REVIEW ARTICLE

Drug Safety 2006; 29 (5): 397-419
0114-5916/06/0005-0397/$39.95/0

Effects Of Maternally Administered Drugs On The Fetal And Neonatal Kidney

Farid Boubred, Mariella Vendemmia, Patricia Garcia-Meric, Christophe Buffat, Veronique Millet and *Umberto Simeoni*

Faculté de Médecine, Université de la Méditerrannée and Assistance Publique Hôpitaux de Marseille, Hôpital de la Conception, Service de Néonatologie, Marseille, France

Contents

Abstract

The number of pregnant women and women of childbearing age who are receiving drugs is increasing. A variety of drugs are prescribed for either complications of pregnancy or maternal diseases that existed prior to the pregnancy. Such drugs cross the placental barrier, enter the fetal circulation and potentially

alter fetal development, particularly the development of the kidneys. Increased incidences of intrauterine growth retardation and adverse renal effects have been reported. The fetus and the newborn infant may thus experience renal failure, varying from transient oligohydramnios to severe neonatal renal insufficiency leading to death. Such adverse effects may particularly occur when fetuses are exposed to NSAIDs, ACE inhibitors and specific angiotensin II receptor type 1 antagonists. In addition to functional adverse effects, *in utero* exposure to drugs may affect renal structure itself and produce renal congenital abnormalities, including cystic dysplasia, tubular dysgenesis, ischaemic damage and a reduced nephron number. Experimental studies raise the question of potential long-term adverse effects, including renal dysfunction and arterial hypertension in adulthood. Although neonatal data for many drugs are reassuring, such findings stress the importance of long-term follow-up of infants exposed *in utero* to certain drugs that have been administered to the mother.

The number of pregnant women and women of childbearing age undergoing drug treatment has increased constantly over the past few decades.[1,2] Drugs are prescribed for various reasons, which can be either complications of pregnancy or pre-existing maternal diseases that include immune-mediated and rheumatological disorders, cancer and cardiovascular diseases. Such drugs are expected to cross the placenta, reach the fetal circulation and alter the development and function of the fetal kidney. Adverse effects may lead to fetal and neonatal renal failure, with an enhanced risk of perinatal death. It has been known for several years that *in utero* exposure to certain drugs, such as NSAIDs and ACE inhibitors, can cause fetal and neonatal renal dysfunction.[3,4] However, data available regarding materno-fetal pharmacology, the incidence of fetal and neonatal complications, and the long-term consequences of *in utero* exposure to many drugs are scarce.

The effects on the fetal and neonatal kidney of various maternally administered drugs such as selective and nonselective NSAIDs, ACE inhibitors and similar agents, corticosteroids, immunosuppressive and antineoplastic drugs, antibacterials and other drugs are reviewed (figure 1 shows the sites of action of these agents).

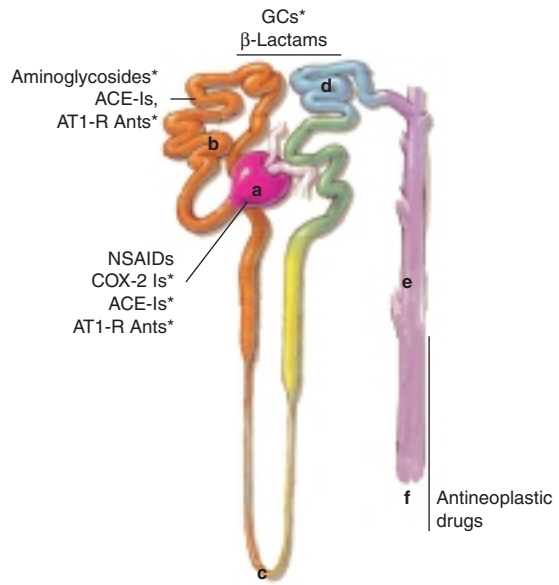

Fig. 1. Nephron with the segments that are the principal targets of maternally administered drugs: (**a**) glomerulus with afferent and efferent arterioles; (**b**) proximal tubule; (**c**) loop of Henle; (**d**) distal tubule; (**e**) collecting duct; and (**f**) urinary tract. **ACE Is** = ACE inhibitors; **AT1-R Ants** = angiotensin II type 1 receptor antagonists; **COX-2 Is** = selective cyclo-oxygenase 2 inhibitors; **GCs** = glucocorticoids; * signifies that drugs may induce a reduction of nephron number.

1. Kidney Structure and Functional Development

The development of the definitive kidney, the metanephros, takes place after the formation and involution of two embryonic kidneys, the pronephros (a non-functional organ) and the mesonephros (the first functional kidney) from which derives and persists the ureteric bud.[5,6] The metanephros appears in the fifth gestational week, and develops from a specific interaction between the epithelial cells of the ureteric bud and the undifferentiated metanephric mesenchyme. Such interaction is crucial for the differentiation of the mesenchyme and the induction of branching division of the ureteric bud. The ureteric bud branches will evolve into the collecting system (collecting ducts and urinary tract), while the metanephric mesenchyme epithelial transformation will form the nephrons, including the glomeruli, the proximal and distal tubules, and the loop of Henle. The nephrons develop in successive stages from the inner to the outer area of the fetal kidney, in parallel with the vascular system. In humans, nephrogenesis is usually completed by the thirty-sixth week of gestation.[5,6] About 60% of the nephrons develop during the third trimester of gestation, a process that usually continues *ex utero* in preterm infants.[7] Maturation of glomerular filtration and the tubular functions occurs in parallel with the progression of renal growth and nephrogenesis.

During intrauterine life, the homeostasis of the fetus is principally maintained by the placenta. Urine formation, the main constituent of amniotic fluid during the third trimester, begins by 12 weeks of gestation. During fetal life, renal blood flow is relatively low, because of high renal vascular resistance.[6] A fragile balance between vasoconstricting and vasodilating mediators controls renal vascular tone and, thus, glomerular filtration. The renin angiotensin system (RAS), especially angiotensin II, principally increases the tone of glomerular efferent arterioles, whereas vasodilating prostaglandins counterbalance this effect through their preferential, vasodilating effect on glomerular afferent arterioles. Both contribute to the maintenance of the glomerular filtration rate and participate in the control of the intra-renal distribution of blood flow. In addition to their functional effects, angiotensin II and prostaglandins are involved in the promotion and control of nephrogenesis, along with many factors including transcriptional factors (e.g. the products of paired box gene 2 [PAX-2] and the Wilm's tumour suppressor gene [WT1]), growth factors (insulin-like growth factor, epidermal growth factor, transforming growth factor), oncogens, and extracellular matrix.[8]

Numerous perinatal events or inborn disorders lead to a wide range of renal development disorders during fetal life, including renal hypoplasia and agenesis, collecting system abnormalities, glomerular growth abnormalities, renal dysplasia, tubular dysgenesis, and nephron deficits.[9,10]

The final number of nephrons (on average 1 million per kidney) is defined at birth in the term newborn. This number varies widely among individuals, reflecting the roles of genetic factors and the fetal environment. Several factors can modulate nephrogenesis, including maternal malnutrition, maternal hyperglycaemia, intrauterine growth retardation, vitamin A deficiency, and fetal exposure to drugs.[9] Perinatal events may further alter kidney development and lead to a reduction in the definitive nephron number. It has long been suspected – since the study by Brenner et al.[11] in the 1980s – that a reduced glomerular number, especially when acquired during the perinatal period, is associated with an enhanced risk of arterial hypertension and renal insufficiency in adulthood. The inborn deficit of renal mass induces a significant increase in single nephron glomerular filtration rate within the remaining nephrons, enhanced renal vascular resistance, sodium and water retention, and elevated arterial blood pressure.[11] Such adaptations are aimed at

maintaining renal haemodynamic and glomerular function, as well as the kidney's excretory capability, and may result in an accelerated progression towards glomerulosclerosis, proteinuria, renal insufficiency and hypertension. Interestingly, nephron number deficits (of around 30%) have been observed in growth-restricted human fetuses and also recently in necropsic observations from adult men who presented with essential hypertension.[12,13]

2. NSAIDs and Tocolytic Agents

2.1 Nonselective NSAIDs

It has been established that prostaglandins play a key role in the onset of preterm labour.[14] Since the 1970s, NSAIDs have been used as effective tocolytic agents. Indometacin was the reference medication, delaying delivery for at least 48 hours and for up to 7–10 days.[15] The placenta is readily permeable to indometacin, even during early gestation, allowing for similar maternal and fetal drug concentrations.[16] However, the use of indometacin has been limited by severe fetal and neonatal adverse effects, as well as by an enhanced risk of perinatal death.[17-21] Adverse effects include premature closure of the fetal ductus arteriosus and neonatal pulmonary hypertension, necrotising enterocolitis, intraventricular haemorrhage, and renal failure.[17-19] The incidences of such adverse effects are variable.[22,23]

Cantor et al.[24] reported the first case of severe oligohydramnios that resulted from NSAID administration for rheumatoid arthritis during pregnancy in 1980, and other reports (including from our group) followed.[24,25] Renal effects of *in utero* exposure to NSAIDs vary from transient fetal oligohydramnios, to severe and lethal renal failure in the newborn.[19] Soon after the initiation of indometacin therapy, a reduction of fetal urine production and oligohydramnios occurs.[26] Such effects, which are frequent and mostly transient, have been the basis for the treatment of polyhydramnios using NSAIDs.[27] The incidence and severity of neonatal renal impairment remains debatable.[28,29] Initial controlled trials of indometacin for tocolysis were not designed to clearly assess the incidence of neonatal renal dysfunction.[15] The available information originates essentially from retrospective or observational studies, with an incidence varying from 1.5% to 20%.[20,21] In a retrospective cohort study of 818 pregnancies in which the mother was treated with indometacin for preterm labour, Marpeau et al.[21] reported a rate of neonatal complications of 1.8%, increasing to 13% when indometacin was administered close to delivery. Impairment of renal function, which was severe in many cases, was the most frequent complication (80%). Conflicting data on the incidence of neonatal renal dysfunction result from several factors, including its definition. The criteria chosen to assess neonatal renal function, usually urinary output and serum creatinine concentration, may inaccurately estimate renal dysfunction since endogenous creatinine clearance, serum creatinine levels and urinary output vary according to gestational age, birthweight and postnatal age in days.[7,30,31] When the neonatal glomerular filtration rate (GFR) is assessed via inulin clearance, the gold standard for the measurement of GFR, preterm infants exposed *in utero* to indometacin exhibit abnormal renal function.[32]

Prostaglandins are essential for maintaining perinatal renal blood flow and tubular function.[6] Fetal oliguria principally results from two mechanisms involving both the glomerular and tubular segments. Experimental and human studies show that NSAIDs induce a decrease in fetal GFR (as a consequence of renal blood flow reduction) and increased urinary osmolality.[32-34] Van der Heidjen et al.[32] confirmed such findings in preterm infants born after prenatal exposure to NSAIDs. They noted a reduction of inulin clearance, and free water and osmolar clearances. The latter effect may be due to enhanced

arginine vasopressin levels and activity on renal collector tubules.[34] However, severe renal impairment leading to fetal or neonatal death has also been reported in the literature.[3,25,35,36] Severe renal dysfunction includes profound and persistent oligohydramnios despite withdrawal of indometacin, and severe and prolonged neonatal renal insufficiency with persistent anuria and electrolytic disorders requiring prolonged peritoneal dialysis. The risk of neonatal renal failure seems to be increased by prolonged and cumulative doses of indometacin, a short time-period between treatment and delivery, pre-existing fetal distress, and low birthweight.[21] Numerous reports have described neonatal renal failure in multiple pregnancies, especially monochorionic twin pregnancies, probably due to an enhanced renal hypoperfusion by the combination of the inhibition of prostaglandin release and alterations of the RAS.[37]

In addition to the changes in renal function, structural alterations of the kidney associated with antenatal exposure to indometacin have been reported. Severe renal hypoperfusion induced by NSAIDs may disturb the development of the fetal kidney and lead to irreversible renal injuries involving the glomerular and tubular segments.[3,36] Histopathological post mortem examination of the kidneys of anuric newborns identified a singular renal nephrotoxicity that was attributable to NSAIDs.[3,36] The kidneys are normal in appearance and size. However, histological examination usually reveals abnormal glomeruli and tubules, with various degrees of ischaemic injury and fibrosis within the medullary area, cortical necrosis, focal tubular and glomerular microcysts in developing nephrons, and loss of differentiation between proximal and distal tubules. Such alterations are associated with increased expression of renin in the juxtaglomerular apparatus.[3,36] These alterations may result from a defect in nephrogenesis due to the inhibition of prostaglandin release, as a reduced renal mass has been reported in rhesus monkeys that have been exposed *in utero* to indometacin.[38]

A peculiar situation occurs with aspirin (acetylsalicylic acid). Aspirin is used in low dosages throughout pregnancy in woman at risk for pre-eclampsia and intrauterine growth retardation.[39] Aspirin is a nonselective NSAID that causes irreversible inhibition of COX-1 and COX-2. Although no fetal or neonatal renal impairment has been observed, administration of aspirin to pregnant rats alters the fetal kidney at an ultra-structural level.[40]

2.2 Selective Cyclo-Oxygenase-2 Inhibitors

The prostaglandin endoperoxide G/H synthases (PGHS), which include the cyclo-oxygenases (COX), are involved in the conversion of membrane bound arachidonic acid into prostaglandins. Prostaglandins are produced in many organs, especially the placenta, the fetal membranes and the fetus.[41] Three enzyme isoforms have been isolated; type-1, type 2 (PGHS-1 or COX-1, and PGHS-2 or COX-2) and recently a third type. The third COX isoform – a splice variant of COX-1 called COX-3 – has been shown to be involved in the analgesic and anti-inflammatory effects of certain drugs such as paracetamol (acetaminophen) and other NSAIDs.[42,43] In contrast to COX-1 and COX-2, the location and activity of COX-3 in the placenta, fetal membranes and the fetus, in particular the fetal kidney, have not yet been studied. COX-1 is a constitutive enzyme, with stable expression throughout gestation.[41,44] It is responsible for the undesirable effects of the nonselective NSAIDs, especially gastrointestinal haemorrhage. In contrast, COX-2 expression is induced by pathological conditions such as inflammatory diseases or cancer.[45] During pregnancy, COX-2 is involved in the onset of labour; its activity increases progressively throughout gestation.[46] Thus, the use of selective inhibitors of COX-2, which are recent-generation NSAIDs, has been proposed to prevent preterm de-

livery with the expectation of fewer fetal and maternal adverse effects than would be seen in patients receiving nonselective NSAIDs.

In fact, COX-2 is constitutively expressed in the fetal kidney and appears to be essential for its development and function. In human and animal (rodent) fetuses, the expression and activity of COX-2 are intense and follow the maturation and formation of nephrons.[47,48] The activity and expression of COX-2 predominantly occur in the *macula densa* and the thick ascending limb of Henle. COX-2 knock-out mice exhibit abnormal renal development, including small kidneys, immature glomeruli, dysplastic tubules, medullary hypoplasia, and cortical microcysts.[49-51] The majority of such mice develop renal dysplasia with glomerular and tubular fibrosis, leading to renal insufficiency in adult life, and premature death (at 8 weeks of age).

Three selective COX-2 inhibitors have currently been suggested for the prevention of preterm delivery: sulindac, nimesulide and celecoxib. Sulindac and nimesulide are, respectively, 16- and 25-fold more selective for COX-2 than indometacin.[52,53] Clinical and pharmacological data concerning the perinatal use of these new drugs are limited. Selective COX-2 inhibitors appear as effective as indometacin in preventing preterm delivery in humans and animals.[14,54-57] No information is available on the transplacental transfer and maternal-fetal pharmacokinetics of nimesulide and celecoxib in humans. However, sulindac, a prodrug, easily crosses the placenta. Its active sulphide metabolite, produced in the liver, can cross the placenta and reach the fetal circulation. Transplacental transfer appears to occur at low rates after a single oral dose of sulindac in pregnant women (gestational range from 24–36 weeks). However, human placental perfusion models suggest that sulindac sulphide, formed through maternal hepatic metabolism of sulindac, may reach the fetus in high concentrations.[58,59] Moreover, fetal ductal constriction has been observed after a short course of sulindac treatment.[56] Adverse fetal effects related to selective exposure to COX-2 inhibitors may thus be observed.

Like indometacin, selective COX-2 inhibitors may cross the placenta and alter the development and function of the fetal kidney.[60-69] Recently, Kömhoff et al.[60] showed, in mice fetuses, that *in utero* exposure to selective COX-2 inhibitors impairs glomerulogenesis (decreases glomerular size) and reduces renal cortical development. Selective COX-2 inhibitors can decrease fetal urine outflow and lead to oligohydramnios.[61-65] This is due to the reduction of the GFR and free water clearance.[66-68] This effect is comparable to that observed after prenatal exposure to indometacin. Indeed, in a small prospective randomised study, 2 days of administration of nimesulide (200mg twice daily), sulindac (200mg twice daily) and indometacin (100mg twice daily) resulted in significant and transient reductions in the amniotic fluid index that appeared to be comparable between the three drugs.[69]

Similar to the situation seen with in-utero exposure to indometacin, neonatal renal failure can occur after prenatal administration of selective COX-2 inhibitors. Six cases of renal failure in newborns exposed in utero to nimesulide have been reported recently.[65,70-75] Nimesulide was prescribed as a tocolytic agent or as an analgesic, over a prolonged period in three cases, throughout the last part of pregnancy.[71-73] Renal biopsies in three infants (on the 20th and 8th and 10th post-natal days, respectively), showed impaired glomerular development, interstitial fibrosis, abnormal tubular differentiation and tubular dysgenesis in the third case.[71,72,75] As with indometacin, the risk of neonatal renal failure due to in utero exposure to selective COX-2 inhibitors is likely to be enhanced by prolonged drug administration, especially throughout the third trimester of pregnancy, and a short time interval to delivery (table I).[14] To our knowledge, no cases of renal failure have been reported in newborns ex-

Table I. Effects of prenatal exposure to nimesulide on the fetal and neonatal kidney

Case report	Duration of exposure (stage of gestation)	Gestational age at birth (weeks)	Neonatal renal failure	Histology
Sawdy et al.[64] (1997)	17wk (16–33wk)	33	–	–
Peruzzi et al.[71] (1999)	6wk (26–32wk)	32	+ (peritoneal dialysis)	Interstitial fibrosis; altered development of glomeruli
Balasubramaniam et al.[72] (2000)	8wk (30–38wk)	At term	+ (peritoneal dialysis)	Interstitial oedema; abnormal tubular differentiation
Landau et al.[70] (1999)	2wk (end of gestation)	At term	+ (transient; maximum creatinine level 210 μmol/L)	–
Paternoster et al.[65] (2003)	25d (28–32wk)	32	Hyperkalaemia	–
Benini et al.[73] (2004)	3mo (4–7mo)	33	+ (transient; maximum creatinine level 165 μmol/L)	–
Magnani et al.[74] (2004)	4wk (30–34wk)	At term	+ (maximum creatinine level 300 μmol/L)	–
Sankari et al.[75] (2006)	Last 2mo	At term	+ (maximum creatinine level 435 μmol/L)	Tubuar dysgenesis
Holmes and Stone[62] (2000)	3wk (24–27wk)	38	–	–
Locatelli et al.[61] (2001)	7d (21–27wk)	24–31	–	–

d = day/s; **mo** = month/s; **wk** = week/s; **+** indicates that renal failure was present; **–** indicates that renal failure was absent.

posed *in utero* to sulindac or celecoxib, but data are insufficient to estimate the real incidence of such complications.

NSAIDs should be avoided during pregnancy, especially during the third trimester beyond 32 weeks gestation. NSAIDs are considered to increase perinatal morbidity and mortality. However, neonatal adverse effects seem to be minimal as long as the duration of treatment is short (<72 hours), the doses are low, and delivery does not occur soon after treatment.[14] Indeed, there is no evidence for continuing tocolytic therapy after effective tocolysis has been achieved, and NSAIDs seem to provide no benefit in preventing the recurrence of preterm labour.[76,77] There is still a need for randomised controlled trials involving selective COX-2 inhibitors or nonselective NSAIDs that are designed to compare specific neonatal renal outcomes and other morbid events, in order to resolve the risk/benefit issue, and to determine the optimal regimen.

2.3 Other Tocolytic Agents

Most tocolytic agents are effective in delaying delivery, but no evidence of their beneficial effects on major neonatal outcomes has been demonstrated in numerous clinical trials. Calcium channel antagonists, β-adrenoceptor agonists, oxytocin antagonists and magnesium sulphate have all been proposed for the prevention of preterm delivery. No specific adverse effects on fetal and neonatal renal functions have been reported in the literature. However, biological modifications of neonatal renal function have been found in preterm infants exposed *in utero* to ritodrine (a β-adrenoceptor agonist), including reduced GFR, increased arginine-vasopressin levels and higher plasma renin activity.[78] Although neonatal renal failure has not been reported, tocolytic drugs that are eliminated via the kidneys should be used with caution.

3. Antihypertensives

Arterial hypertension is found in 5–10% of pregnancies and is a leading cause of maternal and perinatal mortality and morbidity. Approximately one percent of this is accounted for by chronic hypertension, pre-existing to pregnancy.[79] While antihypertensive treatment is needed in severe hypertension, there is no consensus on requirements in

mild to moderate hypertension. A variety of drugs are available for the treatment of hypertension during pregnancy. However, some of them do alter the structure and/or function of the fetal kidney, with potential consequences for neonatal well-being.

3.1 ACE Inhibitors

ACE inhibitors competitively block the conversion of angiotensin I to angiotensin II. They decrease angiotensin II and aldosterone release while also preventing the catabolism of bradykinin. ACE inhibitors decrease systemic blood pressure by reducing systemic vascular resistance. They are effective, widely used antihypertensive agents, especially in women of child-bearing age.[80,81]

When administered during pregnancy, ACE inhibitors easily cross the placental barrier, as indicated by comparable plasma concentrations in the maternal blood and umbilical venous cord blood.[82] A variety of serious fetal complications that are associated with a high mortality rate have been reported. Such complications result from the direct pharmacological effects of the ACE inhibitors.[83,84] They comprise a typical fetopathy termed 'ACE inhibitor fetopathy'.[85] Intrauterine growth retardation, marked fetal and neonatal arterial hypotension (refractory to treatment), oligohydramnios, renal failure, limb deformities and pulmonary hypoplasia, hypocalvaria and an increased rate of fetal loss have been reported.[85,86] In contrast, elective exposure during the first trimester of pregnancy is not associated with an enhanced risk of teratogenicity.[87-89]

Since the beginning of the eighties, several authors have reported excess perinatal death in animal offspring exposed *in utero* to ACE inhibitors (captopril or enalapril).[90,91] In 1981, Guignard et al.[92] reported the first death of a newborn exposed *in utero* to captopril, administered in the third trimester for pregnancy-induced hypertension. The newborn presented with renal failure. Following this, numerous cases were reported involving a wide range of adverse effects on the fetal and neonatal kidney, varying from transient oligohydramnios (when treatment was arrested rapidly) to severe (requiring peritoneal dialysis) and lethal renal failure.[83-85,93,94] The magnitude of such adverse renal effects is not precisely quantifiable, but the risks are increased with long-term administration and when fetal exposure occurs during the second and third trimester.[86] When therapy is discontinued before the second trimester, few or no adverse renal effects are observed.[93]

Such adverse renal effects result from structural and functional alterations of the fetal kidney. ACE inhibitor effects on renal development include disruption of medullary tubulogenesis and proximal tubular dysgenesia.[85,95] Upon gross inspection, the kidneys appear normal, but histological examination shows a dilatation of the tubules and Bowman's spaces, diminished or absent differentiation and growth of the proximal tubules, increased medullary mesenchyme, and (in some reports) ischaemic injury. During the fetal and postnatal periods, angiotensin II is essential to maintain fetal systemic haemodynamics and glomerular filtration. Under such circumstances, a prolonged reduction of systemic and renal blood flow, resulting from decreased placental perfusion, fetal hypotension, and alteration of intrarenal haemodynamics, causes an impairment of GFR, and in turn leads to oligohydramnios and neonatal renal failure.[96-98] In addition to this ischaemic aetiology, renal tubular dysgenesis may occur with prolonged RAS inhibition, as a consequence of deprivation from the growth-stimulating effects of the RAS components on tubular development. A similar mechanism may explain the association of renal tubular dysgenesis and hypoplastic skull bones when ACE inhibitors are administered over the long-term.[99]

3.2 Angiotensin II Receptor Type 1 Antagonists

More recently, new RAS inhibitors acting as angiotensin II receptor antagonists have become available. In particular, selective angiotensin II receptor type 1 (AT1-R) antagonists have been proposed as an alternative to ACE inhibitors when adverse effects occur during ACE inhibitor treatment.

Angiotensin II exerts its effects through type 1 and type 2 receptors. Both receptor types are abundant in the human fetal kidney, especially in the glomeruli and proximal tubules.[100] While the AT1-R contributes to the stimulation of growth in the fetal kidney, angiotensin II may induce apoptosis in kidney cells through the AT2-R.[100] Thus, antagonism of the AT1-R stimulates renin and angiotensin II release and potentially results in overactivity of the AT2-R. The molecules used in clinical practice belong to the 'sartans' group (such as losartan and candesartan cilexetil).

Experimental studies, reported in 1995 by Spence et al.,[101] have demonstrated that AT1-R antagonists do cross the placenta, altering systemic and intrarenal haemodynamics, and impairing kidney development, in a fashion similar to that of ACE inhibitors. Administration of the AT1-R antagonist losartan during days 1–12 of postnatal life in the rat (i.e. during late nephrogenesis) has been shown to result in a significant (40%) reduction in the nephron number and the development of arterial hypertension in adulthood.[102]

Few fetal adverse effects of prenatal exposure to selective AT1-R antagonists have been reported in humans (table II). Recently, Saji et al.[103] reported the first case of a fetal toxic effect of losartan. Among the 16 cases of *in utero* AT1-R antagonist exposure reported in the literature,[104-113] four infants presented without any adverse effects at birth,[105,111] the treatment having been stopped before the middle of the second trimester of gestation, while 12 infants experienced severe fetal or neonatal renal failure.[106-110,112,113] Only four of the seven living newborns who exhibited acute renal failure at birth survived.[108,110,112,113] Histological examinations have been performed in a few cases and the findings have been similar to those described for fetal exposure to ACE inhibitors. Martinovic et al.[106] observed that, in addition to tubular dysgenesis, there was a thickening of arterial and arteriolar wall, and a diffuse, abnormal extension of renin expression in the juxtaglomerular apparatus and smooth muscle. No other teratogenic effects were reported. However, a recent report detailed a case of an unilateral renal agenesis with a duplex pelvicalyceal system associated with hypoplastic skull bones in a newborn exposed *in utero* to long-term candesartan cilexetil.[109] A case of neonatal renal failure associated with hypoplastic skull bones (hypocalvaria) has also recently been reported in a patient exposed antenatally to valsartan.[112]

AT1-R antagonists and ACE inhibitors are contraindicated during pregnancy. However, inadvertent first trimester exposure is not considered as a potential indication for termination of pregnancy. Treatment should be discontinued soon after the pregnancy is confirmed, and patients should be switched to other antihypertensive agents.

3.3 Other Antihypertensives

Other antihypertensive agents such as β-adrenoceptor antagonists, methyldopa, calcium channel antagonists, diuretics and hydralazine are frequently used in pregnancies complicated by hypertension.

No adverse effects of other antihypertensives on fetal or neonatal renal functions in humans have been reported in the literature. However, diuretics, especially furosemide (frusemide), may affect renal function. In a series of experiments, fetal exposure to furosemide resulted in disturbances in ionic exchange and the ability to concentrate urine in newborn rats and delayed differentiation of the glomeru-

Table II. Effects of prenatal exposure to specific angiotensin II type 1 receptor (ATR-1) antagonists on the fetal and neonatal kidney

Case report	Drug (dosage)	Gestational age at birth (weeks)	Drug stopped (weeks)	Congenital abnormalities	Histology	Outcome
Saji et al.[103] (2001)	Losartan (50 mg/day)	32	20–31	Oligohydramnios; hypoplastic skull bones	Pulmonary hypoplasia	Stillborn
Lambot et al.[104] (2001)	Losartan (dosage NR)	36	36	Oligohydramnios	Tubular dysgenesis, dilated glomeruli	Neonatal death (day 4)
Hinsberger et al.[110] (2001)	Candesartan cilexetil (7 mg/day)	39	39	Renal failure maximum serum creatinine level 530 μmol/L	–	Surviving
Chung et al.[105] (2001)	Valsartan (80 mg/day)	38	7	–	–	Surviving
	Valsartan (80 mg/day)	38	10	–	–	Surviving
	Valsartan (80 mg/day)	32	18	–	–	Surviving
Martinovic et al.[106] (2001)	Valsartan (80 mg/day)	27	24	Hypoplastic skull bones; anhydramnios	Tubular dysgenesis; enhanced renin expression	Termination of pregnancy
	Valsartan (NR)	32	28	Hypoplastic skull bones; anhydramnios	Tubular dysgenesis; enhanced renin expression	Termination of pregnancy
	Losartan (50 mg/day)	34	34	Severe oligohydramnios	–	Neonatal death (day 4)
Briggs et al.[107] (2001)	Valsartan (NR)	33	24	Anhydramnios	–	Stillborn
Pietrement et al.[108] (2003)	Telmisartan (40 mg/day)	34	34	Oligohydramios; renal failure (maximum serum creatinine level 510 μmol/L)	–	Surviving
Cox et al.[109] (2003)	Candesartan cilexetil (NR)	32	32	Oligohydramios; renal failure with unilateral renal aplasia and abnormal collecting system; hypoplastic skull bones	Tubular dysgenesis	Neonatal death (day 3)
Berkane et al.[111] (2004)	Valsartan (NR)	38	20	–	–	Surviving without renal failure
Vendemmia et al.[112] (2005)	Candesartan cilexetil (16 mg/day)	23	27	Oligohydramnios; face and limb deformities	Bilateral renal dysgenesis	Termination of pregnancy
	Valsartan (12 mg/day)	36	36	Oligohydramnios; face and limb deformities; hypocalvaria	–	Surviving
Bos-Thompson et al.[113] (2005)	Valsartan (80 mg/day)	38	25	Oligohydramnios; face and limb deformities; moderate hypocalvaria	–	Renal failure (maximum serum creatinine level 215 μmol/L). Surviving

NR = not reported; – indicates absence of congenital abnormalities or renal histological examination.

li.[114] In humans, administration of furosemide to pregnant women has been shown to increase fetal urinary output, without significant adverse renal effects in the newborn.[115]

4. Corticosteroids

During fetal development, plasma levels of cortisol are low, lower than levels in the maternal circulation, and they increase near term.[116,117] This is due to low fetal hypothalamic-pituitary axis activity and to placental inactivation of maternal cortisol by type 2 11β-hydroxysteroid dehydrogenase (11β-HSD).[118] The activity of this enzyme decreases when fetal growth retardation or pre-eclampsia occurs, allowing an overexposure of the fetus to maternal corticosteroids.[119-121]

In pregnant women, glucocorticoids are mainly used to accelerate fetal lung maturation when preterm delivery is imminent. In such situations, dexamethasone and betamethasone, both being able to cross the placenta unaltered by the placental 11β-HSD, are commonly used.[122] In other cases, glucocorticoids are prescribed, usually from before the beginning of pregnancy, as immunosuppressive agents in a wide range of immune-mediated or rheumatological disorders, or for the prevention of allograft rejection. Prednisone, prednisolone and methylprednisolone are used in such situations. Such non-fluorinated corticosteroids are metabolised by the placenta, and concentrations in the fetal plasma are around 10-fold lower than those in the maternal circulation.[123]

It has long been known that prolonged administration of glucocorticoids during gestation, both in animals and humans, leads to fetal growth retardation.[124-126] Although conflicting results exist in the literature regarding the effects of prenatal betamethasone or dexamethasone on fetal growth, both treatments, especially repeated courses of such, seem to increase the risk of reduced birthweight.[127]

In utero exposure to glucocorticoids affects the development of the kidney and influences its maturation. Glucocorticoids are known to have profound effects on cell proliferation, differentiation-maturation, and cell death. The literature is limited regarding the effects of antenatal corticosteroids on fetal renal development. *In vitro* exposure to a corticosteroid (hydrocortisone) in mouse metanephric organ culture alters renal development and leads to cyst formation.[128] The administration of dexamethasone (0.1 mg/kg/day) to pregnant rats from the start of gestation, is associated with reduced birthweight, nephron deficit (60% in 20 day-old rat), a lower GFR, and elevated blood pressure as adults in the offspring.[129] Ortiz et al.[130] demonstrated that even a short duration of prenatal dexamethasone administration (0.2 mg/kg/day for 2 days) at gestational days 15–16 and 17–18 reduced the glomerular number in the adult rat by 30% and led to hypertension, without significantly affecting the birthweight. These results have been confirmed in fetal sheep.[131] This 'critical window' corresponds to an early stage of kidney development in both species. The mechanism by which glucocorticoids alter the fetal kidney structure is unclear. Several pathways have been postulated. *In utero* exposure to glucocorticoids may: (i) alter the cell differentiation/proliferation ratio towards reduced proliferation; (ii) reduce ureteric bud branching; (iii) alter the gene expression of different factors involved in kidney development; or (iv) affect nephrogenesis by inducing a state of gestational diabetes in the mother leading to fetal overexposure to glucose.[9] Interaction with the RAS is another suspected mechanism. Indeed, cortisol administration to normal sheep fetuses reduces AT1-R and renin gene expression.[132] Hence, exogenous glucocorticoids, at a specific time of kidney development, may affect the RAS and in turn lead to a nephron deficit. In humans, a case of renal hypoplasia with the presence of cysts was reported in an infant exposed *in utero* to both dexamethasone and

gentamicin.[133] However, this clinical case alone and the unusual drug combination do not allow any definite conclusions. Little information is available regarding long-lasting adverse effects of prenatal glucocorticoid exposure on renal function in humans and their association with cardiovascular complications in adulthood. The few outcome studies that have evaluated the long-term effects of prenatal administration of dexamethasone for congenital adrenal hyperplasia have not shown any significant adverse effects.[134] However, the follow-up period is currently too short to draw definitive conclusions. Recently, a relationship between exposure to dexamethasone in the last trimester and elevated blood pressure during adolescence has been suggested.[135] Further studies are needed to confirm such findings.

In addition to inducing structural changes, prenatal administration of glucocorticoids has a maturational effect on fetal and neonatal renal function.[136] When administered during pregnancy to enhance fetal lung maturation, dexamethasone and betamethasone have been shown to have positive effects on GFR and tubular function and to improve systemic haemodynamics in newborn infants.[136,137] Administration of dexamethasone 48 hours before delivery increases GFR (assessed by endogenous creatinine clearance) and sodium reabsorption during the first two postnatal weeks.[138] The mechanism of action of glucocorticoids on the fetal and neonatal kidney remains unclear and appears to involve both direct and indirect effects. Van den Anker et al.[139] reported an improvement in the GFR of preterm infants exposed *in utero* to dexamethasone and indometacin just before birth. Such findings suggest a vasodilatory action of glucocorticoids on the glomerular microvessels (afferent and efferent arterioles), with an increase in the functional glomerular surface area. Such changes, as observed in animal studies, lead in turn to improvement in renal blood flow and, therefore, in the GFR.[140-142] Moreover, glucocorticoids have a direct effect on tubular function that includes increasing the activity of Na^+/K^+ adenosine triphosphatase and increasing the expression and activity of tubular ionic transporters, resulting in decreased urinary sodium excretion and increased urinary flow.[143-145]

Such favourable effects on the GFR and tubular functions are partially attributable to an improvement in the cardiovascular status and mean arterial pressure. This effect is mediated by the actions of the glucocorticoids on sodium metabolism, renal sympathetic nerve activity and vascular sensitivity to angiotensin II.[146,147] Premature infants exposed *in utero* to corticosteroids need less blood pressure support and experienced less hyperkalaemia than infants who were not exposed.[148,149]

5. Antineoplastic and Immunosuppressive Drugs

5.1 Antineoplastic Drugs

Cancer complicates approximately 1 in 1000 pregnancies.[150] Breast, haematological and gynaecological cancers are the more frequently observed cancers during pregnancy.

There are no large trials evaluating the effects of chemotherapy on fetal development, and the available data derives, essentially, from case reports and small observational case series. Antineoplastic drugs interfere with cell division and growth through various mechanisms. Such drugs may alter DNA, RNA or protein synthesis, leading to cell death. Many drugs are nonspecific and produce varying degrees of deleterious effects in normal tissues, especially those characterised by rapid cell division and a high rate of differentiation. Such a state is also seen in the fetus and such agents could potentially affect the development of various organs.

Few data are available regarding the placental transfer and fetal pharmacology of antineoplastic

drugs in humans. Animal studies confirm, however, that transplacental transfer occurs.[151-156]

Fetal complications may depend on the choice, timing and dosage of antineoplastic agents, as well as on the duration of therapy and drug combinations used. Early miscarriage and congenital malformations occur more frequently when antineoplastic drugs, especially alkylating and antimetabolite agents, are administered during the first trimester.[157] The incidence of congenital malformations varies from 7% to 17%. An abnormal renal collecting system has been reported in an infant born after *in utero* exposure to cyclophosphamide administered for the treatment of maternal leukaemia.[158] Similarly, a few reports describe an association between *in utero* exposure to vincristine, chlorambucil, busulfan, or fluorouracil and organ abnormalities, including renal and ureteral maldevelopment.[159] When such drugs are administered during the second and third trimesters, enhanced risks of preterm birth, low birthweight and intrauterine growth restriction, haematological disorders such as myelosuppression, and stillbirth have been reported.[160-163] Intrauterine growth retardation may result from the combination of direct drug toxicity and alterations in maternal nutritional status. Scant data exist regarding the effects of antineoplastic drugs on the fetal kidney, either in humans or in animals. In pregnant rats, cisplatin exposure has been shown to induce mitochondrial damage in the fetal kidney.[164] No adverse renal effects during the neonatal period, or later in adult life, have been reported in the literature on antineoplastic drugs in humans. However, long-term follow-up is important in such children, since *in utero* exposure to antineoplastic agents may affect fetal growth and organogenesis and may predispose to later disorders such as malignancies, sterility, or other disorders.[165] Indeed, platinum-DNA adducts have been detected in the cord blood lymphocytes following *in utero* carboplatin exposure in the children of women receiving treatment for ovarian carcinoma.[166] Their presence, which indicates fetal tissue exposure, necessitates the long-term follow-up of such children, especially with regard to growth and renal function.

New anticancer therapies that block the action of growth factors are now in clinical trials. No information is yet available about their effects in human pregnancy, especially their effects on fetal growth and organogenesis.[1] More information is needed to safely permit their use during pregnancy.

5.2 Immunosuppressive Drugs

For the past few decades, the number of pregnancies in patients receiving immunosuppressive drugs has increased. Immunosuppressive drugs are prescribed for reasons such as the prevention of organ or tissue graft rejection and the treatment of various autoimmune and rheumatic diseases. These drugs are required to control maternal disease, as well as to ensure a successful pregnancy outcome. Corticosteroids, calcineurin inhibitors, purine metabolism inhibitors, monoclonal antibodies, cytotoxic agents (alkylating agents and methotrexate) and other drugs prescribed for other anti-inflammatory agents (gold, D-penicillamine, antimalarials, or sulphasalazine, NSAIDs) may be administered in such conditions.[2,167] They cross the placental barrier to varying degrees, but few studies have evaluated their transplacental transfer in human pregnancy.[167-170]

Pregnancies in women being treated with immunosuppressive drugs are characterised by a higher incidence of maternal and obstetric complications, such as pre-eclampsia, gestational diabetes, preterm rupture of the membranes, and fetal loss. The incidence of prematurity (range: 15–65%), intrauterine growth restriction and, thus, neonatal morbidity is higher than in the general population.[2,151,167,170-174] Such observations may be explained by factors including maternal disease and obstetric complica-

tions, maternal nutrition status, and direct fetal drug toxicity.

Few human data regarding the fetal renal effects of immunosuppressive drugs are available. No major fetal and neonatal renal adverse effects have been reported in the literature.[169] A few drugs, such as the calcineurin inhibitors, and tacrolimus and chlorambucil, have been demonstrated to potentially affect renal development.[175,176]

5.2.1 Ciclosporin

Ciclosporin is a calcineurin inhibitor. Calcineurin is an enzyme in helper T lymphocytes. It participates in the transcription of genes coding for cytokines, and interferes with T-cell proliferation.[177] Ciclosporin passively crosses the placental barrier to varying degrees.[178,179] When administered to pregnant women, ciclosporin is associated with preeclampsia and intrauterine growth restriction.[172] The nephrotoxicity of ciclosporin is well documented in the adult, but few data exist regarding its effects on the fetus. In animal studies (rabbit), administration of ciclosporin during gestation (gestational days 14 to 18 and 20 to 24) affected fetal growth and nephrogenesis leading to a permanent nephron deficit (average of 25–30%).[176] Merlet-Benichou et al.[9] found, in rat metanephric organ cultures, that ciclosporin alters nephrogenesis by arresting nephron formation. The authors suggested a possible prevention of the conversion of the metanephric mesenchyme into epithelium. In humans, no alteration of renal function in newborns has been reported. Infants exposed *in utero* to ciclosporin have not shown any abnormalities in renal function and morphology in childhood.[180-182] However, data are still scarce, and the duration of follow-up is insufficient (the maximal age at the end of follow-up was 7 years) to draw definitive conclusions about the occurrence of adverse effects in adulthood.

5.2.2 Tacrolimus

Tacrolimus is a macrolide that is prescribed to prevent graft rejection. It easily crosses the placental barrier, and cord blood concentrations are half those in the maternal blood.[183,184] A small number of publications refer to tacrolimus administration during pregnancy.[184-187] In contrast to ciclosporin, antenatal exposure to tacrolimus is loosely associated with intrauterine growth restriction. However, mild and transient renal dysfunction, such as oliguria in the first 48 hours of postnatal life and hyperkalaemia, have been observed.[187] In a series of 100 pregnancies exposed to tacrolimus, the incidence of renal dysfunction was about 15%.[187] The underlying mechanisms of these renal effects remain unclear.

5.2.3 Chlorambucil

Chlorambucil is an alkylating agent, used in combination with other drugs for the treatment of various immune-mediated diseases.

This drug has a selective effect on renal development. In pregnant rats, when administered early in gestation, chlorambucil slows both glomerular and tubular development and leads to renal and ureteral hypoplasia.[188] In humans, renal agenesis may occur when this drug is administered during the first trimester of pregnancy.[189]

5.2.4 Other Immunosuppressive Drugs

Few data are available on recent immunosuppressive drugs (basiliximab, daclizumab, sirolimus, leflunomide, tumor necrosis factor (TNF)- antagonists).[1] No abnormal renal functions or morphological alterations associated with exposure to these drugs have been reported in newborn infants. However, close follow-up of pregnant women who receive such drug is essential.

6. Antibacterials

Antibacterials, especially the β-lactams, are widely used during pregnancy, without known adverse fetal and maternal effects.

In utero exposure to antibacterials may impair fetal kidney development in animals. However no abnormalities in renal structure or function have been reported in humans. Two groups of antibacterials have been associated with alterations in fetal kidney development in the literature: these are the aminoglycosides and the β-lactams.

6.1 Aminoglycosides

The nephrotoxic effects of the aminoglycosides on the adult and neonatal kidney are well documented.[190,191] Aminoglycosides are mainly eliminated via glomerular filtration and are reabsorbed in the proximal tubules by a specific receptor localised in the brush border of tubular cells (megalin-mediated endocytosis).[192] The nephrotoxicity of such drugs is linked to their accumulation in the renal cortex, especially in the proximal tubular cells, which is correlated with the duration of exposure, and their action on the metabolism of phospholipids in the cellular lysosomal compartment.[193] This interaction leads to the formation of 'myeloid bodies', which are characteristic of the nephrotoxic effect of the aminoglycosides.[192] Nephrotoxicity seems to depend on the size of the doses, the regimen, the duration of exposure, and the class of aminoglycoside.[192,194,195] Once-daily administration, reduction of doses when renal function is impaired, and shortening the course of therapy may reduce the risk of nephrotoxicity.[192] There is a substantial amount of experimental literature on the effects of gentamicin on the developing kidney. When given to pregnant rats, gentamicin easily crosses the placenta, and concentrates in the kidney tissue.[196] Similarly, transplacental transfer of other amynoglycosides (amikacin and tobramycin) and their accumulation in the fetal kidney has been observed in humans.[197,198] The drug concentration in the fetal kidney of the rat was found to be lower than the concentrations found in human fetuses.[196,199] In pups born to rats that had been exposed to gentamicin (75 mg/kg/day from day 10 to term), the final number of nephrons was reduced by 20% and the kidneys exhibited focal tubular lesions.[195,200] Furthermore, rapid progression of sclerotic glomerular lesions with proteinuria was found in 3-month-old offspring.[201] The nephron number deficit results from a defect in the branching morphogenesis of the ureteric bud, which affects the first branching division.[202] Such a toxic effect corresponds, in fact, to the first stage of renal development, as gentamicin exposure during the late stages of nephrogenesis has not been shown to induce a nephron deficit.[200] Other investigators, using a similar experimental design, have shown a delay of renal maturation with an alteration of the glomerular basement membrane of the juxtamedullary nephron following gentamicin exposure.[203] As in adults, the renal tubules of the fetus are the target of maternally administered aminoglycosides in animals. Structural changes, as described in adults, and tubular dysfunction have been observed in newborn pups exposed prenatally to gentamicin.[201,204] Amikacin and netilmicin have less severe renal effects than gentamicin.[199] Tobramycin, another aminoglycoside, may alter renal organogenesis in the rat by a different pathway. *In utero* exposure to tobramycin (30–60 mg/kg/day) during the early stages of nephrogenesis (within gestational days 10–19) leads to a disruption of the maturation of the proximal tubules.[205]

Recently, Locksmith et al.[206] showed that a single administration of high-dose gentamicin during pregnancy was associated with no additional neonatal adverse effects compared with conventional treatment. In this study, fetal serum peak levels of gentamicin were closer to the optimal neonatal values observed in the literature. Interestingly, other

authors have demonstrated that newborn infants receiving aminoglycosides display an elevation in urinary markers of tubular damage, without a significant alteration of GFR.[207,208] Renal abnormalities such renal hypoplasia with cysts and bilateral hydronephrosis have been reported in newborn infants exposed *in utero* to gentamicin.[133,209]

6.2 β-Lactams

The aminopenicillins and a third-generation cephalosporin, ceftriaxone, have been studied *in vivo* in pregnant rats, and *in vitro* using rat metanephric organ culture.[210]

Both ampicillin and amoxicillin alter kidney development in a dose dependant manner. These drugs easily cross the placental barrier.[211] *In utero* exposure to these antibiotics (100 mg/kg/day for 5 days) during early stage of renal organogenesis (within gestational days 11–15) has been shown to induce a 10% reduction of final nephron number in pups and to cause cystic tubule dilatation and interstitial inflammation in the cortex area. An increased rate of apoptosis in the mesenchyme area is the event that is suspected to lead to oligonephronia.[210]

In contrast, prenatal administration of ceftriaxone (50–500 mg/kg/day) to pregnant rats has no effect on the fetal nephron number, but causes interstitial inflammation affecting the medullary area.[210]

7. Neonatal Management

The main function of the kidneys is regulation of the volume and composition of extracellular fluid. Alteration of this regulation may occur when glomerular and/or tubular functions are impaired. A newborn infant with a GFR of around 20 mL/min/1.73m^2 body surface area, which would correspond to a state of severe renal failure in an adult, can be considered to be in a state of 'physiological renal insufficiency'. The renal function of newborns whose mothers are treated with drugs has to be carefully evaluated during the first days of life, since the severity of neonatal renal failure varies widely. Antenatally, the suspicion of severe neonatal renal failure should be high when oligohydramnios is present.

Daily urinary output, systemic blood pressure, cardiac and respiratory rates, ECG parameters, neurological parameters, glycaemia, blood gases, plasma and urine biochemical parameters and fluid intake must be carefully monitored. Laboratory parameters should be assessed within the first 2 days of life and repeated according to their clinical evolution. An ultrasonographic examination of the kidneys and urinary tract with renal artery perfusion assessment by Doppler ultrasound is useful for evaluating renal morphology, corticomedullary differentiation, and renal perfusion.

Renal failure is usually considered in neonates whose plasma creatinine levels are higher than 1.5 mg/dL (about 130 μmol/L) for at least 48 hours. However, the postnatal evolution of plasma creatinine levels in normal newborns is characterised by an increase during the first 24–48 hours, followed by a progressive decrease during the first 2–3 postnatal weeks (depending on gestational age). Plasma creatinine levels are higher in preterm and low birthweight infants, compared with term newborns. In extremely premature infants, the initial increase in plasma creatinine levels continues throughout the first week of life. Oliguria (defined as a urinary output <1 mL/kg/h), oedema and systemic hypertension are commonly observed in neonatal renal failure.[212] However, polyuria (urinary output >3 mL/kg/h) with dehydration may occur in association with dysnatraemia and hypokalaemia.[212] The typical changes in plasma biochemical values observed in renal failure are summarised in table III. Hyponatraemia is dilutional in oliguric renal failure, and reflects sodium depletion in non-oliguric renal failure. Increased urinary sodium levels (urinary Na^+ >20 mmol/L) and fractional excretion of sodium (FE_{Na} = urinary Na^+ level × plasma creatinine level

Table III. Biochemical parameters required for assessment of renal function in newborns exposed to potentially nephrotoxic drugs, and typical plasma parameters changes associated with renal failure in newborn infants

Biological parameters requiring assessment	Changes in plasma biochemical parameters
Plasma	
sodium, potassium, chloride, creatinine, urea, albumin, calcium, phosphorus, uric acid, bicarbonate, magnesium, osmolarity and cystatin C levels	Increase in creatinine, urea, uric acid, phosphorus, potassium Decreases in bicarbonate, calcium and magnesium levels
Urine	
sodium, potassium, chloride, creatinine, urea, albumin, calcium, phosphorus, density and osmolality, β2-microglobulin, NAG and GGT levels	Increase or decrease in sodium levels
Measurement of blood and urinary pH	

GGT = γ glutamyl transferase activity (marker of tubular damages); **NAG** = N-acetyl-β-D glucosaminidase activity (marker of tubular damages).

× 100 / serum Na^+ level × urinary creatinine level), a low urinary osmolality and density, and a decreased urine/plasma urea ratio (<10) reflect the inability of the damaged tubules to modify the glomerular filtrate.[212]

Conservative management is sufficient in most cases of neonatal renal failure. Meticulous attention to fluid and electrolyte balance is essential, and fluid and electrolyte intake must be adapted to diuresis and biological parameters. The aims of treatment are to maintain fluid balance and homeostasis, and to avoid or correct metabolic complications such as hyperkalaemia, metabolic acidosis, hypocalcaemia and hypermagnesaemia (which may enhance the cardiac toxicity of hyperkalaemia). Nutritional support, by enteral and/or parenteral nutrition if needed, is essential in order to promote anabolism and prevent catabolism. Drugs with pharmacokinetic profiles that are likely to being affected by alterations in renal function have to be prescribed accordingly. When conservative management fails to control complications (volume overload, systemic hypertension, congestive cardiac failure, severe hyponatraemia, hyperkalaemia, metabolic acidosis), renal replacement therapy is indicated. Peritoneal dialysis and haemo(dia)filtration techniques can be used in accordance with the required rapidity and intensity of extrarenal depuration, and the available resources.

8. Conclusion

The number of pregnant women and women of childbearing age who are receiving drugs is constantly increasing. Drugs may cross the placenta and can alter the function and/or structure of the fetal kidney. The newborn infant may in turn exhibit renal failure and be at increased risk of neonatal death. Selective COX-2 inhibitors and nonselective NSAIDs, and ACE inhibitors and AT1-R antagonists are the main drugs affecting the development and function of perinatal kidney.

The effects of maternally administered drugs on the fetal and neonatal kidney depend on factors such as their pharmacological class, its transplacental transfer, the cumulative dose used, the timing of the administration with relation to the pregnancy, and the fetal status. Few data are available regarding the pharmacological characteristics of drugs used during human pregnancy; most information originates from animal experiments (in rodents especially). Further human pharmacological studies and prospective trials need to be performed in order to assess risk/benefit ratios, and to evaluate the incidence of adverse renal effects. Moreover, efforts are needed to register any potential adverse effects of maternally administered drugs on the fetus and neonate and to disseminate this information, as cases of severe renal failure in neonates exposed to drugs

that are known to affect the perinatal kidney are still being reported.

In a number of cases, newborn infants who have been exposed *in utero* to drugs that may potentially affect renal function do not exhibit clinical renal failure in their first postnatal days. However, experimental studies suggest that prenatal exposure to certain drugs – such as glucocorticoids, immunosuppressive and antineoplastic agents, aminoglycosides, and drugs interfering with prostaglandin release and the RAS – may lead to chronic renal deficiency and hypertension in adulthood. Such long-term effects are associated with abnormalities in renal development and reduced nephron numbers. Care is needed when extrapolating data from animal studies to humans, since there are major interspecies differences in renal sensitivity to drugs; thus, long-term follow-up of infants exposed *in utero* to potentially nephrotoxic drugs is needed.

Acknowledgements

The authors would like to warmly thank Rodolfo and Paola Giniger for their contribution to the illustration of the manuscript.

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the contents of this review.

References

1. Kimberly KL. Chemotherapy and pregnancy. Clin Obstet Gynecol 2002; 45: 153-64
2. Ostensen M. Rheumatological disorders. Best Pract Res Clin Gynecol 2001; 15: 953-69
3. Van der Heijden BJ, Carlus C, Narcy F, et al. Persistent anuria, neonatal death, and renal microcystic lesions after prenatal exposure to indomethacin. Am J Obstet Gynecol 1994; 171: 617-23
4. Pryde PG, Sedman AB, Nugent CE, et al. Angiotensin-converting enzyme inhibitor fetopathy. J Am Soc Nephrol 1993; 3: 1575-82
5. Woolf A. The kidney: embryology. In: Barratt TM, Avner ED, Harmon WE, editors. Pediatric nephrology. 4th ed. Baltimore (MD): Williams & Wilkins, 1999: 1-19
6. Guillery EN, Nuyt AM, Robillard JE. Functional development of the kidney in utero. In: Polin R, Fox W, editors. Fetal and neonatal physiology. 2nd ed. Philadelphia (PA): WB Saunders & Company, 1998: 1560-73
7. Gallini F, Laggio L, Romagnoli C. Progression of renal function in preterm neonates with gestational age ≤32 weeks. Pediatr Nephrol 2000; 15: 119-24
8. Burrow CR. Regulatory molecules in kidney development. Pediatr Nephrol 2000; 14: 240-53
9. Merlet-Benichou C, Gilbert T, Vilar J, et al. Nephron number: variability is the rule. Causes and consequences. Lab Invest 1999; 79: 515-26
10. Woolf AS. A molecular and genetic view of human kidney and urinary tract malformation. Kidney Int 2000; 500-12
11. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure: less of one, more of the other. Am J Hypertens 1988; 1: 335-47
12. Hinchliffe SA, Lynch MR, Sargent PH, et al. The effect of intrauterine growth retardation on the development of renal nephrons. Br J Obstet Gynaecol 1992; 99: 296-301
13. Keller G, Zimmer G, Gerhard M, et al. Nephron number in patients with primary hypertension. N Engl J Med 2003; 348: 101-8
14. Loudou JA, Groom KM, Bennett PR. Prostaglandin inhibitors in preterm labour. Best Pract Res Clin Obstet Gynaecol 2003; 17: 731-44
15. Keirse M. Indomethacin tocolysis in preterm labour. In: Enkin M, Keirse M, Renfrew M, Neilson J, editors. Pregnancy and children module of the Cochrane Database of Systematic reviews. London: BMJ Publishing Group. Oxford: Cochrane Collaboration 1995: 04383
16. Moise KJ, Ou CN, Kirshon B, et al. Placental transfer of indomethacin in the human pregnancy. Am J Obstet Gynecol 1990; 162: 549-54
17. Norton M, Merrill J, Cooper B, et al. Neonatal complications after the administration of indomethacin for preterm labor. N Engl J Med 1993; 25: 1603-7
18. Souter D, Harding J, McCowan L, et al. Antenatal indomethacin: adverse fetal effects confirmed. Aust N Z J Obstet Gynaecol 1998; 38: 11-6
19. Cuzzolin L, Dal Cere M, Fanos V. NSAID-induced nephrotoxicity from the fetus to the child. Drug Saf 2001; 24: 9-18
20. Jacqz-Aigrain E, Guillonneau M, Boissinot C, et al. Maternal and neonatal effects of indomethacin during pregnancy: a study of 18 cases. Arch Fr Pediatr 1993; 50: 307-12
21. Marpeau L, Bouillie J, Barrat J, et al. Obstetrical advantages and perinatal risks of indomethacin: a report of 818 cases. Fetal Diagn Ther 1994; 9: 110-5
22. Vermillon S, Newman R. Recent indomethacin tocolysis is not associated with neonatal complications in preterm infants. Am J Obstet Gynecol 1999; 181: 1083-6
23. Panter K, Hannah M, Amankwa K, et al. The effect of indomethacin tocolysis in preterm labor, perinatal outcome: a randomized placebo-controlled trial. BJOG 1999; 106: 467-73
24. Cantor B, Tyler T, Nelson RM, et al. Oligohydramnios and transient neonatal anuria: a possible association with maternal use of prostaglandin synthetase inhibitors. J Reprod Med 1980, 3

25. Simeoni U, Messer J, Weisburd P, et al. Neonatal renal dysfunction and intrauterine exposure to prostaglandin synthesis inhibitors. Eur J Pediatr 1989; 148: 371-3
26. Kirshon B, Moise KJ, Wasserstrum M, et al. Influence of short-term indomethacin therapy on fetal urine output. Obstet Gynecol 1988; 72: 51-3
27. Cabrol D, Jannet D, Pannier E. Treatment of symptomatic polyhydramnios with indomethacin. Eur J Obstet Gynecol Reprod Biol 1996; 66: 11-5
28. Abbasi S, Gerdes JS, Sehdev HM, et al. Neonatal outcome after exposure to indomethacin in utero: a retrospective case cohort study. Am J Obstet Gynecol 2003; 189: 782-5
29. Butler O'Hara M, D'Angio CT. Risk of persistent renal insufficiency in premature infants following the prenatal use of indomethacin for suppression of preterm labor. J Perinatol 2002; 22: 541-6
30. Bueva A, Guignard JP. Renal function in preterm neonates. Pediatr Res 1994; 36: 572-7
31. Chevalier RL. Developmental renal physiology of the low birth weight preterm-newborn. J Urol 1996; 156: 714-9
32. Van der Heijden AJ, Provoost AP, Nauta J, et al. Renal function impairment in preterm neonates related to intrauterine indomethacin exposure. Pediatr Res 1988; 24: 644-8
33. Walker MPR, Moore TR, Brace RA. Urinary and cardiovascular responses to indomethacin infusion in the ovine fetus. Am J Obstet Gynecol 1992; 167: 834-43
34. Walker MPR, Moore TR, Brace RA. Indomethacin and arginine vasopressin interaction in the fetal kidney: a mechanism of oliguria. Am J Obstet Gynecol 1994; 171: 1234-41
35. Kaplan BS, Restaino I, Raval DS, et al. Renal failure in the neonate associated with in-utero exposure to non-steroidal anti-inflammatory agents. Pediatr Nephrol 1994; 8: 700-4
36. Bernstein J, Werner AL, Verani R. Nonsteroidal anti-inflammatory drug fetal nephrotoxicity. Pediatr Dev Pathol 1998; 1: 153-6
37. Mahieu-Caputo D, Muller F, Joly D, et al. Pathogenesis of twin-twin transfusion syndrome: the renin-angiotensin system hypothesis. Fetal Diagn Ther 2001; 16: 241-4
38. Novy MJ. Effects of indomethacin on labor, fetal oxygenation and fetal development in rhesus monkeys. Adv Prostaglandin Thromboxane Res 1978; 4: 285-300
39. Duley L, Henderson-Smart D, Knight M, et al. Antiplatelet agents for preventing and treating pre-eclampsia and its complications. Cochrane Database Syst Rev 2004; 1: CD004659
40. Espiridiao S, Oliveira-Filho RM, Simoes MJ, et al. Liver and kidney ultrastructural changes caused by acetylsalicylic acid treatment during pregnancy in rats. Exp Obstet Gynecol 2002; 29: 37-9
41. Slater DM, Dennes WJ, Sawdy RJ, et al. Expression of cyclooxygenase types 1 and 2 in human fetal membranes throughout pregnancy. J Mol Endocrinol 1999; 22: 125-30
42. Chandrasekharan NV, Dai H, Roos KL, et al. COX-3 a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci U S A 2002; 99: 1396-31
43. Botting R, Ayoub SS. COX-3 and the mechanism of action of paracetamol/acetaminophen. Prostaglandins Leucot Essent Fatty Acids 2005; 72: 85-7
44. Slater D, Allport V, Bennett P. Changes in the expression of the type 2 but not type 1 cyclooxygenase enzyme in chorion-decidua with the onset of labour. Br J Obstet Gynaecol 1998; 105: 745-88
45. Mazhar D, Ang R, Waxman J. COX inhibitors and breast cancer. Br J Cancer 2006; 13: 346-50
46. Sawdy RJ, Slater DM, Dennes WJ, et al. The roles of the cyclooxygenases types one and two in prostaglandin synthesis in human fetal membranes at term. Placenta 2000; 21: 51-7
47. Khan KNM, Stanfield KM, Dannenberg A, et al. Cyclooxygenase-2 expression in the developing human kidney. Pediatr Dev Pathol 2001; 4: 461-6
48. Kömhoff M, Gröne HJ, Klein T, et al. Localization of cyclooxygenase-1 and 2 in adult and fetal human kidney: implication for renal function. Am J Physiol 1997; 272: F460-8
49. Dinchuk JE, Car BD, Focht RJ, et al. Renal abnormalities and an altered inflammatory response in mice lacking cyclooxygenase 2. Nature 1995; 378: 406-9
50. Morham SG, Langenbach R, Loftin CD, et al. Prostaglandin synthetase-2 gene disruption causes severe renal pathology in the mouse. Cell 1995; 83: 473-82
51. Norwood VF, Morham SG, Smithies O. Postnatal development and progression of renal dysplasia in cyclooxygenase-2 null mice. Kidney Int 2000; 58: 2291-300
52. Warner TD, Giuliano F, Vojnovic I, et al. Nonsteroid drug selectivities for cyclo-oxygenase 1 rather than cyclo-oxygenase 2 are associated with human gastrointestinal toxicity: a full vitro analysis. Proc Natl Acad Sci USA 1999; 96: 7563-8
53. Panara MR, Padovano R, Sciulli MG, et al. Effects of Nimesulide on constitutive and inducible prostanoid biosynthesis in human being. Clin Pharmacol Ther 1998; 63: 672-81
54. Stika CS, Gross GA, Leguizamon G, et al. A prospective randomized safety trial of celecoxib for treatment of preterm labor. Am J Obstet Gynecol 2002; 187: 653-60
55. Carlan SJ, O'Brien WF, O'Leary TD, et al. Randomized comparative trial of indomethacin and sulindac for the treatment of refractory preterm labour. Obstet Gynecol 1992; 79: 223-8
56. Kramer WB, Saade GR, Belfort M, et al. A randomized double-blind study comparing the fetal effects of sulindac to terbutaline during the management of preterm labor. Am J Obstet Gynecol 1999; 180: 396-401
57. Poore KR, Young IR, Hirst JJ. Efficacy of the selective prostaglandin synthetase type 2 inhibitor nimesulide in blocking basal prostaglandin production and delaying glucocorticoid-induced premature labor in sheep. Am J Obstet Gynecol 1999; 180: 1243-53
58. Kramer WB, Saade G, Ou CN, et al. Placental transfer of sulindac and its active sulfide metabolite in humans. Am J Obstet Gynecol 1995; 172: 886-90
59. Lampela ES, Nuuten LH, Ala-Kokko TI, et al. Placental transfer of sulindac, sulindac sulfide, and indomethacin in a human placental perfusion model. Am J Obstet Gynecol 1999; 180: 174-80
60. Kömhoff M, Wang JL, Cheng HF, et al. Cyclooxygenase-2-selective inhibitors impair glomerulogenesis and renal cortical development. Kidney Int 2000; 57: 414-22

61. Locatelli A, Vergani P, Bellini P, et al. Can a cyclo-oxygenase type-2 selective tocolytic agent avoid the fetal side effects of indomethacin. BJOG 2001; 108: 325-6
62. Holmes RP, Stone PR. Severe oligohydramnios induced by cyclooxygenase-2 inhibitor. Obstet Gynecol 2000; 96: 810-1
63. Peek MJ, McCarthy A, Kyle P, et al. Medical amnioreduction with sulindac to reduce cord complications in monoamniotic twins. Am J Obstet Gynecol 1997; 176: 334-6
64. Sawdy R, Slater D, Fisk N, et al. Use of cyclo-oxygenase type-2 selective non-steroidal anti-inflammatory agent to prevent preterm delivery. Lancet 1997; 350: 265-6
65. Paternoster DM, Snijders D, Manganelli F, et al. Anhydramnios and maternal thrombocytopenia after prolonged use of nimesulide. Eur J Obstet Gynecol Reprod Biol 2003; 108: 97-8
66. Khan KN, Paulson SK, Verburg KM, et al. Pharmacology of cyclooxygenase-2 inhibition in the kidney. Kidney Int 2002; 61: 1210-9
67. Kajino H, Roman C, Clyman RI. Renal effects of cyclooxygenase-2 inhibition in fetal lambs. Biol Neonate 2002; 82: 257-62
68. Prevot A, Mosig D, Martini S, et al. Nimesulide, a cyclooxygenase-2 preferential inhibitor, impairs renal function in the newborn rabbit. Pediatr Res 2004; 55: 254-60
69. Sawdy RJ, Lye S, Fisk NM, et al. A double-blind randomized study of fetal side effects during and after the short-term maternal administration of indomethacin, sulindac, and nimesulide for the treatment of preterm labor. Am J Obstet Gynecol 2003; 188: 1046-51
70. Landau D, Shelef I, Polacheck H, et al. Perinatal vasoconstrictive renal insufficiency associated with maternal nimesulide use. Am J Perinatol 1999; 16: 441-4
71. Peruzzi L, Gianoglio B, Porcellini MG, et al. Neonatal end-stage renal failure associated with maternal ingestion of cyclo-oxygenase-type 1 selective inhibitor nimesulide as tocolytic. Lancet 1999; 354: 1615
72. Balasubramaniam J. Nimesulide and neonatal renal failure. Lancet 2000; 355: 575
73. Benini D, Fanos V, Cuzzolin L, et al. In utero exposure to nonsteroidal anti-inflammatory drugs: neonatal renal failure. Pediatr Nephrol 2004; 19: 232-4
74. Magnani C, moretti S, et al. Neonatal chronic renal failure associated with maternal ingestion of nimesulide as analgesic. Eur J Obstet Gynecol Reprod Biol 2004; 116: 244-5
75. Sankari V, Khubchandani S, Andaka P, et al. Renal tubular dysgenesis associated with in utero exposure to nimesulide. Pediatr Nephrol 2006; 21: 274-6
76. Humphrey RG, Bartfield MC, Carlan SJ, et al. Sulindac to prevent recurrent preterm labor: a randomized controlled trial. Obstet Gynecol 2001; 98: 555-62
77. D'Ercole C, Bretelle F, Shojai R, et al. Tocolysis: indications and contraindications: when to start and when to stop. J Gynecol Obstet Biol Reprod (Paris) 2002; 31 (7 Suppl.): 84-95
78. Hansen NB, Oh W, La Rochelle F, et al. Effects of maternal ritodrine administration on neonatal renal function. J Pediatr 1983; 103: 774-80
79. Lindberg BS. Epidemiology of hypertension during pregnancy. Int J Technol Assess Health Care 1992; 8 Suppl.: 57-62
80. Williams GH. Converting enzyme inhibitors in the treatment of hypertension. N Engl J Med 1988; 319: 1517-24
81. Magee LA. Treating hypertension in women of child-bearing age and during pregnancy Drug Saf. 2001; 24: 457-74.
82. Tabacova SA, Kimmel CA. Enalapril: pharmacokinetic/dynamic inferences for comparative developmental toxicity: a review. Reprod Toxicol 2001; 15: 467-78
83. Shotan A, Widerhorn J, Hurst A, et al. Risks of angiotensin-converting enzyme inhibition during pregnancy: experimental and clinical evidence, potential mechanisms, and recommendations for use. Am J Med 1994; 96: 451-6
84. Hanssens M, Keirse MJ, Vankelecom F, et al. Fetal and neonatal effects of treatment with angiotensin-converting enzyme inhibitors in pregnancy. Obstet Gynecol 1991; 78: 128-35
85. Pryde PG, Sedman AB, Nugent CE, et al. Angiotensin-converting enzyme inhibitor fetopathy. J Am Soc Nephrol 1993; 3: 1575-82
86. Quan A. Fetopathy associated with exposure to angiotensin inhibitors and angiotensin receptor antagonist. Early Hum Dev 2006; 82: 13-28
87. Lip GYH, Churchill D, Beevers M, et al. Angiotensin-converting enzyme inhibitors in early pregnancy. Lancet 1997; 350: 1446-7
88. Feldkamp M, Jones KM, Ornoy A, et al. Postmarketing surveillance for angiotensin-converting enzyme inhibitor use during the first trimester of pregnancy-United States, Canada, and Israel, 1987-1995. JAMA 1997; 277: 193-4
89. Steffenson FH, Nielsen GL, Sorensen HT, et al. Pregnancy outcome with ACE-inhibitor use in early pregnancy. Lancet 1998; 351: 596-7
90. Brought-Pipkin F, Turner SR, Symonds EM. Possible risk with captopril in pregnancy: some animal data. Lancet 1980; I: 1256
91. Keith IM, Will JA, Weir EK. Captopril: association with fetal death and pulmonary vascular changes in the rabbit. Proc Soc Exp Biol Med 1982; 170: 378-83
92. Guignard JP, Burgener F, Calame A. Persistent anuria in a neonate: a side effect of captopril [abstract]. Int J Pediatr Nephrol 1981; 2: 133
93. Muller PR, James A. Pregnancy with prolonged fetal exposure to an angiotensin-converting enzyme inhibitor. J Perinatol 2002; 22: 582-4
94. Filler G, Wong H, Condello AS, et al. Early dialysis in a neonate with intrauterine lisinopril exposure. Arch Dis Child Fetal Neonatal Ed 2003; 88: F154-6
95. Lasaitiene D, Chen Y, Guron G, et al. Perturbated medullary tubulogenesis in neonatal rat exposed to renin-angiotensin system inhibition. Nephrol Dial Transplant 2003; 18: 2534-41
96. Robillard JE, Weismann DN, Gomez RA, et al. Renal and adrenal responses to converting-enzyme inhibition in fetal and newborn life. Am J Physiol 1983; 244: R249-56
97. Lumbers ER, Burrell JH, Menzies RI, et al. The effects of a converting enzyme inhibitor (captopril) and angiotensin II on fetal renal function. Br J Pharmacol 1993; 110: 821-7
98. Buttar HS. An overview of the influence of ACE inhibitors on fetal-placental circulation and perinatal development. Mol Cell Biochem 1997; 176: 61-71
99. Barr M, Cohen MM. ACE inhibitor fetopathy and hypocalvaria: the kidney-skull connection. Teratology 1991; 44: 485-95

100. Wolf G. Angiotensin II and tubular development. Nephrol Dial Transplant 2002; 17: 48-51
101. Spence SG, Allen HL, Cukierski MA, et al. Defining the susceptible period of developmental toxicity for the AT1-selective angiotensin II receptor antagonist losartan in rats. Teratology 1995; 51: 367-82
102. Woods LL, Rasch R. Perinatal ANG II programs adult blood pressure, glomerular number and renal function in rats. Am J Physiol 1998; 275: R1593-9
103. Saji H, Yamanaka M, Hagiwara A, et al. Losartan and fetal toxic effects. Lancet 2001; 357: 363
104. Lambot MA, Vermeylen D, Noël JC. Angiotensin II-receptor inhibitors in pregnancy. Lancet 2001; 357: 1619-20
105. Chung NA, Lip GYH, Beevers M, et al. Angiotensin II-receptor inhibitors in pregnancy. Lancet 2001; 357: 1620-1
106. Martinovic J, Benachi A, Laurent N, et al. Fetal toxic effects and angiotensin II-receptor antagonists. Lancet 2001; 358: 241-2
107. Briggs GG, Nageotte MP. Fatal fetal outcome with the combined use of valsartan and atenolol. Ann Pharmacother 2001; 35: 859-61
108. Pietrement C, Malot L, Santerne B, et al. Neonatal acute renal failure secondary to maternal exposure to telmisartan, angiotensin II-receptor antagonist. J Perinatol 2003; 23: 254-5
109. Cox RM, Anderson JM, Cox P. Defective embryogenesis with angiotensin II-receptor antagonists in pregnancy. BJOG 2003; 110: 1038-40
110. Hinsberger A, Wingen AM, Hoyer PF. Angiotensin-II receptors inhibitors in pregnancy. Lancet 2001; 19: 1620
111. Berkane N, Carlier P, Vertraete L, et al. Fetal toxicity of valsartan and possible reversible side effects. Birth defect Res A Clin Mol Teratol 2004; 70: 547-9
112. Vendemmia M, Garcia-Meric P, Rizzotti A, et al. Fetal and neonatal consequences of antenatal exposure to type 1 angiotensin II receptors-antagonists. J Matern Fetal Neonatal Med 2005 Aug; 18 (2): 137-40
113. Bos-Thompson MA, Hillaire-Buys D, Muller F, et al. Fetal toxic effects of angiotensin II receptor antagonists: case report and follow-up. Ann Pharmacother 2005; 39: 157-61
114. Mallie JP, Gerard A, Gerard H. Does the in-utero exposure to furosemide delay the renal maturation? Pediatr Pharmacol 1985; 5: 131-8
115. Guignard JP, Gouyon JB. Adverse effects of drugs on the immature kidney. Biol Neonate 1988; 53: 243-52
116. Klemcke HG. Placental metabolism of cortisol at mid- and late gestation in swine. Biol Reprod 1995, 53: 1293-301
117. Beitins IZ, Bayard F, Ances IG, et al. The metabolic clearance rate, blood production, interconversion and transplacental passage of cortisol and cortisone in pregnancy near term. Pediatr Res 1973; 7: 509-19
118. Benediktson R, Calder AA, Edwards CRW, et al. Placental 11β-hydroxysteroid dehydrogenase type 2 is the placental barrier to maternal glucocorticoids: ex vivo studies. Clin Endocrinol 1997; 46: 161-6
119. Stewart PM, Rogerson FM, Masson JI. Type II 11β-hydroxysteroid dehydrogenase messenger RNA and activity in human placenta and fetal membranes-its relationship to birth weight and putative role in fetal adrenal steroidogenesis. J Clin Endocrinol Metab 1995; 80: 885-90
120. McTernan CL, Draper N, Nicholson H, et al. Reduced placental 11β-hydroxysteroid dehydrogenase type 2 mRNA levels in human pregnancies complicated by intrauterine growth restriction: an analysis of possible mechanisms. J Clin Endocrinol Metab 2001; 86: 4979-83
121. Kajantie E, Dunkel L, Turpeinen U, et al. Placenta 11β-hydroxysteroid dehydrogenase-2 and fetal cortisol/cortisone shuttle in small preterm infants. J Clin Endocrinol Metab 2003; 88: 493-500
122. Brown RW, Chapman KE, Kotelevtsev Y, et al. Cloning and production of antisera to human placental 11 beta-hydroxysteroid dehydrogenase type 2. Biochem J 1996; 313: 1007-17
123. Betins IZ, Bayard F, Ances IG, et al. The transplacental passage of prednisone and prednisolone in pregnancy near term. J Pediatr 1972; 81: 936-45
124. Reinisch JM, Simon NG, Karow WG, et al. Prenatal exposure to prednisone in humans and animals retards intrauterine growth. Science 1978, 8
125. Celsi G, Kistner A, Aizman R, et al. Prenatal dexamethasone causes oligonephronia, sodium retention, and higher blood pressure in the offspring. Pediatr Res 1998; 44: 317-22
126. Benediktsson R, Lindsay RS, Noble J, et al. Glucocorticoid exposure in utero: a new model for adult hypertension. Lancet 1993; 341: 339-41
127. Newnham JP, Moss TJ. Antenatal glucocorticoids and growth: single versus multiple doses in animal and human studies. Semin Neonatol 2001; 6: 285-92
128. Avner ED, Piesco NP, Sweeney WE, et al. Hydrocortisone-induced cystic metanephric maldevelopment in serum free organ culture. Lab Invest 1984; 50: 208-18
129. Celsi G, Kistner A, Aizman R, et al. Prenatal dexamethasone causes oligonephronia, sodium retention, and higher blood pressure in the offspring. Pediatr Res 1998; 44: 317-22
130. Ortiz LA, Quan A, Weinberg A, et al. Effect of prenatal dexamethasone on rat renal development. Kidney Int 2001; 59: 1663-9
131. Wintour EM, Moritz KM, Johnson K, et al. Reduced nephron number in adult sheep hypertensive as a result of prenatal glucocorticoid treatment. J Physiol 2003; 549: 929-35
132. Segar JL, Bedell K, Page WV, et al. Effect of cortisol on gene expression of the renin-angiotensin system in fetal sheep. Pediatr Res 1995; 37: 741-6
133. Hulton SA, Kaplan BS. Renal dysplasia associated with in utero exposure to gentamicin and corticosteroids. Am J Med Genet 1995; 58: 91-3
134. Hughes IA. Congenital adrenal hyperplasia: 21 hydroxylase deficiency in the newborn and during infancy. Semin Reprod Med 2002; 20: 229-42
135. Doyle LW, Ford GW, Davis NM, et al. Antenatal corticosteroid therapy and blood pressure at 14 years of age in preterm children. Clin Sci 2000; 98: 137-42
136. Cattarelli D, Chirico G, Simeoni U. Renal effects of antenatally or postnatally administered steroids. Pediatr Med Chir 2002; 24: 157-62
137. Jahnukainen T, Chen M, Berg U, et al. Antenatal glucocorticoids and renal function after birth. Semin Neonatol 2001; 6: 351-5

138. Al-Dahan J, Stimmler L, Chantler C, et al. The effect of antenatal dexamethasone administration on glomerular filtration rate and renal sodium excretion in premature infants. Pediatr Nephrol 1987; 1: 131-5
139. Van den Anker JN, Hop W, De Groot R, et al. Effects of prenatal exposure to betamethasone and indomethacin on the glomerular filtration rate in the preterm infant. Pediatr Res 1994; 36: 578-81
140. Stonestreet BS, Hansen NB, Laptook AR, et al. Glucocorticoids accelerate renal function maturation in fetal lambs. Early Hum Dev 1983; 8: 331-41
141. Baylis C, Handa R, Sorkin M. Glucocorticoids and control of glomerular filtration rate. Semin Nephrol 1990; 10: 320-9
142. Berry LM, Polk DH, Ikegami M, et al. Preterm newborn lambs renal and cardiovascular responses after fetal or maternal antenatal betamethasone. Am J Physiol 1997; 227: R1972-9
143. Celsi G, Wang ZM, Akusjärvi G, et al. Sensitive periods for glucocorticoid regulation of NA+,K(+)−ATPase mRNA in developing lung and kidney. Pediatr Res 1993; 33: 5-9
144. Guillery EN, Karniski LP, Mathews MS, et al. Role of glucocorticoids in the maturation of renal cortical Na/H exchange activity during fetal life in sheep. Am J Physiol 1995; 268: F710-7
145. Petershack JA, Nagaraja SC, Guillery EN. Role of glucocorticoids in the maturation of renal cortical Na-K ATPase during fetal life in sheep. Am J Physiol 1999; 276: R1825-32
146. Segar J, Lumbers E, Nuyt AM, et al. Effects of antenatal glucocorticoids on sympathetic nerve activity at birth in preterm sheep. Am J Physiol 1998; 274: R160-7
147. Tangalakis K, Lumbers E, Moritz K, et al. Effects of cortisol on blood pressure and vascular reactivity in ovine fetus. Exp Physiol 1992; 77: 709-17
148. Moise A, Wearden M, Kozinetz C, et al. Antenatal steroids are associated with less need for blood pressure support in extremely premature infants. Pediatrics 1995; 95: 845-50
149. Omar SA, DeCristofaro JD, Agarwal BI, et al. Effects of prenatal steroids on potassium balance in extremely low birth weight neonates. Pediatrics 2000; 106: 561-56
150. Waalen J. Pregnancy poses tough questions for cancer treatment. J Natl Cancer Inst 1991; 83: 900-2
151. Boike GM, Deppe G, Young JD, et al. Chemotherapy in a pregnant rat model 1. Mitomycin-C: pregnancy specific kinetics and placental transfer. Gynecol Oncol 1989; 34: 187-90
152. Boike GM, Deppe G, Young JD, et al. Chemotherapy in a pregnant rat model 2. 5-Fluoracil: non-linear kinetics and placental transfer. Gynecol Oncol 1989; 34: 191-4
153. Furr BJ, Jordan VC. The pharmacology and clinical use of Tamoxifen. Pharmacol Ther 1984; 25: 127-205
154. Turchi JJ, Vilasis C. Anthracyclines in the treatment of malignancy in pregnancy. Cancer 1988; 61: 435-40
155. Pascal MJ, Macias RI, Garcia-Del-Pozo J, et al. Enhanced efficiency of the placental barrier to cisplatin through binding to glycocholic acid. Anticancer Res 2001; 21: 2703-7
156. D'Incalci M, De Palo G, Semprini AE. Transplacental passage of cyclophosphamide. Cancer Treat Rep 1982; 8: 1681-2
157. Doll DC, Ringenberg QS, Yarbro JW. Antineoplastic agents and pregnancy. Semin Oncol 1989; 16: 337-46
158. Zemlickis D, Lishner M, Erlich R, et al. Teratogenicity and cardiogenicity in a twin exposed in utero to cyclophosphamide. Teratog Carcinog Mutagen 1993; 13: 139-43
159. Zemlickis D, Lishner M, Degendorfer P, et al. Fetal outcome after in utero exposure to cancer chemotherapy. Arch Intern Med 1992; 152: 573-6
160. Berry DL, Theriault RL, Holmes FA, et al. Management of breast cancer during pregnancy using a standardized protocol. J Clin Oncol 1999; 17: 855-61
161. Mulvihill JJ, MacKeen EA, Rosner F, et al. Pregnancy outcome in cancer patients; experience in a large cooperative group. Cancer 1987; 60: 1143-50
162. Norgard B, Pedersen L, Fonager K, et al. Azathioprine, mercaptopurine and birth outcome: a population-based cohort study. Aliment Pharmacol Ther 2003; 17: 827-34
163. Reynoso EE, Shepherd FA, Messner HA, et al. Acute leukemia during pregnancy: the Toronto Leukemia Study Group experience with long term follow-up of children exposed in utero to chemotherapeutic agents. J Clin Oncol 1987; 5: 1098-106
164. Gerschenson M, Paik CY, Gaukler EL, et al. Cisplatin exposure induces mitochondrial toxicity in pregnant rats and their fetuses. Reprod Toxicol 2001; 15: 525-31
165. Partridge AH, Garber JE. Long-term outcomes of children exposed to antineoplastic agents in utero. Semin Oncol 2000; 27: 712-26
166. Koc ON, McFee M, Reed E, et al. Detection of platinum-DNA adducts in cord blood lymphocytes following in utero platinum exposure. Eur J Cancer 1994; 30A: 716-7
167. Bermas BL, Hill JA. Effects of immunosuppressive drugs during pregnancy. Arthritis Rheum 1995; 38: 1722-32
168. Saarikoski S, Seppala M. Immunosuppression during pregnancy: transmission of azathioprine and its metabolites from the mother to the fetus. Am J Obstet Gynecol 1973; 115: 1100-6
169. Ramsey-Goldman R, Schilling E. Immunosuppressive drug use during pregnancy. Rheum Dis North Am 1997; 23: 149-67
170. Armenti VT, Moritz MJ, Davison JM. Drug safety issues in pregnancy following transplantation and immunosuppression: effects and outcomes. Drug Saf 1998; 19: 219-32
171. Armenti VT, Wilson GA, Radomski JS, et al. Report from the National Transplantation Pregnancy Registry: outcomes of pregnancy after transplantation. Clin Transpl 1999, 111-9
172. Lamarque V, Leleu MF, Monka C, et al. Analysis of 629 pregnancy outcomes in transplant recipients treated with sandimmun. Transplant Proc 1997; 29: 2480
173. Davison JM. Pregnancy in renal allograft recipients: problems, prognosis and practicabilities. Clin Obstet Gynecol 1994; 8: 501-25
174. Miniero R, Tardivo I, Curtoni ES, et al. Pregnancy after renal transplantation in Italian patients: focus on fetal outcome. J Nephrol 2002; 15: 626-32
175. Prevot A, Martini S, Guignard JP. In utero exposure to immunosuppressive drugs. Biol Neonate 2002; 81: 73-81
176. Tendron A, Decramer S, Justrabo E, et al. Cyclosporine A administration during pregnancy induces a permanent nephron deficit in young rabbits. J Am Soc Nephrol 2003; 14: 3188-96
177. Yamashita M, Katsumata M, Iwashima M, et al. T cell receptor-induced calcineurin activation regulates T helper type 2 cell

development by modifying the interleukin 4 receptor signaling complex. J Exp Med 2000; 191: 1869-79

178. Venkataramanan R, Koneru B, Wang CCP, et al. Cyclosporine and its metabolites in mother and baby. Transplantation 1988; 46: 468-9
179. Claris O, Picaud JC, Brazier JL, et al. Pharmacokinetics of cyclosporine A in 16 newborn infants of renal or cardiac transplant mothers. Dev Pharmacol Ther 1993; 20: 180-5
180. Giudice P, Dubourg L, Hadj-Aïssa A, et al. Renal function of children exposed to cyclosporine in utero. Nephrol Dial Transplant 2000; 15: 1575-9
181. Shaheen FA, Al-Sulaiman MH, Al-Khader AA. Long term nephrotoxicity after exposure to cyclosporine in utero. Transplantation 1993; 56: 224-5
182. Saïd MH, Abokassem A, Hadj-Aïssa A, et al. Renal function of children born to transplanted women under cyclosporine A [abstract]. Pediatr Nephrol 1996; 10: C153
183. Jain A, Venkataramanan R, Fung JJ, et al. Pregnancy after liver transplantation under tacrolimus. Transplantation 1997; 64: 559-65
184. Farley DE, Shelby J, Alexander D, et al. The effect of two new immunosuppressive agents, FK506 and didemnin B, in murine pregnancy. Transplantation 1991; 52: 106-10
185. Jain AB, Reyes J, Marco A, et al. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. Transplantation 2003; 76: 827-32
186. Hou S. Pregnancy in chronic renal insufficiency and end-stage renal disease. Am J Kidney Dis 1999; 33: 235-52
187. Kainz A, Harabacz I, Cowlrick IS, et al. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. Transplantation 2000; 70: 1718-21
188. Kavlock RT, Rehnberg BI, Rogers EH. Chlorambucil induced congenital renal hypoplasia: effects on basal renal function in the developing rat. Toxicology 1986; 40: 247-58
189. Steege JF, Caldwell DS. Renal agenesis after first trimester exposure to chlorambucil. South Med J 1980; 73: 1414-5
190. Appel G. Aminoglycoside nephrotoxicity. Am J Med 1990; 88: 16s-20s
191. Fanos V, Cataldi L. Antibacterial-induced nephrotoxicity in the newborn. Drug Saf 1999; 20: 245-67
192. Nagai J, Takano M. Molecular aspects of renal handling of aminoglycosides and strategies for preventing the nephrotoxicity. Drug Metab Pharmacokinet 2004; 19: 159-70
193. Giuliano RA, Verpooten GA, De Broe ME. The effects of dosing strategy on kidney cortical accumulation of aminoglycosides in rats. Am J Kidney Dis 1986; 8: 297-303
194. Sens MA, Hennigar GR, Hazen-Martin DJ, et al. Cultured human proximal tubule cells as a model for aminoglycoside nephrotoxicity. Ann Clin Lab Sci 1988; 3: 204-14
195. Mallié JP, Gerard H, Gerard A. In utero gentamycin induced nephrotoxicity in rats. Pediatr Pharmacol 1986; 5: 229-39
196. Gilbert T, Lelievre-Pegorier M, Merlet-Benichou C. Immediate and long-term renal effects of fetal exposure to gentamicin. Pediatr Nephrol. 1990 Jul; 4: 445-50
197. Bernard B, Abate M, Thielen PF, et al. Maternal-fetal pharmacological activity of amikacin. J Infect Dis 1977; 135: 925-32
198. Bernard B, Garcia-Cazares SJ, Ballard CA, et al. Tobramycin: maternal-fetal pharmacology. Antimicrob Agents Chemother 1977; 11: 688-94
199. Mallié JP, Coulon G, Billerey C, et al. In utero aminoglycosides-induced nephrotoxicity in the rat. Kidney Int 1988; 33: 36-44
200. Gilbert T, Lelièvre-Pégorier M, Malienou R, et al. Effects of prenatal and postnatal exposure to gentamicin on renal differentiation in the rat. Toxicology 1987; 43: 301-13
201. Gilbert T, Lelievre-Pegorier M, Merlet-Benichou C. Long-term effects of mild oligonephronia induced in utero by gentamicin in the rat. Pediatr Res 1991; 30: 450-6
202. Gilbert T, Gaonach S, Moreau E, et al. Defect of nephrogenesis by gentamicin in rat metanephric organ culture. Lab Invest 1994; 70: 656-66
203. Smaoui H, Mallie JP, Cheignon M, et al. Glomerular alterations in rat neonates after transplacental exposure to gentamicin. Nephron 1991; 59: 626-31
204. Smaoui H, Schaeverbeke M, Mallie JP, et al. Transplacental effects of gentamicin on endocytosis in rat renal proximal tubule cells. Pediatr Nephrol 1994; 8: 447-50
205. Mantovani A, Macri C, Stazi AV, et al. Tobramycin-induced changes in renal histology of fetal and newborn Sprague-Dawley rats. Teratog Carcinog Mutagen 1992; 12: 19-30
206. Locksmith GJ, Chin AJ, Vu T, et al. High compared with standard gentamicin dosing for chorioamnionitis: a comparison of maternal and fetal serum drug levels. Obstet Gynecol 2005; 105: 473-9
207. Gouyon JB, Aujard Y, Abisror A, et al. Urinary excretion of N-acetyl-glucosaminidase and beta-2-microglobulin as early markers of gentamicin nephrotoxicity in neonates. Dev Pharmacol Ther 1987; 10: 145-52
208. Langhendries JP, Mattot M, Francois A, et al. Validity of N-acetyl-beta-D-glucosaminidase (NAG) determination in assessing netilmicin nephrotoxicity in preterm babies. Biol Neonate 1989; 56: 76-82
209. Yaris F, Kesim M, Kadioglu M, et al. Gentamicin use in pregnancy: a renal anomaly. Saudi Med J 2004; 25: 958-9
210. Nathanson S, Moreau E, Merlet-Benichou C, et al. In utero and in vitro exposure to β-lactams impair kidney development in the rat. J Am Soc Nephrol 2000; 11: 874-84
211. Adamkin DH, Marshall E, Weiner LB. The placental transfer of ampicillin. Am J Perinatol 1984; 7: 310-1
212. Gouyon JB, Guignard JP. Management of acute renal failure in newborns. Pediatr Nephrol 2000; 14: 1037-44

Correspondence and offprints: Dr *Umberto Simeoni*, Service de Néonatologie, Hôpital de la Conception, 147 Boulevard Baille, Marseille, 13005, France.
E-mail: umberto.simeoni@ap-hm.fr