000</td>
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<td>Oxicillin</td>
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<td>6</td>
<td>1000</td>
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<td>Penicillin G</td>
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<td>10 mega</td>
<td>6</td>
<td>10 mega</td>
</tr>
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<td>8</td>
<td>4000</td>
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<tr>
<td>Piperacillin/Clavulanic acid</td>
<td>1.1</td>
<td>4</td>
<td>4000</td>
<td>8</td>
<td>4000</td>
</tr>
<tr>
<td>Subbactam</td>
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<td>8</td>
<td>500</td>
<td>8</td>
<td>500</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>1.5</td>
<td>16</td>
<td>500</td>
<td>8</td>
<td>500</td>
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<td>Cephalosporins</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cefaclor (PO)</td>
<td>0.7</td>
<td>3</td>
<td>1000</td>
<td>8</td>
<td>1000</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>1</td>
<td>14</td>
<td>2000</td>
<td>8</td>
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<tr>
<td>Cefazedone</td>
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<tr>
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<tr>
<td>Cefepime</td>
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<td>15</td>
<td>2000</td>
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Pregnancy and Renal Failure

Contd over page
Table II. Contd.

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<tr>
<th>Drug</th>
<th>Half-life (h)</th>
<th>Dstart (mg)</th>
<th>Normal kidney function&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Renal impairment</th>
<th>Renal failure&lt;sup&gt;c&lt;/sup&gt; (dialysis status) where ( D_{H} = D_{sur} + D_{suppl} )</th>
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<td>AI (h)</td>
<td>MD (mg)</td>
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<td>11 (34)</td>
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Table II continued
Insulin is usually recommended to control blood glucose levels. Glibenclamide (glyburide) does not cross the placenta, unlike tolbutamide and other sulphonylureas, and was as well tolerated as insulin after the 1st trimester. However, glibenclamide should not be used in patients with renal impairment since the half-life of 4 hours is prolonged to 14 hours in renal failure.

4.5 Diabetes Insipidus

Pregnancy can also be successful in women with central or renal diabetes insipidus. Nephrogenic diabetes insipidus can manifest during gestation. Vasopressin and desmopressin can and should be given to patients with neurogenic diabetes insipidus otherwise water deficiency may induce renal failure and oligohydramnios. Overdosing of antidiuretic hormone can induce polyhydramnios. In patients with nephrogenic diabetes insipidus, thiazides and even nonsteroidal anti-inflammatories (NSAIDs) such as diclofenac, should be continued to reduce the urine losses.

5. Drug Use in Pregnancy with Renal Impairment

In pregnant women with renal disease or renal replacement therapy, essential drugs are the antihypertensives, immunosuppressants, anticoagulants, anticonvulsants, and antimicrobial agents. Drugs other than those needed to treat underlying disease should be avoided (table I). Iron treatment is common in pregnant women but supplementation should be given only in women with documented deficiency. Folic acid supplementation would be most effective in the first 4 weeks, where the woman often is not yet aware of the pregnancy. Folic acid supplements reduce the risk of cardiovascular defects, oral clefts and urinary tract defects in the fetus of women taking folate antagonists such as aminopterin sodium, methotrexate, sulfasalazine, pyrimethamine, triamterene, trimethoprim, carbamazepine, phenytoin, primidone, or phenobarbital.

In general, the drug-induced risk for the fetus must be weighed against the disease-related risk.
for the pregnant woman. Recent recommendations state, for example, that antiretroviral drug therapy should be started or continued to HIV-positive women during pregnancy[147] The main risk of drug exposure arises during the first trimester, with the exception of NSAIDs and angiotensin converting enzyme (ACE) inhibitors, which should be avoided in the 3rd trimester. There is a risk of foetal nephrotoxicity with NSAIDs,[148] which is also true for the selective cyclo-oxygenase (Cox)-2 inhibitors.[93,108] Misoprostol used to induce abortion in combination with methotrexate and, with mifepristone, it can induce Möbius’ syndrome and other malformations during first trimester.[144] In the 3rd trimester, misoprostol is used to induce labour.[149]

Myeloproliferative syndromes during pregnancy can be treated with interferon (IFN)-α.[103] Idarubicin given during second trimester to the mother with acute lymphoblastic leukaemia caused cardiotoxicity in the infant.[150] The risk of malformations increases from 3% without any drug to up to 20% in pregnancies requiring antineoplastic therapy mainly during the first week after conception.[8] Alkylation agents such as busulfan, chlorambucil or cyclophosphamide are less powerful teratogens than antimetabolites such as methotrexate or fluorouracil.[8] Conditioning before stem cell transplantation includes alkylation agents and irradiation. However, if they conceive, these women are more likely to have a successful pregnancy outcome after cyclophosphamide than after irradiation.[151]

5.1 Antimicrobials

The drugs most frequently prescribed in pregnant women (12 to 29%) are antimicrobials.[3,4,152] Because of the physiological reflux, complicated urinary tract infections are common in pregnancy. Routine urine dip-stix are recommended and monthly microscopic urine examinations should be carried out in immunosuppressed women. Even an asymptomatic bacteriuria (>10^4 bacteria/ml urine) should be treated with antibiotics in pregnant women with renal disease. Other infections can also occur in pregnancy, mainly if the patient is immunosuppressed (secondary to glomerulonephritis, autoimmune disease or kidney transplant). The antibacterials of choice are penicillins and other β-lactams.[39,42,50]

Although the data are very limited, the use of fluconazole during the 1st trimester appears to be teratogenic with continuous daily doses of ≥400mg.[85] This risk for adverse outcomes is low with fluconazole, especially after short, low-dose course for vaginal yeast infections.[46] Itraconazole use was found to have an acceptable safety profile in prospective studies.[48,153]

Tetracyclines are associated with tooth and bone dysplasias in the infants.[142] Quinolones can cause cartilaginous defects.[52,53] Gentamicin can induce oligonephronia in the fetus.[38]

5.1.1 Antiviral Drugs

The dosage of most antiviral drugs, such as aciclovir and ganciclovir, must be adjusted to renal function (table II). It is possible to use combined antiretroviral therapy which includes protease inhibitors in pregnant women infected with HIV.[52,53,154] Drugs rated as non-toxic in animal studies [US Food and Drug Administration (FDA) category B] are didanosine, saquinavir, ritonavir and nelfinavir.[56] Efavirenz, delavirdine mesylate, zalcitabine and zidovudine are rated as proven toxic (FDA category C) in animals or not studied.[56] Peripartal zidovudine is effective and non-teratogenic in clinical studies, with effective intracellular triphosphate levels obtained in cord blood and no malformations reported.[52,53,59-61] Didanosine clearance was significantly increased antepartum compared with postpartum clearance (1028 vs 707 ml/min) in women infected with HIV.[115] Lamivudine can freely cross the placenta to the fetus[57] and, therefore, the dose must be adjusted to the renal function of the mother (table II).

5.2 Antihypertensives

Nearly every patient with renal disease has an associated elevated blood pressure and the risk of gestosis is increased in these women. An antihypertensive medication is the rule in pregnant
women with renal disease and a kidney trans-
plant. However, the target blood pressure
should not be too low. Foetal growth retardation is
increased the more blood pressure is below
160/100mm Hg.

ACE inhibitors and angiotensin II AT1 receptor
blockers are contraindicated in pregnancy. All
women who can conceive a pregnancy should
be advised to discontinue ACE inhibitors when
they become pregnant, at least in the 2nd or 3rd
trimester. There is an ACE inhibitor-related
foetopathy with vascular malformations, pulmo-

dary hypoplasia and neonatal anuria. The same
toxic effects are reported for AT1 blockers such as
losartan. The use of β-Blockers, diuretics and
calcium channel antagonists is controversially de-
bated (table I). Furosemide causes a decrease in the
intervillous blood flow to a greater extent than
hydralazine or metoprolol.

5.3 Immunosuppressive Drugs

Patients with glomerulonephritis or kidney
transplants must often receive maintenance immu-

nosuppressive therapy. The immunosuppressive
regimen should not be changed during pregnan-
cy. This holds true for patients with systemic
diseases as well as for those with transplants. Ac-
gcording to published opinion there is an agreement
that low-dose corticosteroids, azathioprine, cyclo-

sporin and tacrolimus have good safety in preg-
nancy. Intrauterine growth retardation and post-natal complications are more likely to result
from impaired transplant function than from toxic
effects of tacrolimus, as discussed with 5 reported
cases.

A prednisone dose of 7.5 mg/day was associated
with a better outcome than 10 mg/day in pregnant
transplant recipients. Corticosteroids such as
dexamethasone and betamethasone do cross
the placenta, and these agents can induce a tran-
sient although reversible hypertrophic cardiomy-
opathy in the fetus. An association between high-dose corticosteroids and palate clefts has been
suspected.

In patients with kidney transplants, serum cre-
atinine values can improve during pregnancy. This
can be misleading because cyclosporin concentra-
tions tend to decrease. Since hepatic clearance of
cyclosporin increases, a 30% higher cyclosporin
do is required in pregnancy – this metabolic ef-
fect might be supported by the liver function of the
fetus as the cyclosporin dose requirements increase
during the 3rd trimester. Therefore, cyclo-

sporin overdose often occurs after delivery in the
mother as a result of increasing serum creatinine
levels. Cyclosporin inhibits the P-glycoprotein out-
wards-transporter causing increased toxicity with
digoxin, saquinavir and paclitaxel. Cyclo-


sporin allegedly can cause a growth retardation. However, renal function of children exposed to
cyclosporin in utero developed normally.

Insufficient data are available to exclude toxicity during pregnancy with the use of sirolimus
(rapamycin), muromonab-CD3 (OKT3 antibody),
antithymocyte globulin, and interleukin-2 receptor
(CD25) monoclonal antibodies. Cyclophos-
phamide, methotrexate, chlorambucil, sulfasalazine,
and probably also leflunomide should be avoid-
ed. With cyclophosphamide, concern centres on
embryopathy with growth retardation, cleft mal-
formation, oligodactyly, hypoplastic thumb, and
growth defects. With a general rate of 2.0 to
3.5 per 100 live births, the rate of congenital mal-
formations is 33.3 for chlorambucil, 22.2 for cyclo-

sporamide, 8.8 for high dose aspirin but 3.7 for
azathioprine.

5.4 Anticoagulants

The overall risk of thromboembolism in preg-
nancy is 6 times greater than in the nonpregnant
state. A special problem arises in those women
with nephrotic syndrome, with antiphospholipid
syndrome or who need anticoagulation during
pregnancy for other reasons. Oral anticoagulation
with warfarin or dicoumarol should be discouraged
because of fetal bleeding, stillbirth, teratogenicity,
the special fetal warfarin syndrome and warfarin
embryopathy. Anticoagulation must be achieved
with the use of low-dose aspirin and parenteral hep-
arin. Subcutaneous low molecular weight heparins (LMWHs) can also be used during pregnancy using a weight-adjusted twice daily dosage of LMWH and monitoring of anti-Xa heparin levels. Low dose heparin is not sufficient for anticoagulation, especially for patients with artificial heart valves. The thrombotic risk for the mother is 0.3% with warfarin but 5% even with weight-adjusted subcutaneous LMWHs.

5.5 Erythropoetin

There is no risk associated with the use of erythropoetin during pregnancy. A higher dosage of erythropoetin is needed in pregnant women because of lower drug potency. The relative resistance requires a doubled dosage of 3 x 4000U per week or more to maintain blood haemoglobin >11 g/dl during pregnancy.

5.6 Anticonvulsants

Cerebral convulsions and epilepsy are not frequent in patients with renal failure. Anticonvulsive therapy is associated with an increased risk of malformations, particularly with carbamazepine and valproic acid. There is an interaction between anticonvulsants and folic acid, as well as with the metabolism of vitamin K with the risk of neural tube defects and early neonatal bleeding. Valproic acid is teratogenic, but phenobarbital and phenytoin are less problematic. Monitoring of anticonvulsant drug concentrations and vitamin K concentrations might be advisable.

5.7 Antidepressants

Therapy with tricyclic antidepressants, or fluoxetine and other selective serotonin re-uptake inhibitors (SSRIs) is not associated with an increased risk for mother or child. Since most psychotropic drugs are lipophilic, a dose adjustment to renal function is required only with lithium. With normal renal function lithium dosage has to be increased in normal pregnancy since GFR increases and drug concentration monitoring is required twice weekly during gestation. Lithium dosages must be considerably reduced in pregnant women with renal impairment. There is an increased risk of lithium-induced teratogenicity during the 1st trimester with perinatal death and cardiovascular anomalies that clearly should be balanced against the benefits for the mother.

5.8 Tocolysis

Nifedipine is the first choice agent to terminate premature contractions. Ritodrine and terbutaline can lead to hypokalaemia. This might result in problems in women with salt loosing interstitial renal syndromes. The use of indomethacin and other NSAIDs for tocolysis is controversial.

5.9 Lipid Lowering Drugs

HMG-CoA reductase inhibitors such as pravastatin and atorvastatin should not be used in pregnancy because they inhibit steroid synthesis in the fetus. Lipid lowering drugs should be used in women who are potentially concepive only in combination with contraceptives.

6. Conclusion

Women with renal diseases no longer have to remain childless. Drugs of choice are available for the treatment of hypertension and for immunosuppression, and should be given during gestation. Individualised drug dosage adjustment to kidney function may be another essential contribution to optimising the medical management of pregnant women with renal diseases.

Acknowledgements

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