

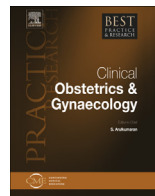


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### Immunosuppressive drugs and fetal outcome



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Successful pregnancies have been reported in all types of solid-organ transplant recipients on a variety of immunosuppressive regimens. Immunosuppression is essential to maintain the transplanted organ and maternal health, thus the safety of these medications continues to be studied. This article reviews

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information in the literature and data from the National Transplantation Pregnancy Registry (NTPR) in the United States related to immunosuppressive medication and pregnancy. Although most maintenance immunosuppressive regimens have not been shown to affect the outcome of posttransplant pregnancies, mycophenolic acid products are associated with an increased incidence of spontaneous abortion and an increase in the incidence and a specific pattern of birth defects. When counseling transplant recipients about the prospect and safety of pregnancy, the health of the mother, her graft, and the developing fetus must all be taken into account.

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## Background

In 1963, Joseph Murray and colleagues reported the first known pregnancy after kidney transplantation [1]. The recipient received a kidney from her identical twin sister; therefore, immunosuppression was not an issue. The recipient delivered a healthy baby boy at 40 weeks via cesarean section. Since that first report, there have been many advances in immunosuppression and thousands of solid-organ transplant recipients worldwide have had successful pregnancies after transplantation [2–6].

From the 1960s to the 1980s, immunosuppressive regimens for transplantation were limited to azathioprine and prednisone. Then, the era of calcineurin inhibitors was ushered in with cyclosporine, used in combination with the prior medications. In the early 1990s, a second calcineurin inhibitor, tacrolimus, was introduced. Tacrolimus and cyclosporine have the same intracellular mechanism, and are not used together but are used in combination with other immunosuppressives. In the mid-1990s, the mycophenolate drugs were introduced and largely replaced azathioprine [7]. Sirolimus, an anti-proliferative agent in its own class, appeared in the late 1990s, and unlike calcineurin inhibitors, is not nephrotoxic [8,9]. In an effort to improve both efficacy and decrease side effects, the different immunosuppressive medications are used in various combinations. The most common post-transplantation regimen currently prescribed is tacrolimus plus mycophenolate with or without prednisone.<sup>10</sup>

Immunosuppressive regimens are classified into three general categories: (1) *induction agents*, used in the first week posttransplant, include biological agents such as antilymphocyte sera (polyclonal or monoclonal antibodies) or interleukin-2 (IL-2) receptor blockers; (2) *antirejection agents*, used to treat rejection episodes, include high-dosage, short-term treatments such as corticosteroids or antilymphocyte sera; and (3) *maintenance regimens*, started soon after transplantation to provide long-term immunosuppression. Maintenance regimens are initiated at higher dosages and are lowered through the posttransplant first year. Maintenance immunosuppressive therapy will be taken by almost all pregnant solid-organ transplant recipients.

In general, it is recommended that women refrain from taking medications during pregnancy unless it is necessary. As most transplant recipients must take immunosuppressive medications to preserve their transplant function, the National Transplantation Pregnancy Registry (NTPR) was established in the United States in 1991 to study the safety of these medications during pregnancies in transplant female recipients and in pregnancies fathered by transplant recipients. The NTPR is an active registry that continuously collects and analyzes data from transplant recipients, their health-care providers, and medical records review. The different types of solid-organ recipients and the number of pregnancies in the NTPR as of December 2013 are summarized in Table 1 [3]. A unique feature of the registry is long-term follow-up; early participants have been followed up for over 20 years and some are now grandparents. The NTPR is a multicenter condition-based registry, and as such, it can address evolving concerns in the transplant community and adapts to the introduction of new immunosuppressive therapies. Case and center reports, meta-analyses, and registry reports are crucial to the understanding of the effect of these therapies during pregnancy on the recipient, their transplant, and the developing child.

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