

EXPERT  
REVIEWSBreastfeeding and tacrolimus:  
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**Evaluation of:** Bramham K, Chusney G, Lee J, Lightstone L, Nelson-Piercy C. Breastfeeding and tacrolimus: serial monitoring in breast-fed and bottle-fed infants. *CIASN* 8(4), 563–567 (2013).

Successful pregnancy after transplantation has become more common and more recipients are choosing to breastfeed their infants, despite the controversy surrounding the safety of breastfeeding while the mother is taking immunosuppressive medications, such as tacrolimus. Data collected to date by the National Transplantation Pregnancy Registry have not revealed specific problems related to breastfeeding; however, individual circumstances must be considered when counseling transplant recipients regarding breastfeeding. Bramham *et al.* reported on a series of transplant recipients who were maintained on tacrolimus during pregnancy and lactation and concluded that women should not be discouraged from breastfeeding while on tacrolimus. Recently, other authors have also supported the option of breastfeeding while recipients are maintained on tacrolimus. Herein, we review the Bramham article and discuss the key issues to be considered regarding the compatibility of breastfeeding and immunosuppression.

**KEYWORDS:** breastfeeding • pregnancy • tacrolimus • transplantation**Summary of methods & results**

The study by Bramham *et al.* was conducted to assess the level of neonatal tacrolimus exposure by analyzing tacrolimus levels in maternal, cord and infant blood and in breast milk [1]. Women taking tacrolimus during pregnancy and lactation who exclusively breastfed their infants were assessed. Cord and maternal blood samples were collected at delivery, and postnatal infant blood and breast milk samples were also collected. The tacrolimus levels in these samples were analyzed by liquid tomography and tandem mass spectrometry and compared with samples from bottle-fed infants whose mothers took tacrolimus. In both groups, infant blood levels of tacrolimus declined over the first 2–3 weeks postdelivery, and moreover, the breastfed babies did not have higher tacrolimus levels compared with the bottle-fed infants. The authors clearly state the limitations of their study, which include incomplete sample collection in all of the pairs and the lack of long-term outcome data. The authors conclude that the ingestion of tacrolimus by infants via breast milk, being negligible, should not discourage women from breastfeeding, if monitoring of infant blood levels of tacrolimus is available.

**Discussion**

With more successful pregnancy outcomes reported in the literature in all types of solid-organ transplant recipients, it is not surprising that women raise questions that would be expected after such positive outcomes, such as whether they can breastfeed [2,101]. A number of medications are necessary to support the female transplant recipient, not the least of which are immunosuppressive agents. The question that has always arisen among transplant physicians is whether even minimal exposure may ultimately lead to some long-term adverse effects in the offspring. Given the potential that these agents may have some harmful effect on the newborn, the authors Bramham *et al.*, begin their paper by restating that women traditionally have been advised not to breastfeed while taking one of the common immunosuppressive agents, tacrolimus, based on the theoretical risks of neonatal immunosuppression [1]. This is related to the assumption that it would be present in breast milk and thus absorbed by the newborn.

There have been literature reports that support breastfeeding in the transplant recipient population. Early case reports pointed to the possibility that tacrolimus may be compatible with breastfeeding [3,4]. A study by Easterling and

colleagues concluded that very little tacrolimus is excreted in the breast milk and is unlikely to elicit adverse effects in the nursing infant [5]. In a follow-up of tacrolimus-breastfed babies in a letter to the editor, whole blood tacrolimus concentration measured in four neonates ranging between days 15 and 27 after delivery was undetectable [6]. The clinical follow-up of these babies did not identify any adverse outcome that might be related to tacrolimus.

Bramham *et al.* point out in their discussion that tacrolimus is 75–99% protein-bound, which would suggest low excretion into breast milk [1]. Anecdotally, higher tacrolimus doses by weight are required to be therapeutic in transplanted children, due to greater volumes of distribution and blood clearance, so that the exposure *in utero* and via breast milk is much lower than that experienced by transplanted children.

The National Transplantation Pregnancy Registry (NTPR), established in 1991, studies the safety of pregnancy in transplant recipients, and data collected include information about breastfeeding. To date, NTPR data include over 39 participating mothers taking tacrolimus postpartum who breastfed more than 45 infants [7]. FIGURE 1 displays that over the period of the most complete data collection to date in this area (1994–2012), there has been a steady increase in the number of kidney recipients who report to the NTPR that they chose to breastfeed.

In the NTPR data, approximately 50% of the newborn are premature and have a low birth weight, although typically they are not severely premature and their birth weight is compatible with their gestational age [101]. The numerous benefits of breastfeeding are well documented, especially in the preterm gastrointestinal tract, which leads one to assume in this population that there is a particular advantage to breastfeeding [8–11].

It is interesting to note the evolution and resolution of concerns regarding the treatment of recipients who become pregnant. The first successful pregnancy after kidney transplantation occurred in one of two identical twins in 1958 [12]. Immunosuppression was not an issue in this outcome, but there were concerns over the pelvic placement of the transplanted organ and its impact

on the progress of the pregnancy and delivery. Over time, with the introduction of prednisone and azathioprine, some concerns were raised as to whether azathioprine might cause chromosomal damage in the newborn [13]. With the introduction of cyclosporine came the concern of higher rates of fetal growth restriction [14]. As each new agent came along, new concerns were raised. The message for transplant recipients has been quite positive, yet with each pregnancy there remains a concern for an adverse event. To date, only mycophenolic acid products can be shown to be associated with adverse outcomes, a higher rate of spontaneous abortions and a particular pattern of birth defects [15,16]. The package insert has been modified to reflect these findings and it now recommends that recipients avoid pregnancy while taking mycophenolic acid [17,18].

What would appear to be true, as has been the case throughout the past 50 years, is that an initial, almost knee-jerk response is to think that pregnancy and transplantation are not a good combination, one being bad for the other either by posing risks to the transplanted graft, or the medications and the mother's health posing risks to the developing fetus. Although there is a small percentage of recipients for whom pregnancy is associated with poor outcome, whether that be birth defect, graft rejection or deterioration of graft function, many publications worldwide support the success of pregnancy in most transplant recipients. It would appear that breastfeeding is heading in that same direction. We should keep in mind, as is noted in several publications, that the fetus is exposed to immunosuppression throughout its entire development, so when breastfed, these infants are not experiencing a shift from no exposure to having exposure.

In the context of this area of study, the paper from Bramham and colleagues is another important contribution. Despite the admitted study limitations, it is well carried out and will help clinicians guide their patients in the decision-making process, and perhaps the topic of breastfeeding should be broached at the time of pregnancy counseling. Future studies are needed to continue to

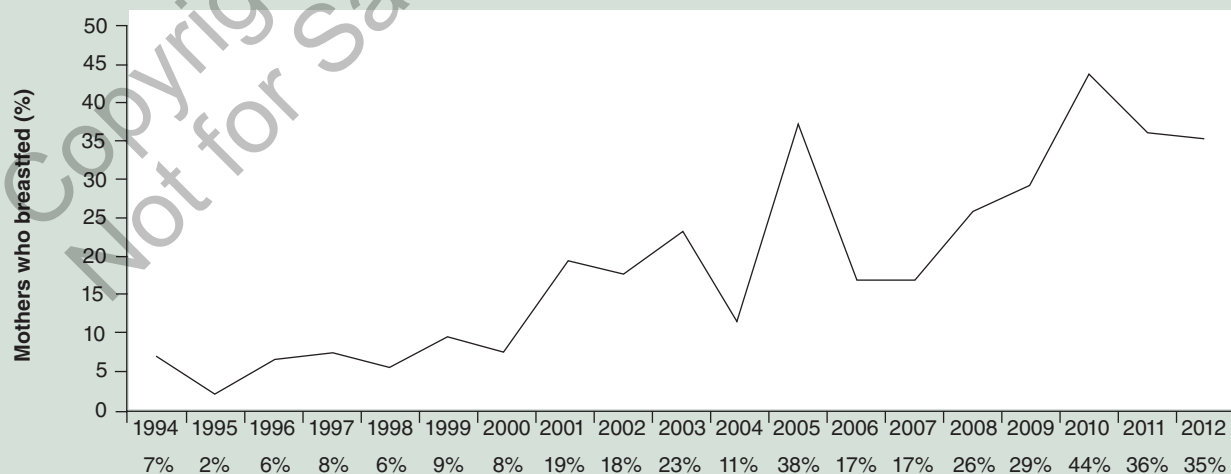


Figure 1. The National Transplantation Pregnancy Registry: trend in breastfeeding practices of kidney recipients.

clarify the interrelationship of drug levels in breast milk, maternal blood and infant blood.

Continued case studies, center reports, reports to the NTPR and reports such as this one will help to clarify these issues and contribute to the growing body of knowledge regarding breastfeeding while taking immunosuppressive agents.

### Five-year view

The Bramham group lacked long-term follow-up information about the infants in their study. The NTPR follows all types of solid organ recipients and their offspring, with some being followed into early adulthood with children of their own. As more recipients choose to breastfeed on tacrolimus, registry data will accumulate, providing a more reliable assessment of whether even low levels of tacrolimus exposure impact the long-term development of the offspring.

Further study of tacrolimus dosing during pregnancy is warranted, in light of the difficulty of interpreting trough levels due to the variations in pharmacokinetics of tacrolimus during pregnancy.

The levels of tacrolimus to which an infant is exposed *in utero* and postpartum could be understood better by establishing guidelines for tacrolimus dosing during pregnancy [19].

It is likely that, over the next 5 years, immunosuppression will continue to remain a mainstay of therapy for transplant recipients and new immunosuppressive agents will become available. Continued study and follow-up of breastfed infants of transplant recipients is thus going to be essential to determine whether these new agents are compatible with breastfeeding.

### Financial & competing interests disclosure

Support for the NTPR has been provided by grants from its founding sponsor, Novartis Pharmaceuticals Corporation, as well as Astellas Pharma US Inc., Genentech Inc., Pfizer Inc., Teva Pharmaceuticals USA, Sandoz Inc and Bristol-Myers Squibb Company. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

### Key issues

- Successful pregnancy after transplantation has led to an increase in the number of recipients choosing to breastfeed while taking immunosuppressive medications, such as tacrolimus, despite concerns regarding the lack of information on the safety of breastfeeding while taking these medications.
- The results of several recent studies including this one support the concept that breastfeeding while taking tacrolimus should not be discouraged.
- The study reviewed herein showed that babies breastfed by mothers taking tacrolimus showed the same rapid decline in serum tacrolimus levels after birth as bottle-fed infants.
- As breastfeeding is especially beneficial for preterm infants and over 50% of babies born to kidney transplant recipients are premature, there would appear to be a particular advantage to establishing the safety of breastfeeding in this population.
- Future research and continued reporting of cases in the literature and pregnancy registries are expected to further allay the concerns surrounding breastfeeding while taking immunosuppressive medications.
- Future research should include studies that will lead to the establishment of guidelines for dosing, the measurement of levels of tacrolimus during pregnancy, and the long-term follow-up of children breastfed by recipients being maintained on immunosuppression.

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