Pregnancy in Renal Transplant Recipients: More Questions Answered, Still More Asked

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In this issue of *CJASN*, Bramham *et al.* identified pregnant kidney transplant recipients being managed by practitioners participating in the UK Obstetric Surveillance System, comparing their outcomes with those of a cohort consisting of two women without kidney transplants that had delivered at the same hospital just before the transplant recipients' delivery (1). This article is one of several following a 2006 published survey performed by the Women's Health Committee of the American Society of Transplantation (AST) to ascertain how pregnancies in transplant patients were managed, with the authors concluding that "Transplant recipients, now conceiving for more than 40 years require an evidence-based approach to their care" (2). The article by Bramham *et al.* is a welcome response to this call.

Uneasiness over managing pregnancies in transplant recipients is nothing new. Ever since Edith Helm, the first pregnant transplant recipient, delivered a healthy baby boy by caesarian section on March 10, 1958 (3), there have been safety concerns for the mother, the infant, and the allograft. In this respect, we have had single case reports, center series, registry data, consensus conference publications, and systemic reviews to guide us in managing these high-risk patients; however, most of these publications have intrinsic design flaws that have left the transplant community with many unanswered questions. Furthermore, despite the existence of this literature, the AST survey found that advice for pregnant transplant patients was based on "attending physician's discretion" in 64.5%, patient desires in 47.4%, and literature reviews and literature searches <20% of the time (2). In the study by Bramham *et al.*, the fact that there were women who underwent caesarian sections with the stated indication of having kidney transplants indicates that nearly 7 years after the AST survey results were published, some treating physicians are still not basing management on what is in the literature.

The report by Bramham and colleagues actually confirms, but with better documentation than previous publications, that although most pregnancies in kidney transplant recipients are successful, they are high-risk endeavors. This seems more a function of the associated issues and comorbidities that often affect individuals with kidney transplants (*e.g.*, hypertension) or immunosuppression side effects rather than the kidney transplant *per se*. Regardless of the underlying pathophysiology, these pregnancies are associated with a high rate of preeclampsia diagnoses, preterm deliveries, caesarian sections, and small for gestational age infants. In addition, the study identified prognostic factors for a poor outcome. The factors include the presence in the first trimester of a serum creatinine level >1.4 mg/dl, multiple prior kidney transplants, and presence of diastolic hypertension in the last two trimesters. Is any of this surprising or new? Not really. These findings largely overlap with results of a systematic review and meta-analysis and what has been reported to the National Transplant Pregnancy Registry (NTPR) (4,5). The study did, however, contain a few unexpected observations, including the findings that the incidence of gestational diabetes was not higher and that proteinuria and prepregnancy hypertension did not appear to portend a poor prognosis. Another observation was that approximately half of the patients failed to demonstrate the expected decrease in serum creatinine during gestation reflective of the increase in GFR expected in normal gestation, but this absence *per se* was not associated with a bad outcome.

Although much of these authors' information may be familiar, the study contains an important take-home message that prepregnancy counseling is crucial. It provides an opportunity to avoid unplanned pregnancies by educating about increased fertility after transplantation and reinforcing the importance of contraception use. With this in mind, it is interesting to note that the authors questioned whether some of the study pregnancies were unplanned. Counseling also facilitates pregnancy planning, enabling prospective parents to make informed decisions. Knowledge of the risks may alter whether our patients decide to proceed with pregnancy. For example, an important consideration for prospective parents is the reality that infants born preterm and small for gestational age are an at-risk population. Early after birth, there are very serious risks such as neonatal death, necrotizing enterocolitis, and respiratory distress syndrome (6,7). Even those infants who make it through the early period may have impaired growth and neurocognitive deficits. And as the first cohort of small premature infants that survived come into adulthood, data emerge supporting the observations by Van Assche *et al.* (8,9) regarding nongenetic fetal transmission emerging later as the Barker hypothesis of the fetal origins of

disease (10). Small for gestational age infants may be at increased risk in their adulthood of developing diabetes, hypertension, stroke, and hypercholesterolemia (11–13). Thus, prospective parents need to consider that having a premature infant is challenging under the best of circumstances, but undoubtedly even more so when it occurs to a woman with a kidney transplant who has her own medical issues to manage. However, it is fair to say that despite the increased risks, many considering pregnancy will opt to proceed and the majority will have successful pregnancies. Still, for some prospective parents, being aware of the potential risks may persuade them to pursue other approaches toward having children, such as adoption or using a surrogate.

Does this study mark the end of the pregnancy during transplant story? Have all of our questions been answered? Certainly not. Despite the study by Levidiotis *et al.* (14) showing that a live birth does not adversely affect the survival of the patient or the allograft, many still wonder whether pregnancy adversely affects the graft. This issue is not addressed by this study. In addition, with the ever-changing immunosuppression strategies, we will always question the effect of new medications on the developing fetus. A current case in point is belatacept, which is a US Food and Drug Administration pregnancy category C drug. There are no human studies that provide pregnancy safety data. Even if immunosuppression were no longer a consideration (*e.g.*, if we ever achieve tolerance in transplantation), we will then wonder whether pregnancy could affect that immunologic tolerant state. There is also a question of whether a female kidney donor adds risks to her own future pregnancies (15). Finally, we still lack prospective data despite a proliferation of large pregnancy trial networks in which accruing such data are possible. Put another way, we will always have questions. Consequently, even with this beautifully designed study that has verified observations made over the years, it is important for the transplant community to support registries like the NTPR. We need to advise our patients to contact NTPR and report on their outcomes (both good and bad). The registry serves many important roles, including being able to detect and document changing trends in pregnancy outcomes, and may provide clues when unanticipated problems arise with immunosuppressive medications.

The article by Bramham *et al.* leaves one considering whether pregnancy in transplant recipients is a glass more half full than half empty or *vice versa*. I am not going to answer that for you, but I will leave you to decide. Either way, with the current publication, you are now in a better position to inform and counsel your kidney transplant patients and their partners and help them consider their options and decide if pregnancy and its potential risks is a journey they wish to take.

Disclosures

None.

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