

# Safety of tacrolimus in pregnancy

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## Abstract

**Question** I have a 30-year-old patient who had a kidney transplant 2 years ago. She is now planning a pregnancy. She has been treated with tacrolimus since her transplant. Will it be safe for the fetus if she continues to take it during the pregnancy or should she switch to a different antirejection medication?

**Answer** If your patient is stable while taking tacrolimus, there is no reason to switch. The current available information does not suggest that tacrolimus increases the risk of major congenital malformations above the baseline risk in the general population. Premature birth and low birth weight are often reported in this population; however, these effects are frequently reported in pregnant transplant patients treated with other immunosuppressant agents and probably reflect the effects of the maternal condition. As there are some reports of hyperkalemia and renal impairment in infants exposed to tacrolimus in utero, kidney function and electrolytes should be monitored in exposed neonates.

## Sécurité du tacrolimus durant la grossesse

### Résumé

**Question** J'ai une patiente de 30 ans qui a subi une greffe de rein il y a 2 ans. Elle planifie actuellement une grossesse. Elle prend du tacrolimus depuis sa transplantation. Est-ce sécuritaire pour le fœtus si elle continue ce traitement durant la grossesse ou devrait-elle changer pour un médicament antirejet différent?

**Réponse** Si votre patiente est stable en prenant du tacrolimus, il n'y a pas de raison de changer. Les renseignements actuellement disponibles n'indiquent pas que le tacrolimus augmente le risque de malformations congénitales majeures au-delà du risque normal dans la population en général. On signale souvent des cas de naissance prématurée et de faible poids à la naissance chez les femmes greffées du rein; toutefois, ces issues sont souvent rapportées chez de telles patientes enceintes qui prennent d'autres agents immunosuppresseurs et sont probablement attribuables aux effets de l'état de santé maternel. Étant donné qu'on a certains signalements d'hyperkaliémie et d'atteintes rénales chez les nourrissons exposés in utero au tacrolimus, il faudrait surveiller la fonction rénale et les électrolytes chez les nouveau-nés exposés.

In 2012 there were 2287 solid-organ transplants performed in Canada. By the end of 2012 there were 6593 women living in Canada with functioning transplanted kidneys<sup>1</sup>; approximately 22% of them were 20 to 44 years old. Thus, a substantial number of recipients are women of childbearing age. As all transplant recipients require immunosuppressant therapy, and as tacrolimus is a widely used immunosuppressant (for transplant recipients and for patients with certain autoimmune conditions), more and more fetuses are exposed to it.

### Pharmacokinetics

Tacrolimus is highly bound to plasma proteins (albumin) and erythrocytes (orosomuroid and hemoglobin), which are present in lower levels during pregnancy, resulting in potential changes in tacrolimus

concentrations. However, if no change in unbound intrinsic clearance of tacrolimus is seen, this decrease would lead to a fall in whole blood concentration, but no change in the unbound concentration. In clinical practice, trough tacrolimus concentrations are measured in whole blood; thus, dose titration during pregnancy to keep the trough concentrations in the therapeutic range might lead to an increase in the unbound concentrations, resulting in toxicity. Monitoring of tacrolimus levels in pregnant patients with anemia and hypoalbuminemia using plasma or unbound trough concentrations might better predict drug efficacy than whole blood concentrations do. If whole blood concentrations are the only assay available, red blood cell count and serum albumin concentration should be taken into account when considering dose titration.<sup>2,3</sup>

### Pregnancy and neonatal outcomes

Tacrolimus has been shown to cross the placenta into the fetal circulation in humans.<sup>4</sup>

There have been reports of case series of human pregnancies with tacrolimus exposure (approximately 200 pregnancies) in post-transplant patients. Most authors reported favourable pregnancy outcomes, with no evidence of increased risk of congenital malformations. However, all authors report higher rates of preterm delivery and low birth weight. There are also several reports of transient neonatal hyperkalemia and renal dysfunction, which resolve in infancy without further adverse effects.<sup>5-10</sup>

In 2012, the National Transplantation Pregnancy Registry (NTPR) reported data on fetuses exposed to tacrolimus in pregnant recipients of kidney (n=334), liver (n=180), pancreas-kidney (n=50), heart (n=45), and small-bowel (n=2) transplants. The outcomes reported were spontaneous abortion rates of 22% to 33%, stillbirth rates of 0% to 2%, live birth rates of 65% to 74%, premature birth rates of 43% to 72%, mean gestational age of about 34 to 36 weeks, and low birth weight rates of 29% to 53%.<sup>11</sup> The report is available on request from the NTPR ([www.ntpr.giftoflifeinstitute.org](http://www.ntpr.giftoflifeinstitute.org)). Although no comparisons have been made, these values seem to be within ranges reported in transplant patients regardless of treatment received.<sup>12,13</sup>


A study comparing pregnancy outcomes of 23 kidney recipients (29 pregnancies) taking different immunosuppressive therapies reported no statistical difference in perinatal or maternal complications and graft survival rates (11 taking cyclosporine, 9 taking tacrolimus, 1 taking mycophenolate mofetil, and 12 taking azathioprine). Of the 29 pregnancies, 26 resulted in live births, 2 in stillbirths, and 1 in a miscarriage. The median birth weight of the newborns was 2650 g (range 900 to 4350 g). Perinatal complications were reported in 58.6% of the pregnancies, with premature birth being the most common (35.7%). No major congenital malformations were reported in the 9 infants born to women taking tacrolimus.<sup>14</sup>

A 2008 abstract based on data from the NTPR reported 3 infants (4.2%) with birth defects among 102 pregnancies in kidney transplant recipients treated with tacrolimus (without mycophenolate mofetil) during pregnancy. No difference in the incidence of birth defects was reported among liver, pancreas-kidney, and heart recipients. However, an increase in incidence of birth defects was reported in the fetuses of kidney recipients exposed to tacrolimus in combination with mycophenolate mofetil, which probably reflects the known teratogenicity of mycophenolate mofetil.<sup>15</sup>

### Conclusion

The current available data do not suggest an increased risk of major congenital malformations following in utero exposure to tacrolimus. An increased risk of low birth weight and preterm birth was reported; however, it

is probably related to the maternal condition and not to the medication. Owing to reports of hyperkalemia and renal impairment in exposed infants, renal function and potassium levels should be monitored in such newborns.

As all transplant recipients require immunosuppressant therapy, based on the above data tacrolimus can be considered a viable option during pregnancy. 

### Competing interests

None declared

### References

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