Cyclosporine A (CsA), introduced in the early 1980s, soon became the mainstay of immunosuppression in transplantation. When first introduced, concern was raised about the safety of its use in pregnancy (1). These early reports in fact suggested that cyclosporine might be associated with an increased incidence of intrauterine growth retardation, and clinicians at that time were faced with the decision as to whether to proceed with pregnancy with this newer agent versus switching to agents where there was more familiarity, i.e., azathioprine or prednisone. Known toxicities of CsA include nephrotoxicity and hypertension. Cyclosporine is lipophilic, associated with variable bioavailability, and a microemulsion formulation, Neoral®, with decreased interpatient and intrapatient variability, was approved in 1995. This formulation has more predictable pharmacokinetics and generic versions are now available. Patients currently on cyclosporine therapy are typically on the new formulation.

In a study published in this issue, additional concerns are raised with regard to CsA use during pregnancy (2). The authors had previously shown that rabbits exposed in utero to CsA during the 14th to 18th day of gestation, present with a 25% nephron reduction. The current study assessed the long-term systemic and renal effects of CsA induced nephron reduction, and it was found in this rabbit model that CsA in utero exposure is also associated with systemic hypertension and progressive renal insufficiency in adulthood. In the live born pups at one month, no significant difference was observed in various renal function parameters studied between the control and CsA treated groups. However, from 11 wk onward, deterioration in renal function was noted in the treated group. Arterial hypertension worsened with age as well. Again at one month of age, BP was not significantly different between the control and treated groups, yet a 15% increase was noted at 11 wk, with a 35% increase at 35 wk, equivalent to adulthood.

The findings of Dr. Semama and his colleagues raise important issues. It is worthwhile to evaluate these issues in light of the developments and evaluation of pregnancy safety over the last fifty years in the fields of transplantation and teratology. The first known post-transplant pregnancy occurred in 1958, reported in 1963, in a patient who had received a kidney from her identical twin (3). She delivered a healthy baby boy by cesarean section. Beginning in the 1960s, immunosuppressive regimens were based on azathioprine and prednisone and continued until the 1980s, when CsA became the primary immunosuppressive agent, usually in combination with azathioprine and/or prednisone. A well-documented case report was published in 1976 presenting a management scheme for a renal recipient who was followed closely during her pregnancy. This transplant recipient was maintained on prednisone and azathioprine and delivered a healthy baby boy at 36 wk. The patient maintained stable graft function throughout pregnancy. The authors, John Davison and his colleagues, emphasized the necessity for close follow-up of transplant recipients during pregnancy and derived from the review of the literature at the time and the management of this patient, a set of criteria for counseling female transplant recipients contemplating pregnancy. The authors also concluded that pregnancy did not appear to have an adverse effect on the transplant function, but there remained the questions as to the potential for effects not only on the newborn but also that pregnancy could have a long-term effect on the function of the transplanted organ (4).

In the CsA era, case reports, center reports and registry data have supported the concept that successful pregnancy outcomes are possible for mother and newborn in the presence of stable graft function and well-controlled maternal comorbidities, such as hypertension. While the incidences of prematurity and low birth weight are greater than seen in the general population, there has been no increase in the structural malformation rate of the newborn. Prematurity and low birth weight have been common outcomes among the offspring of female transplant recipients, regardless of immunosuppressive regimen. Successful pregnancy outcomes have been reported in non-renal CsA recipients as well.

In the field of teratology, lessons learned from thalidomide exposures reinforced principles that medications taken during pregnancy could affect the gross structural development of the conceptus. Many factors can impact the severity of these effects, including the route of administration, the time of exposure, dose, as well species of animal studied in experimental models. In the ensuing years, it became evident that events in late gestation might also be affected, except the end result of these exposures could be more subtle behavioral or functional problems, which might only be apparent on the microscopic level. Dr. Semama and his colleagues evaluated both functional and structural parameters in their rabbit model with structural changes noted on histologic grounds. Thus, just as gross structural defects can be a result of medication exposures, histodifferentiation can be susceptible, but effects during this period of development are not readily apparent at birth. Despite many
medication exposures during pregnancy, however, it is estimated that only a small percentage of developmental defects are classified as teratogen-induced, or malformations that are considered to be the result of environmental or drug exposures during pregnancy (5).

This paper does raise important questions. What should be the endpoint of determining effects of potentially fetotoxic or teratogenic therapies during pregnancy? Is the absence of a developmental or structural defect at birth an adequate assessment, or is it necessary to do more detailed surveillance throughout childhood or even into early adulthood before we can accurately determine whether immunosuppressive therapies administered in utero might not have had some untoward effect on development? Not only from a standpoint of nephrotoxicity, there has been some concern among investigators that immunosuppressive therapy might affect the immune system development of the offspring (6). Scott and colleagues raised the issue of effects of in utero exposure to immunosuppressive agents impacting reproductive development that these offspring might not demonstrate until adulthood, and have a study in progress (7). With the concerns of immunosuppression and pregnancy, we initiated a study to evaluate the outcomes of pregnancies in transplant recipients on all types of regimens (8). Established in 1991, the National Transplantation Pregnancy Registry (NTPR) study design includes asking questions about the health and development of the children as we continue to follow the parents. While the reports from parents have been encouraging (9), there has not been a detailed assessment of BP and renal parameters in these offspring as recommended by the authors.

As new medications are released in the United States, the Food and Drug Administration (FDA) has developed a guidance document for the development of pregnancy registries for surveillance of these agents when necessary. There are various methods of study. In some cases multi-drug multi-sponsored registries have developed and in others, single drug based registries have been designed. Among the many issues still to be resolved are the endpoints for follow-up of potentially affected offspring.

This paper brings to light the fact that we have many questions to answer in populations at risk who must take medications during pregnancy. This is further complicated by additional drug exposures to the newborn via breastfeeding (10). All of us involved in the care of these high-risk patients need to be attentive to these issues. Perhaps studies such as the one by Dr. Semama’s group can help caretakers recognize the importance of continued surveillance of high-risk offspring beyond the neonatal period.

As methods of surveillance continue to develop, it is important for us to be cautious as to how we relay this information to our patients. There remain limitations with extrapolation of data from animals to humans. Transplant recipients are required to take immunosuppressive therapies to maintain their health. While we can assure our recipients that we are offering necessary therapies, in some cases it is just not possible to know whether there is the potential for long-term effects that are not yet recognized in their offspring. In the clinical setting, multiple factors such as genetic and familial backgrounds, and other comorbidities, need to be taken into consideration when adverse pregnancy events occur. We must exercise caution in the care of our patients and advise them, and at the same time recognize that ongoing surveillance is necessary.

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References

See related article, “Long-Term Effects of In Utero Exposure to Cyclosporin A on Renal Function in the Rabbit,” on pages 2687–2693.