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# Maternal, foetal and child consequences of immunosuppressive drugs during pregnancy in women with organ transplant: a review

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## ABSTRACT

Although pregnancy remains exceptional in women after heart, liver or lung transplant, obstetricians and nephrologists are regularly confronted with pregnancy in renal transplant recipients. National and international registries have described the epidemiology of maternal, foetal and neonatal complications, and transplantation societies have published recommendations on the monitoring of these high-risk pregnancies. In this review, we summarize the existing data on maternal and foetal complications of pregnancies in women after renal transplant, especially the management of immunosuppression. We also describe the few available data on the middle- and long-term outcomes of their children who were exposed *in utero* to immunosuppressive drugs.

**Keywords:** chronic kidney disease, epidemiology, kidney transplant, pregnancy

## INTRODUCTION

In women with chronic kidney disease (CKD), fertility is reduced due to hypothalamus–pituitary–ovarian axis dysfunction, which makes the chances of spontaneous pregnancy during dialysis very rare [1, 2]. After kidney transplantation, spontaneous fertility is generally restored in <6 months. After the first successful pregnancy in 1958 [3], pregnancy is not an exceptional event any longer in recipients of a kidney transplant. For instance, in France, at least 1026 women gave birth to a child after kidney transplantation in the last 10 years (data from the Agence de la Biomédecine 2018). The number of pregnancies after organ transplant reported in international registries has been steadily increasing, with a rate of live births >70%, although these pregnancies are at high obstetrical and renal risk (e.g. hypertension, eclampsia, intrauterine growth restriction, preterm delivery) [1, 2].

The current international recommendations stress that pregnancy in transplant recipients requires good planning [3–5]. Scientific societies recommend waiting at least 1 to 2 years after graft and confirmation of the good organ functioning. After kidney transplantation, pregnancy may be envisaged (i) at least 6–12 months after a rejection episode [4, 6, 7]; (ii) when creatinine

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concentration is stable, preferably <133 μmol/L; (iii) in the absence of or with minimal proteinuria (<0.5 g/day); and (iv) when hypertension is well controlled (target blood pressure <135/85 mmHg, according to the last National Institute for Health and Care Excellence clinical guidelines) [8].

Moreover, the immunosuppressive therapy regimen should be switched to drugs that are less toxic for the foetus already before conception. Corticosteroids, azathioprine and calcineurin inhibitors (tacrolimus or cyclosporine) are commonly prescribed during pregnancy. Mycophenolate mofetil and mammalian target of rapamycin inhibitors are contraindicated and should be stopped 6 weeks before contraception interruption [3, 4, 7].

However, pregnancies do not always occur in these optimal conditions. The risk of developing complications is increased in case of chronic hypertension, proteinuria or graft dysfunction before pregnancy. A recent literature review by the Italian Society of Nephrology showed that successful pregnancies are possible also in these non-ideal situations, although reliable data are limited [7]. Moreover, accidental pregnancies can also occur, for instance shortly after organ transplantation. The few reports of successful pregnancies warn against systematic termination, but stress the need for close follow-up. Moreover, the future parents should be fully informed about the risks linked to the foetus' exposure to mycophenolate mofetil, angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists [7].

Each pregnancy in a transplant recipient requires an individualized and multidisciplinary approach to inform the patient about the maternal–foetal and child risks and to ensure the close monitoring of these high-risk pregnancies. Clinical (blood pressure, weight) and laboratory (renal function, proteinuria) parameters should be monitored every 2–4 weeks, and pregnant women should be seen alternately by their obstetrician and nephrologist throughout the pregnancy [4, 5]. Data on children and adults exposed *in utero* to immunosuppressive drugs are limited and more cohort studies are needed to precisely assess the consequences of *in utero* exposure to immunosuppressive drugs and, often, also to other medications, such as antihypertensive drugs. Moreover, such pregnancies are at high risk of intrauterine growth restriction, preeclampsia and premature birth.

In this review, after summarizing the epidemiological data from international registries and the maternal complications, we will describe the available data on the consequences of *in utero* exposure to immunosuppressive drugs before and after birth (i.e. in childhood and young adult life).

## EPIDEMIOLOGICAL DATA

Analysis of several national and international registries allows description of the epidemiology of pregnancies in women with a kidney transplant. The first article was published in 1992 [9]. More recently, the results of the UK [10], Australian/New Zealander [11] and American [12] registries have been published. Finally, a meta-analysis that included 50 studies (2000–10) analysed the features of 4706 pregnancies after kidney transplantation [1]. According to this meta-analysis, 73–79% (up to 91% in the UK registry) of pregnancies after kidney transplant will lead to a live birth [1, 10, 12], compared with 66.7% in the American general population [1]. Moreover, spontaneous miscarriage, medical termination and stillbirth will occur in 12–14, 6–8 and 2.5–3% of pregnancies, respectively. The complication rate seems comparable to that of non-transplanted patients with CKD and similar levels of kidney function impairment [13].

Epidemiological data are also available on pregnancies after transplantation of another organ, although they are less frequent. In women with a liver transplant, the findings of the American [12] and UK [10] registries as well as those of an important case–control study [14] were used to collect information on 650 births and to establish specific recommendations [15]. After heart and lung transplantation, pregnancy remains exceptional. The most important series comes from the American registry with 37 births [12]. Although data are limited, the rate of maternal and foetal complications seems higher than that after transplantation of other organs.

Pregnant transplant-recipient women are at high risk of complications not only because of the graft and chronic treatment with immunosuppressive drugs, but also because of their age and/or concomitant pathologies (e.g. diabetes, hypertension, renal disease, renal malformations) [7].

## FOETAL COMPLICATIONS OF PREGNANCY IN KIDNEY TRANSPLANT RECIPIENTS

Like for maternal complications, foetal complications are difficult to assess because besides the direct consequences of *in utero* exposure to immunosuppressive drugs, many confounding factors, such as maternal age, concomitant pathologies (e.g. diabetes, hypertension, genetic disease, renal malformations), can influence the foetal outcome.

The most frequent complication is preterm delivery, which has several possible aetiologies. About half of pregnant women with a kidney transplant will deliver before 37 weeks of gestation, compared with 12% in the general population [1]. Among them, one-fifth women will deliver before 32 weeks of gestation [2]. The mean gestational age is 36 weeks. Often, preterm delivery is induced and labour is triggered due to a maternal medical condition (hypertension, preeclampsia, kidney function deterioration) or a foetal problem (intrauterine growth restriction, foetal heart rhythm abnormalities, foetal abnormalities detected by Doppler ultrasonography). About 20% of babies present intrauterine growth restriction [4]. The mean birthweight is 2400 g for babies of a transplant mother compared with 3300 in the general population [1]. This is a predictable consequence of preterm delivery, but might also be influenced by other factors linked to organ transplantation, *in utero* exposure to immunosuppressive drugs and/or maternal hypertension.

Concerning congenital anomalies, study populations are often too small to offer enough statistical power. Nevertheless, except for genetic kidney diseases, such as autosomal dominant polycystic kidney disease or congenital abnormalities of the urinary tract [7], pregnancies in transplant recipients treated with azathioprine, corticosteroids or calcineurin inhibitors do not seems to be associated with a major increase of the risk of congenital anomalies in newborns [4, 16, 17]. In a prospective cohort, the rate of congenital anomalies in the foetus was 5% in transplant recipients and 2% in the general population. This difference was not significant [2]. Sporadically, congenital kidney defects have been reported, for instance kidney agenesis in a 26-week foetus that died few hours after delivery and was exposed *in utero* to prednisone, cyclosporine and azathioprine [18], or multicystic dysplastic kidney after maternal treatment with tacrolimus [19].

## IMMUNOSUPPRESSIVE THERAPY DURING PREGNANCY

During and just before pregnancy, immunosuppression management is a challenge for the transplant specialist who must

try to control the risk of graft rejection, preserve the anti-infection immunity to limit the occurrence of maternal–foetal infections, and also protect the foetus from the toxicity and teratogenicity of the used drugs. As the immunosuppressive therapy cannot be interrupted during pregnancy, it often relies on the association of corticosteroids at low dose, azathioprine and/or calcineurin inhibitors. Nevertheless, the safety of these compounds for the foetus is based on low-level evidence and essentially on experience [4, 20]. Prednisone [21], azathioprine, cyclosporine [22] and tacrolimus [23, 24] have been detected in breast milk, but in small concentrations. Therefore, recommendations have evolved in recent years, and today many transplant programmes recommend breast feeding [25]. The foetal consequences of the exposure to immunosuppressive therapy are detailed in the following paragraphs. Complementary data are available in online databases, such as Reprotox (https://reprotox.org).

## Corticosteroids

The limited trans-placental passage of prednisolone, about 10% of the maternal concentration [20], is explained by the fact that it is catalysed by the placental 11-beta-hydroxysteroid dehydrogenase [26]. Recent epidemiological data come essentially from the short-term use of corticosteroids for foetal lung maturation, at high dose, at the end of pregnancy. In the 1970s, when low-dose prednisone was used chronically for infertility treatment, birthweight was significantly lower in the prednisone than in the control group [27]. The risk of malformations seems to be comparable to that in the general population [28]. Some cases of transient corticotropin deficiency [21, 29] and thymic hypoplasia [30] have been described. Moreover, the risk of gestational diabetes and premature rupture of membranes might be increased [7]. In the mouse, birthweight is significantly lower in the group exposed to corticosteroids, at low and also at high dose, and the risk of cleft palate is high [21]. This has never been reported in humans. Consequently, corticosteroids can be used, including for bolus injection.

## Azathioprine

Azathioprine metabolism is complex and leads to the production of many metabolites. The trans-placental passage of azathioprine and its first metabolite is low, 1–5% and 1–2% of the maternal concentration, respectively, and foetal liver does not synthesize the enzyme needed for its activation [3, 22]. The three toxic metabolites do not cross the placental barrier and are not found in umbilical cord blood. Only 6-thioguanine nucleotides, known for their blood toxicity, cross the placental barrier (22–91% of the maternal concentration) [31]. Clinical data come from cohorts of transplant recipients, but also from women with systemic lupus erythematosus or inflammatory intestinal diseases. The frequency of congenital anomalies varies from 0 to 11.8% in the different studies, without any description of a recurrent pattern of malformations [32]. In similar comparisons, birthweight is higher after *in utero* exposure to azathioprine than cyclosporine [10, 30]. The risk of leucopoenia and thrombocytopenia linked to the trans-placental passage of 6-thioguanine nucleotides is reduced by adapting azathioprine posology to the maternal level of leukocytes [33]. In animal models, azathioprine causes congenital defects (cleft palate, skeletal anomalies, haematological anomalies), chromosome abnormalities and reduced fertility, but only when used at more than four times the authorized maximum pharmacological dose [32, 34]. At the usual dose, lower birthweight has been reported [35]. Therefore, azathioprine is authorized during pregnancy.

## Calcineurin inhibitors

Cyclosporine and tacrolimus are essential molecules in the anti-rejection management of transplant-recipient pregnant women. During pregnancy, especially in the third trimester, pharmacokinetic and pharmacodynamic variations (upregulation of cytochrome P450 3A4, increased plasma volume, lower drug-binding cell and albumin levels [25]) lead to a decrease in plasma concentrations and an increase in the daily calcineurin inhibitor dose by approximately 25% [20, 36, 37]. Monitoring should be biweekly or monthly, according to the European Best Practice Guidelines recommendations [3], and even weekly during the third semester [20].

Cyclosporine crosses the placenta and the concentration in the foetus/neonate varies between 37 and 64% of the maternal concentration [16]. The cyclosporine metabolites present in the maternal blood at birth could also be measured in the umbilical cord blood of two children [38]. In cohorts, neither mutagenic nor teratogenic effects have been described [3, 39]. In animal models, exposure to cyclosporine of rat embryos at Day 9 post-conception for 48 h does not cause major morphological alterations, which appear only at high dose (i.e. 10–20 μg/mL) [26, 40]. Conversely, in the mouse, exposure to therapeutic doses of cyclosporine might cause cardiac toxicity, linked to the increased synthesis of heat shock proteins [41]. In the haematological compartment, cyclosporine might inhibit the suppression of self-reactive lymphocytes in the thymus [42], possibly hindering T-cell maturation [20] and increasing the risk of autoimmune diseases [43]. However, no long-term clinical data are available to support these hypotheses. Therefore, cyclosporine is authorized during pregnancy.

Tacrolimus crosses the placenta (foetal/neonatal concentration about 50% of the maternal concentration) [22, 26], but foetal exposure is minimized by the placental expression of glycoprotein P, a transporter that brings the drug back in the maternal circulation. There are very few basic and epidemiological data on tacrolimus. In cohort studies, the risk of congenital anomalies does not seem to be increased, with an incidence estimated at about 5%, similar to the general population [19, 44]. In the rat, morphometric anomalies and embryotoxic effects are observed with high doses of cyclosporine (≥10 μg/mL) and also with low doses of tacrolimus. In the same study, neural tube closure defects were detected after exposure to elevated doses [26]. Despite the few experimental results, and mainly on the basis of cohort data, tacrolimus is authorized during pregnancy, like for cyclosporine.

## Mycofenolate mofetil

The use of mycophenolate mofetil is associated with a very high risk of malformations (about 23%) [20, 39, 45] and of miscarriage (50%) [20, 45]. Moreover, ear, mouth, fingers and ocular organ malformations tetrad have been described [46], particularly anomalies of the external or middle ear and of the eye (coloboma), congenital heart defects (inter-atrial or inter-ventricular communication), facial malformations (cleft lip, cleft palatine, micrognathism, orbital hypertelorism), finger malformations (polydactyly, syndactyly), oesophagus atresia and spina bifida. Consequently, mycophenolate mofetil is contraindicated during pregnancy. Its use must be interrupted

6 weeks before stopping contraception. The Kidney Disease: Improving Global Outcomes and European Best Practice Guidelines suggest switching from mycophenolate mofetil to azathioprine before conception [3, 22]. As a precautionary measure, men also must use a contraceptive method during and up to 90 days after mycophenolate mofetil interruption due to a theoretical genotoxic risk, although no foetal anomaly has been described in children born from men treated with mycophenolate mofetil [46, 47].

### Sirolimus

Only few series of pregnancies in women treated with sirolimus have been reported [12, 48, 49]. The most important concerns seven pregnancies that included three miscarriages during the first trimester and one case of structural malformations in a child exposed *in utero* to sirolimus and mycophenolate mofetil [50]. In this series, all women with full-term pregnancy did stop sirolimus as soon as pregnancy was detected. Currently, neither teratogenic/mutagenic nor carcinogenic effects of sirolimus have been described in animals [22]. Conversely, it seems that the risk of foetal death *in utero* is increased in animals when sirolimus is associated with cyclosporine [51]. Sirolimus is contraindicated during pregnancy.

### Belatacept

Currently, no data are available in humans. Only three transplant recipients who took belatacept during pregnancy and whose children did not present any congenital abnormality have been described [52, 53]. No teratogenic effect of belatacept has been observed in animals according to the manufacturer [53].

### Anti-thymocyte globulins and polyclonal immunoglobulins

The use of these anti-rejection agents during pregnancy has never been evaluated in clinical trials. Only few case reports are available [54]. In pregnant women treated with anti-thymocyte globulins, the immunological regulation at the level of the placenta could be altered, but the underlying mechanism is not understood [55]. Anti-thymocyte globulins might affect thymus development and induce chronic reduction of T-cell immunity. Few cases have been reported, the first in 1989, for the treatment of medullary aplasia during pregnancy. No foetal malformation was observed [56]. The first description of anti-thymocyte globulin administration for the treatment of acute graft rejection in a pregnant transplant recipient was in 2016. The patient went into labour at 37 weeks of gestation, and the foetus had intrauterine growth restriction, without any evident foetal malformation or infection at 6 months post-partum [57]. No data are available about the long-term consequences on the immune system of *in utero* exposure to anti-thymocyte globulins [54]. Maternal immunoglobulins G (IgG) cross the placental barrier from 16 weeks of gestation via an active mechanism of pinocytosis that involves a receptor for the fragment crystallizable (Fc) region of IgG. Initially, foetal IgG concentrations are about 10% of the maternal concentrations, but they can reach 100% starting from Week 26 of gestation [58], and exceed that value during the last 4 weeks of pregnancy. Therefore, polyclonal immunoglobulins must cross the placental barrier. Currently, no data is available on their use in animal models, and no adverse event has been described [22, 30].

### Rituximab

Like maternal IgG, rituximab can cross the placental barrier via its Fc. When used during pregnancy, it has been detected at variable concentrations (30–120% of the mother's concentration) in umbilical cord blood [59, 60]. In humans, there are no data concerning its use in pregnant transplant recipients. However, several internal medicine and haematology case series have been published [61, 62]. Among the 102 patients treated during pregnancy or <6 months before pregnancy, 74 had a live birth of which 60% were at term. There were three malformation syndromes without specific phenotype. B-cell depletion was found in 9 of 23 children without infectious complications, and with a normalization of B lymphocyte concentration at 6 months after birth [62]. In monkeys, no teratogenic effect has been described [61]. Despite the reassuring data in humans, it is recommended to use an efficient contraception system during the 12 months following an injection of rituximab.

### Basiliximab

Currently, no data are available in humans [22], and no teratogenic effect has been reported in animals [51].

## LATE COMPLICATIONS IN CHILDREN EXPOSED *IN UTERO* TO IMMUNOSUPPRESSIVE DRUGS

The long-term outcomes in children have been poorly studied and the post-natal effects of *in utero* exposure to immunosuppressive drugs are difficult to analyse due to the presence of confounding factors (e.g. birth term, mother's age, diseases, socioeconomic level, exposure to other drugs). Most of the published studies, in animals and in humans, have reported short- or middle-term findings, at most up to 12 years after birth, and did not find major medical or developmental consequences during childhood. Most of these few studies focused on general development (weight, height), immune function, renal and cardiovascular consequences, or neurocognitive and behavioural development [63].

### General development

Recently, Bachmann *et al.* confirmed the major risk of prematurity after *in utero* exposure to immunosuppressive drugs [64]. In this study ($n = 28$ women with kidney transplant and $n = 32$ pregnancies), the authors collected information on the physical and motor development (weight, height, cranial perimeter, tone and posture) of 32 children conceived after a transplant, from their birth to the age of 2 years. These children were exposed *in utero* to different immunosuppressive drugs (tacrolimus, cyclosporine, prednisolone and azathioprine, as monotherapy or in combination, depending on the treatments prescribed to the mothers) and were compared with a group of children born from ordinary pregnancies (controls). These studies found that birthweight, height and head circumference were lower in *in utero*-exposed children than in the control group. However, at Month 12 after birth, these differences were no longer significant. This standardization of developmental profiles in *in utero*-exposed children was still observed at Month 24 (normal physical exam for 95.2% of children at Month 24).

### Immune function

The immune system functionality in children *in utero* exposed to immunosuppressive drugs has been only partially investigated.

Several authors have analysed immune system components in newborns of kidney-recipient mothers and found that at birth, B- and T-cell counts were significantly lower in these neonates than in controls [65], but not in newborns of mothers with immune disorders [65, 66]. This difference might be explained by the fact that transplant recipients receive higher doses of immunosuppressive drugs even during pregnancy. Some clinical studies have reported higher occurrence of infections in the first year of life in children of kidney-recipient mothers [65, 67]. All these findings emphasize the need for more studies.

## Kidney and cardiovascular consequences

In humans, the definitive number of nephrons is acquired during foetal life, between Weeks 10 and 32 of embryo development. Brenner *et al.* hypothesized that any qualitative or quantitative alteration of nephrons in foetal life might lead prematurely to hypertension or CKD in adult life, and that low weight at birth might predispose to CKD [68, 69]. Children born from transplant recipient mothers are exposed to this risk due to the high rate of preterm births and low birthweight in this population. Moreover, recent studies suggested that small for gestational age (i.e. a weight below the 10th percentile for the gestational age) might be a better marker of CKD in adulthood than low birthweight [70, 71].

In newborns of transplant-recipient mothers, the risk of hypertension or CKD is higher also due to the toxicity of some drugs to which they were *in utero* exposed [72]. This concerns particularly calcineurin inhibitors because their nephrotoxicity in the adult kidney has been amply demonstrated [73]. Some experimental studies in mouse, rat and rabbit models showed that exposure to cyclosporine throughout pregnancy causes a decrease in the number of nephrons and glomeruli at birth and a size reduction of the nephrogenic zone [22, 74, 75]. Qualitative anomalies also have been detected by optic microscopy analysis, particularly tubular lesions associated with areas of interstitial fibrosis [22, 76], glomerular hypertrophy [75], and glomerular retraction or sclerosis [22]. Finally, rabbits exposed *in utero* to cyclosporine are asymptomatic at birth, but progressively develop hypertension, proteinuria and CKD in adult life, with worsening of the histological lesions observed after birth [77]. These data suggest that there might be a middle- or long-term risk of hypertension/CKD linked to the *in utero* exposure to this class of drugs.

Only few follow-up data are available and mostly up to the age of 10 years. In 1993, Shaheen *et al.* reported that in 26 children born from transplant-recipient mothers [78], development and basic renal tests were normal, without any major disease after a mean follow-up of 39 months. Similarly, Willis *et al.* found that in 48 children born from kidney transplant-recipient mothers, general health was unremarkable in 95% and development was normal in 98% of these children, after a median follow-up of 5.2 years (9 months to 18 years) [29]. In two articles, Cochat *et al.* described a case series of 14 children born from 12 transplant-recipient women. Clearance and microalbuminuria as well as blood pressure were normal at the age of $2.6 \pm 1.8$ years ($n = 12$ children tested) [79, 80]. No case of hypertension, proteinuria or kidney disease has been reported in all the small case series on children born from transplant-recipient women [29, 78–80]. As systemic kidney function abnormalities are detected only in adult rodents, despite the presence of histological alterations already at birth, the lack of renal symptoms in children might not be predictive of the absence of long-term effects. However, no long-term data are available on the risk of CKD in adults born from transplant-recipient mothers. Therefore, the results obtained in rodents stress the importance of long-term monitoring of these children.

## Neurocognitive and behavioural development

Very few studies have investigated the neurocognitive and behavioural development in <12-year-old children *in utero* exposed to immunosuppressive drugs. Nulman *et al.* compared the long-term neurodevelopment of 39 children *in utero* exposed to cyclosporine and of 39 controls (not exposed) [81]. In the middle-term (8 years of age), neurocognitive and behavioural scores did not significantly differ between groups [81]. The authors found that preterm birth, birthweight and parents' socioeconomic level influenced the children's neurocognitive development, independently of their *in utero* exposure or not to immunosuppressive drugs. In an American study, 14% of children exposed *in utero* to cyclosporine (mean age 4.4 years, and up to 12 years) required education support compared with 11% in the general population. This might be explained mostly by the higher rate of preterm births rather than by the maternal immunosuppressive treatments [82]. More recently, Schreiber-Zamora *et al.* compared neurological data in children of kidney transplant-recipient mothers and control children (ordinary pregnancies) born at a similar gestational age ($n = 36$/group) [83]. The overall results showed that neurological development (all children were <3 years) was normal in both groups. However, nine children (four in the experimental group and five in the control group) obtained results slightly lower than what was expected for their age, and one child in the experimental group showed moderate retardation. These developmental deviations were mostly associated with prematurity and were mostly transient (normalization at the end of the first year of life). Conversely, neurological deviations observed after the first year of life were considered more severe and were maintained over time. Again, these atypical profiles might be linked more to intrauterine growth restriction and prematurity rather than to *in utero* exposure to immunosuppressive drugs.

As pregnancies in transplant-recipient women have not been a rare event in the last 20 years, studies on the long-term outcomes of the now adult children should be carried out to better inform them and their parents and also other transplant-recipient women planning to have a child. Indeed, most of the available information is limited essentially to growth and weight monitoring during the first years of life. The very few studies on kidney function and neurocognitive/behavioural development used a limited battery of tests and did not consider all possible confounding factors, such as prematurity, intrauterine growth restriction, socioeconomic status. Cohort follow-up studies should be considered with a longitudinal and multidisciplinary approach and up to adulthood.

In conclusion, pregnancy in women after organ transplantation is not exceptional any longer, particularly in women with kidney graft. However, these pregnancies are associated with an elevated risk of preterm birth, preeclampsia and low birthweight, as functions of the multiple maternal risk factors and drug treatments. Therefore, such pregnancies should be carefully planned and closely monitored by a multidisciplinary healthcare team. These children are exposed *in utero* to immunosuppressive drugs that are essential to avoid graft rejection. Although children exposed *in utero* to azathioprine, calcineurin inhibitors and/or corticosteroids do not seem to present major congenital anomalies, the data obtained in rodents indicate that the question of the long-term risk of CKD and hypertension

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linked to preterm birth, low birthweight and *in utero* exposure to drugs, particularly calcineurin inhibitors, is relevant. However, experimental data are limited and should be completed with studies in rodents or other animals. In humans, the short-term studies are rather reassuring, but no data exist on kidney function, proteinuria and arterial blood pressure in these children once they become adults. Moreover, there is no information on the fertility of these young adults, or on transgenerational effects. Therefore, it is now essential to complete the long-term epidemiological studies, notably thanks to the establishment of registries, by proposing a continuous follow-up of these *in utero* exposed adults. This should include CKD screening and the introduction of preventive measures from the youngest age for cardiovascular risk factors, for instance with programmes of therapeutic education for the parents.

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## AUTHORS' CONTRIBUTIONS

H.B., S.M.-G. and C.V. had the idea of this review and wrote the text. J.S. helped with the literature search. J.M.C. and L.D. helped with manuscript writing and reviewing. V.D. and A.L. wrote the manuscript.

## CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest for the present work.

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