

Pregnancy, lactation and calcineurin inhibitors

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- Cyclosporin (CSA) trough levels decline with advancing pregnancy because of an increase in volume of distribution and increased metabolism. Dose adjustment may be required to maintain pretransplant levels. However, evidence of true CSA exposure using limited or fully sampled area under the curve (AUC) is lacking and a decision to adjust the dose must be considered in the light of the following two points.
 - Despite lower maternal CSA levels in pregnancy, the acute rejection risk is low in reported case series (0% in 9 studies, 1–17% in 3 studies) and registry data (CSA 2%, tacrolimus 5%¹). However, no study has compared with non-pregnant-matched controls.
 - In registry data, there is a high prevalence of 2 year post-pregnancy graft loss (kidney and kidney-pancreas) ranging from 4% to 17%.
 - In a meta-analysis of the use of CSA in human pregnancy, the prevalence of major malformation in the foetus was 4.1% (2.6–7.0%), which was higher than, but not significantly different (odds ratio (OR) = 3.8, 95% confidence interval (CI): 0.75–19.6) to, non-calcineurin inhibitors (CNI) pregnancy figures. No specific pattern of malformations has emerged.
 - Compared with the general population, the prevalence of miscarriage, prematurity, low birthweight and pre-eclampsia is increased in pregnant renal transplant recipients taking CNI. Compared with case-matched controls with primary renal disease patients not taking CNI, prematurity and growth retardation but not pre-eclampsia are significantly increased.
 - Tacrolimus use in pregnancy has been associated with transient but marked hyperkalaemia (>7.0 mmol/L) in the neonate.
 - CSA is excreted into breast milk at levels comparable to maternal blood. In 13 of the 14 cases of continued

maternal CSA usage, the neonatal blood levels were undetectable.

- Infants born to mothers taking CNI during pregnancy have been shown to have some evidence of suppressed innate immunity in the first year of life.

BACKGROUND

Renal transplantation often restores fertility in women of child-bearing age and successful pregnancies have been reported in recipients of renal transplants.

Calcineurin inhibitors, namely CSA and tacrolimus, are now firmly-entrenched as part of most primary immunosuppression regimens. The safety of these drugs in pregnancy has not yet been endorsed by their manufacturers.

However, these two agents have now been on the market for over 10 years and there are numerous reports of their use during pregnancy. These include case reports, controlled case series, cohort studies, retrospective studies and national registries on the use of these agents in pregnancy. The aim of this guideline is to review this evidence with a view to establishing:

- The prevalence of drug-related complications to the mother, including pre-eclampsia and acute rejection of the grafted kidney
- The prevalence of adverse effects to the offspring, including malformations, miscarriages/stillbirths, prematurity/low birthweight and longer-term immunological effects
- Whether dose adjustments of the CNI are warranted during pregnancy
- Whether the risk to the infant in breast-feeding is low enough to justify the potential benefit of doing so

SEARCH STRATEGY

Databases searched: Medline (1966 to November Week 4, 2004). MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for pregnancy and breast-feeding. The Cochrane Renal Group Specialized Register of randomized controlled trials was also searched for relevant trials not indexed in Medline.

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WHAT IS THE EVIDENCE?

For obvious ethical reasons, there are no randomized controlled trials on the use of CNI in pregnancy or lactation. Available evidence mainly comes from small case series from single centres, with occasional case-control studies.

The largest single registry of data is the National Transplantation Pregnancy Registry (NTPR) from the USA. This is a voluntary registry established in 1991, to examine the outcomes of pregnancy in the US transplant solid-organ recipients. Information is acquired through questionnaires which are filled out and signed by transplant recipients who are identified by their coordinators, physicians or self-report to the registry. It also includes reports from Canada and Puerto Rico. By 2003, it had accrued 1430 outcomes from 1393 pregnancies; 1083 of these pregnancies were in kidney transplant recipients.

Pharmacokinetic changes during pregnancy

Cyclosporin

Pregnancy is known to be associated with changes in volume of distribution and alteration in gut motility that may affect absorption of drugs, as well as increased metabolism, in part due to microsomal activity of the placenta. Armenti *et al.*,² using data from the NTPR, found that CSA trough levels tend to drop during pregnancy in those with good graft function as well as in those with a degree of graft dysfunction. No studies using C_2 levels or AUC have been performed to date. Kozłowska-Boszko *et al.*³ conducted a study of 15 pregnancies using CSA-based immunosuppression. They found a significant decrease in C_0 plasma levels during the pregnancy despite maintenance of therapeutic dosing. However, no acute rejections were observed and the authors postulate that this was because C_0 levels did not reflect true exposure to CSA.

Burrows *et al.*⁴ studied CSA levels during pregnancy in seven pregnancies. CSA levels fell an average of 25% in the first trimester (range +4% to -51%) compared with pre-pregnancy trough levels; 39% in the second trimester (+68% to -77%), and 36% in the third trimester (-17% to -77%). This was despite an increase in dose of up to 50% in five of the seven mothers. The authors comment that the fall in CSA levels in most of these women was probably related to an increase in distributive mass (to the placenta, amniotic fluid and fetal tissues), but an increase in the rate of drug metabolism may have played a role as well.

Tacrolimus

In 100 pregnancies in 84 patients treated with tacrolimus, 69% of mothers who successfully completed pregnancy did so without a change in tacrolimus dose. Unlike CSA, the whole blood levels of tacrolimus remained remarkably constant throughout the duration of the pregnancy.⁵

Fetal complications of pregnancy: CSA

Congenital malformations

A 2001 meta-analysis of case control and cohort studies⁶ reviewed pregnancy outcome after CSA therapy. Fifteen studies were reviewed relating to major congenital malformations in a total of 410 patients. Six of these studies had control groups of transplants without use of CSA. The result was a calculated OR of 3.83 for major malformations. This was not statistically significant, with a CI of 0.75–19.6, but it is postulated that this is due to the small sample size. Further study would be appropriate to adequately approximate the fetal risks of *in utero* exposure to CSA.

Low birthweight and prematurity

The same meta-analysis reviewed five studies (one with control) relating to low birthweight. This provided an OR of 1.5 (CI: 0.95–2.44) and a prevalence of 43%. This was not statistically significant, but indicates a trend towards low birthweight. Finally, 10 studies looked at preterm delivery (four with control) and revealed an overall OR of 1.52 (CI: 1.00–2.32) and a prevalence of 56.3%.

Post-meta-analysis studies (2001–2004)

Since the date of this published analysis, the CARI literature search yielded seven more primary studies looking at the incidence of malformations in offspring of women taking CSA during pregnancy. Only one of these studies involved purely patients taking CSA-based immunosuppression, but the results are broadly similar to those of the meta-analysis. For a total of 366 pregnancies in these seven studies:

- Prevalence of miscarriage/stillbirth was from 16% to 35%
- Prevalence of prematurity ranged from 35% to 73% (meta-analysis: 56%)
- Figures for low birthweight ranged from 33% to 65%

Registry data from the NTPR 2003^{1,7} reveal a prevalence of 19% for miscarriage, 1% for stillbirth, 50% for low birthweight, 56% for prematurity and 31% for pre-eclampsia. Table 1 compares these figures with the background incidence in the US population.

Tacrolimus

Registry data from the NTPR 2003¹ reveal a prevalence of 22% for miscarriage, 3% for stillbirth, 53% for low birthweight, 55% for prematurity and 29% for pre-eclampsia in pregnant women taking tacrolimus. Table 1 compares these figures with the background incidence in the US population.

Kainz *et al.*⁷ give the largest experience to date of solid organ transplant recipients taking tacrolimus in pregnancy. Of 100 pregnancies, there were three cases of neonatal death and four offspring had congenital anomalies, which differed in each instance.

Neonatal hyperkalaemia

In 27 neonates born to mothers taking tacrolimus for liver transplantation,⁸ 36% were transiently but significantly hyperkalaemic (>7 mmol/L). In a study of 100 pregnancies⁵ in mothers taking tacrolimus, information obtained on 54 neonates revealed eight cases of hyperkalaemia.

Case-control study of immunosuppression in renal disease in pregnancy

Bar *et al.*⁹ conducted a case-control study of immunosuppression in renal transplantation (73 offspring) versus primary renal disease without immunosuppression (49 offspring). Ninety per cent of the transplantation group were taking CNI.

Significant differences in outcome between the two groups were found for prematurity and intrauterine growth retardation, but not for miscarriage, stillbirth or pre-eclampsia.

Maternal complications of pregnancy

Acute rejection

Results from the US National Transplantation Registry 2003 figures reveal a prevalence of biopsy-proven acute rejection during pregnancy of 2% for Neoral and 5% for tacrolimus. However, there is a high prevalence of 2 year post-pregnancy graft loss (kidney and kidney-pancreas) – up to 17%.

Results from the literature search are summarized in Table 2. Thirteen case series gave figures for pregnancy-related acute rejection. In 9/13 series, no acute rejection events occurred. Those with a positive finding had results ranging up to 17%, but at least one of these studies included rejection events in the early post-partum period.

However, no study has compared pregnant patients on CNI with non-pregnant-matched controls.

Pre-eclampsia

Hypertension in pregnant renal transplant recipients is common, but the prevalence of pre-eclampsia will necessarily depend on the defining criteria used for that diagnosis. NTPR data¹ suggest that pre-eclampsia occurs in approximately 30% of pregnant solid organ transplant recipients and is similar for CSA and tacrolimus. Other case series give prevalences ranging from 12% to 29% (see Tables 1 and 2).

Post-partum graft loss

Registry data¹ and two case series suggest that post-partum graft loss^{2,10} may be higher than that occurring during pregnancy. It is unclear whether this is a consequence of pregnancy-related events or changes in maternal immunity in the post-partum period.

Breast-feeding and effects of immunosuppression in the neonate

Cyclosporin and tacrolimus do appear in breast milk and the manufacturers contraindicate breast-feeding. However, the following papers challenge that view.

Cyclosporin

Evidence is limited to two small case series and two case reports only.

Thiru *et al.*¹¹ reported a case of an infant who was breast-fed until 14 months of age while the mother took CSA for a renal transplant. At 5 weeks post-partum, the maternal blood concentration was 260 g/L and the corresponding infant serum level was below the detection limit of 3 g/L. The infant maintained normal renal function and at the age of 2 years, she appeared to have no adverse effects related to CSA exposure.

Nyberg *et al.*¹² reviewed seven cases of mother-infant pairs breast-feeding while on CSA. Breast milk levels were comparable to serum levels in most cases. Random blood levels were below the detection limit of 30 ng/mL in all infants.

Munoz-Flores-Thiagarajan *et al.*¹³ reported a case of an infant who was breast-fed for 10.5 months while the mother was on CSA for kidney-pancreas transplantation. Maternal CSA concentrations ranged from 123 to 230 g/L and breast milk concentrations were on average 84% of maternal serum levels. The infant did not show signs of CSA-related toxicity; he subsequently attained the 46th and 55th percentiles for weight and height, respectively, at 12 months of age. CSA levels in the infant were undetectable at the sensitivity limit of the assay (25 ng/mL) for the entire duration of the study.

Moretti *et al.*¹⁴ reported five mother-infant pairs breast-feeding while taking CSA. Maternal milk concentrations ranged from 75 to 564 g/L, which corresponded to 0.5–2.1% of the weight-adjusted maternal dose. Variations were evident between concentrations in hindmilk and foremilk, possibly because of higher fat content of the former. One infant had a blood concentration of 131 g/L, which is considered therapeutic. Breast-feeding was discontinued as a precaution. Conversely, the other four infants had blood levels below the detection limit of 25 g/L. The authors comment that the amount in human milk appears to be insignificant, unless clearance rate and first pass metabolism of CSA is substantially slow in the infant.

Neonatal effects of CSA exposure in utero

Pilarski *et al.*¹⁵ studied the effects of *in utero* exposure to CSA with or without azathioprine. Differences in CD lymphocyte subset expression were found between those exposed to CSA and azathioprine versus those exposed to CSA alone. The authors concluded that the presence of CSA throughout pregnancy has only a minimal effect on fetal immune development, and appears to have less impact on T cells than does exposure to azathioprine alone. They

also stated that children exposed to CSA *in utero* are not likely to be at risk of developing immunodeficiency or autoimmunity.

Di Paolo *et al.*¹⁶ examined the immune system of six infants born to female kidney transplant recipients who had received CSA and methylprednisolone throughout their pregnancies. None of the children were breast-fed. The authors found a retardation of T, B and NK cell development, mostly lasting up to 1 year of age. They question the clinical relevance of such changes since no clinical signs of immunosuppression were present. But they postulate that classical vaccinations might be delayed to prevent either a suboptimal response or adverse events from live attenuated vaccines.

Armenti *et al.*¹ from the NTPR reported nine cases of breast-feeding in CSA kidney recipients. At last follow up, there were no reports of problems in these children.

Tacrolimus

No case series is available in renal transplant recipients. French *et al.*¹⁷ reported the first case of measurement of tacrolimus levels in human milk. The patient was a liver transplant recipient taking 0.1 mg/kg daily throughout the pregnancy. At 2.5 months of age, the infant was developing well both physically and neurologically. The authors concluded from this that tacrolimus therapy for liver transplantation may be compatible with breast-feeding.

Armenti *et al.*¹ reported five cases of kidney recipients breast-feeding while on tacrolimus. At last follow up, there were no reports of problems in these children.

SUMMARY OF THE EVIDENCE

Table 1 shows a summary of the evidence for adverse maternal and fetal outcomes in pregnant women taking CNI.

Table 2 is a comprehensive list of all studies used in this CARI review. They address the use of CNI in pregnancy in the Neoral and tacrolimus eras (since 1992), predominantly in renal transplant recipients but also include data from other solid organ transplants.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines (2002):¹⁸

There are three recommendations pertinent to this subject area:

1 Acute rejection episodes are uncommon but may occur after delivery. Therefore, immunosuppression should be readjusted immediately after delivery.

2 Pre-eclampsia develops in 30% of pregnant transplant patients, especially those with prior arterial hypertension. Thus, blood pressure, renal function, proteinuria and weight should be monitored every 2–4 weeks, with more attention

during the third trimester. Anti-hypertensive agents should be changed to those tolerated during pregnancy, but ACE inhibitors and ATII receptor antagonists are absolutely contraindicated.

3 Immunosuppressive therapy based on CSA or tacrolimus, with or without steroids and azathioprine, may be continued in renal transplant women during pregnancy. Because of drug transfer into maternal milk, breast-feeding is not recommended.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

1 The meta-analysis published in 2001⁶ recommended that two more cohort studies of similar effect size be conducted in order for statistical significance for malformations to be achieved.

2 Conduct comprehensive pharmacokinetic studies of CNI in pregnancy using C₂ levels, limited sampling strategies or full AUC to determine CNI exposure more precisely.

3 Investigate tacrolimus levels in human milk of renal transplant patients who choose to breast-feed while on the drug. Data so far are restricted to the liver transplant population.

4 Conduct long-term follow up of infants who were breast-fed by mothers taking CNI.

CONFLICT OF INTEREST

Marc Grimer has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1 Summary of the evidence of adverse effects – maternal and offspring

	Sources of information for cyclosporin specifically		Sources of information for tacrolimus specifically		Background incidence in the USA
	Meta-analysis Bar-Oz <i>et al.</i> , 2001 ⁶	NTPR 2003 ¹ (144 pregnancies with Neoral to date)	Kainz <i>et al.</i> , 2000 ⁵ (n = 100)	NTPR 2003 ¹ (62 pregnancies to date)	
Malformations	4.1% (n = 339)	CNI combined 7/164 (4.3%)	5.6% of live births	CNI combined 7/164 (4.3%)	2–3%
Miscarriage/ stillbirth	Not measured	19%	13%	22%	US National Centre for Health Statistics Stillbirths 0.87%
Prematurity	56.3% n = 379	55%	59%	55%	12.3%
Low birthweight	43% (38–75%) n = 314	50%	10% (90% apt for gestational age)	53%	7.9%
Pre-eclampsia	Not measured	31%	8/53 reported cases (15%)	29%	3.9%
Acute rejection during pregnancy	Not measured	2%	9/53 reported cases (17%)	5%	N/A

CNI, calcineurin inhibitors; NTPR, National Transplantation Pregnancy Registry.

Table 2 Studies of CNI use in solid organ transplantation pregnancies since 1992

Study ID (author, year)	Drug	No. of transplants	No. of pregnancies	Full term [†]	Premature [†]	Acute rejection [†]	Miscarriage/ stillbirths [‡]	Live births [‡]	Congenital defects or neonatal death	Pre- eclamptic toxaemia	Low birthweight [†]	Comments
Jain <i>et al.</i> 2004 ¹⁹	TAC 100%	15	22	Mean gestation 34.4 weeks	Nil	Nil	1 (4%)	21 (95%)	Nil	5	Mean 2373 g	Case series
Keitel <i>et al.</i> 2004 ²⁰	CSA 22 TAC 1 Non-CNI 18	41	44	41%	59%	NS	17%	27 (61%)	2 fetal distress 1 oligo-hydraminos	10	Mean 2195 g	Retrospective analysis
Hooi <i>et al.</i> 2003 ²¹	CSA 64% Non-CNI 36%	46	72	65%	35%	Nil	(15%)	68%	NS	14%	47%	Retrospective study
Thompson <i>et al.</i> 2003 ²²	CSA 62% TAC 25%	24	48	44%	56.5%	Nil	16%	68%	NS	29%	33% small for gestational age	Retrospective study
Bar <i>et al.</i> 2003 ⁹	CSA 79% TAC 10%	38	73	20 40%	29 60%	NS	17 (25%)	49 (65%)	2 major anomalies; 10 mild errors of morphogenesis	20%	IUGR figures only	Case-control series of offspring 2-7 years
Sgro <i>et al.</i> 2002 ²³	CSA 31 non-CNI 13	26	44	Mean gestation 36.5 weeks	NS	NS	12 (27%)	32 (72%)	1 multiple anomalies	NS	Mean 2.54 kg	Case-control study
Miniero <i>et al.</i> 2002 ²⁴	CSA/TAC/ Aza	42	56	16 44%	20 55.6%	4 7%	20 (35%)	36 (64%)	Nil	NS	11/20 of those premature	Multicentre retrospective study
Kaimz <i>et al.</i> 2000 ⁷	TAC 100%	83	100	41% full term of the 63 where result known	17% n = 53	17%	24%	68%	Stillbirth 3%, 4 cases of malformation, one 2 EtOH, 3% lost to follow up	8/53	10%	Registry data and random case reports
Little <i>et al.</i> 2000 ⁵	CSA	19	29	6 26%	17 73%	Nil	6 (20%)	23 (80%)	2 neonatal deaths	NS	65.2%	Retrospective study

Crowe <i>et al.</i> 1999 ²⁶	CSA 19 Non-CNI 12	29	33	7	21	Nil	15%	28 (84%)	Nil congenital abnormality but 1 neonatal death	12%	NS	Case series
Barrou <i>et al.</i> 1998 ²⁷	CSA	17	19	Mean gestation 35.2 weeks	9	Pancreas 1 Kidney 0	N/A	19	2 congenital malformations	NS	Mean 2.1 kg	Registry data
McGroarty <i>et al.</i> 1998 ²⁸	CSA 100%	10	15	3 25%	75%	NS	3 20%	12	Nil	NS	83%	Case series
Ehrlich <i>et al.</i> 1996 ²⁹	10% CSA 90% Aza	102	207	Mean gestation 36 weeks		NS	N/A	N/A	8 malformations of varying severity	NS	Mean 2490 g	Registry data
Gaughan <i>et al.</i> 1996 ³⁰	CSA for >5 years when pregnant	15	17	70%	30%	Nil	4	13 23%	Nonneonatal deaths 76% complications 15%	NS	15.4%	Case series
Wong <i>et al.</i> 1995 ³¹	CSA 5 Aza/pred 4	9	16	8 72%	3 27%	Nil	18%	11 69%	1 case SIDS at 4/12 else nil	NS	NS	20 years retrospective study
Armenti <i>et al.</i> 1995 ²	CSA 100%	141	197	46%	54%	11% up to 3/12 p/part	19%	68%	One neonatal death, congenital defects NS.	29%	50% of live births	Case-control study
Armenti <i>et al.</i> 1994 ¹⁰	CSA 100%	115	156	44%	56%	14.5% up to 3/12 p/part	18%	68.6%	21% complications, 6.6% neonatal deaths	25%	49.5%	Registry data
Berardinelli <i>et al.</i> 1992 ³²	CSA 7 Non-CNI 9	16	16	8	8	Nil	N/A	16	Nil at term, 1 premature neonate died day 3	Nil	50%	Case series

Where percentages have been calculated by the table author: ¹percentages quoted for low birthweight (less than 2), premature and full term are percentage of LIVE BIRTHS; ²percentages quoted for acute rejection, miscarriage/stillbirth and live births are percentage of TOTAL NUMBER OF PREGNANCIES. Aza, azathioprine; CSA, cyclosporin; CNI, calcineurin inhibitors; NS, not stated; TAC, tacrolimus.