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Controversies in family planning: intrauterine device placement in solid organ transplant patients☆

Catherine Gordon *,[1], Tabetha Harken [1]

University of Southern California, Irvine, 333 City Blvd West, #1400, Orange, CA 92868

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ABSTRACT

With an ever-increasing number of reproductive-aged women undergoing solid organ transplant and fertility improving after transplant, knowledge of the safety and efficacy of various contraceptive methods is essential to guide patient selection. We present the case of a 22-year-old patient desiring an intrauterine device (IUD) for contraception with a history of liver transplant as a child. The Centers for Disease Control and Prevention (CDC) and American Society for Transplantation (AST) offer conflicting recommendations on the use of IUDs in transplant patients. We review the literature for recommendations on IUD use in this population. While the literature is limited, levonorgestrel (LNG) and copper (Cu) IUDs appear to be safe and effective in solid organ transplant patients, with no evidence of unintended pregnancies or complications compared to those without organ transplant. Ultimately, patient preference should be the primary consideration in contraceptive choice, including between LNG or Cu-IUD.

1. Case

A 22-year-old patient underwent liver transplant as a child for liver failure secondary to biliary atresia and subsequently desired an intrauterine device (IUD) for contraception. The Centers for Disease Control and Prevention (CDC) categorize levonorgestrel (LNG) and copper (Cu) IUDs as Medical Eligibility Criteria 2 in uncomplicated solid organ transplant patients. However, the CDC state that there are no comparative studies examining different types of IUDs and reported cases provide inconsistent results in regard to effectiveness. Additionally, in their 2005 consensus statement, the American Society of Transplantation (AST) recommended against the use of IUDs given concern for decreased effectiveness and risk of infection. Thus, the patient's transplant team had reservations regarding IUD use given her transplant history. A consortium of family planning providers was queried via listserv on recommendations for placement of IUDs in solid-organ transplant patients, as well as which IUD, LNG-IUD or Cu-IUD, is superior in immunocompromised individuals. The aforementioned listserv is confidential and comprised of fellowship-trained family planning specialists. Members may pose questions to the international community of experts to ascertain their opinions regarding clinical cases where data are limited. The following are their responses:

1) One of the most helpful lines that I have used with my transplant colleagues regarding IUDs and immunosuppression is that most immunosuppressants used in the transplant population work by suppressing T-cell activity and have no effect on macrophages.
2) There is also an accepted mechanism in that the cations are toxic to sperm.
3) I regard as outmoded and idle speculation the macrophage hypothesis. There is no evidence that the copper IUD is not safe and effective in [the] immunocompromised. LNG-IUDs are always more effective.
4) LNG will be just as effective. Recent data suggest that copper activity is not immunologically mediated.

2. Literature review

Approximately 33,000 individuals underwent solid organ transplant in 2016 [1]. Women aged 18–49 comprised about 14% of these patients, totaling approximately 4600 women. This number represents greater than a twofold increase from 2006, when approximately 2000 reproductive-aged women underwent solid organ transplant. Regular menstruation returns in about half of all liver and kidney transplant patients [2,3], and most patients report improved libido and sexual function after transplantation [2,4]. Women are advised to wait 18–24 months to attempt to conceive in order to allow for graft stabilization, institution of an immunosuppressive regimen and completion of

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* Corresponding author.
E-mail addresses: cgordon1@uci.edu (C. Gordon), tharken@uci.edu (T. Harken).
[1] Department of Obstetrics & Gynecology, University of California, Irvine.

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infection prophylaxis [5,6]. However, fertility can return as soon as 1 month postoperatively [7]. With reproductive physiology returning to baseline and recommendations to delay childbearing for a period of time, it is imperative that patients have access to safe and effective contraceptive options, and the safety of IUDs should be investigated.

The 2016 US Medical Eligibility Criteria for Contraceptive Use support the use of LNG-IUDs and Cu-IUDs in uncomplicated solid organ transplant patients under Category 2 [8]. For complicated patients (such as those experiencing graft failure, rejection or cardiac allograft vasculopathy), initiation of each IUD is listed as Category 3, with continuation of the IUD listed as Category 2. In contrast, the AST recommends against the use of IUDs in their 2005 consensus statement given concern for decreased effectiveness and increased risk of infection in solid organ transplant patients [9]. As of late 2018, however, the AST website has been updated and now states that the society condones the use of IUDs in uncomplicated patients [10].

The initial concern regarding decreased effectiveness of IUDs in solid organ transplant recipients was derived from a 1981 case report in which two renal transplant patients each had a Cu-IUD placed and experienced unintended pregnancies [11]. To date, there have been no subsequent studies evaluating the efficacy of Cu-IUDs specifically in solid organ transplant patients. However, a 2011 retrospective study, one of the largest studies to date, examined the rate of unwanted pregnancies in Chinese women after renal transplant, and none of the 178 women who received IUDs became pregnant [12]. The article is limited in that it does not mention the type of IUD used, but metal IUDs have been shown to be the most common type of IUD utilized by the Chinese population. For instance, a 10-year review of IUD removal in Chinese women noted that 30% of the IUDs removed were copper, while 63% were composed of stainless steel [13]. Additional concerns regarding the decreased effectiveness of IUDs in transplant patients stem from one of the mechanisms of action of the Cu-IUD. While the copper metal is spermatotoxic, the IUD also stimulates an inflammatory reaction in the uterus, which is unfavorable for both spermatozoa and fertilization, and in the fallopian tubes, with macrophage invasion and disruption of oocytes [14]. In theory, the immunosuppressive medications given to solid organ transplant patients may suppress the immunological response in the uterus activated by the presence of a Cu-IUD. However, many immunosuppressive medications (calcineurin inhibitors, antimetabolites, rapamycin, daclizumab and basiliximab) work by mediating T-cell responses rather than by affecting macrophages [15], which is the mechanism by which the Cu-IUD exerts its effect. Corticosteroids may actually increase the activity of macrophages by activating the proinflammatory substance "macrophage migration inhibitory factor" [16].

By extrapolating data from research conducted with HIV-1-infected women, who are also immunocompromised, it is evident that immunosuppression does not lead to decreased effectiveness of the Cu-IUD. A study conducted in 2001 by Morisson et al. followed HIV-1-infected and noninfected women with Cu-IUDs for 24 months. None of 150 HIV+ patients became pregnant with the IUD in place [17]. A second study in 2007 demonstrated an unintended pregnancy rate of 0.38 pregnancies per 100 woman-years in HIV+ women (CD4+ cell count ≫200 cells/mcL) who had a Cu-IUD [18]. This is superior to national Cu-IUD failure rates (0.4% in the study as compared to the national failure rate of 0.8%) [19]. Furthermore, Achilles et al. demonstrated no alteration in the number of T cells within the upper and lower genital tracts in HIV-negative women with Cu-IUDs, though the authors did find a decrease in activated cervical T cells in Cu-IUD users after 2 months of IUD use compared with baseline [20]. These results suggest that the Cu-IUD is an effective form of contraception among immunosuppressed women. While the immunosuppression in HIV patients is not identical to that of transplant patients on immunosuppressive medication, both lead to a deficiency in T-cell-mediated immunity [15]. However, future studies are needed to assess IUD effectiveness specifically in transplant patients.

The literature maintains no evidence of increased failure rates of the LNG-IUD in solid organ transplant patients. Three case series bolster the effectiveness of the LNG-IUD in this patient population. One describes 11 renal transplant patients, the second 6 solid organ transplant patients (2 renal, 2 cardiac, 1 liver and 1 small bowel), and the third 21 kidney and 2 liver transplant patients [21–23]. Not a single unintended pregnancy was reported with use of LNG-IUD in these women, though the paucity of data should be considered. The mechanism of action of the LNG-IUD relies on the local effects of progestin, which causes thickened cervical mucous, glandular atrophy and slowed tubal motility [14]. Given that the LNG-IUD does not exert its effect through utilization of the immune response, there is little concern for decreased effectiveness of this particular IUD in immunocompromised patients.

The AST consensus guidelines cited concern for infection risk in their recommendation against IUD use. In all three aforementioned articles examining LNG-IUDs in solid organ transplant patients, no cases of pelvic inflammatory disease (PID) were reported [21–23]. Moreover, the 2001 study on Cu-IUDs in HIV+ patients found equivalent rates of IUD complications, which include PID, in HIV-infected and non-HIV-infected women [17]. The overall risk of PID after IUD insertion is very low, approximately 1.54 per 1000 woman-years for Cu-IUD and 1.90 per 1000 woman-years for the LNG-IUD [24]. Additionally, continuation of IUDs already in place is likely safe, as the highest rate of pelvic infection is immediately after IUD placement, with infection 6 times more likely in the first 20 days postplacement compared to 21 days or later [25]. It is important to weigh the risks of an undesired pregnancy against the risk of pelvic infection in this patient population.

3. Conclusion

With increasing numbers of women undergoing solid organ transplant either at a young age or during their reproductive years, and with fertility improving after transplant, it is essential that providers possess knowledge of the safety and efficacy of various contraceptive methods in order to aid in guiding patient selection. The American Congress of Obstetricians and Gynecologists recognizes IUDs as a safe and extremely effective contraceptive method and even recommends the use of long-acting reversible contraceptives as a first-line option in young adults [26]. IUDs are increasingly popular in patients of all ages who desire to delay pregnancy for a number of years or rely on the LNG-IUD to mitigate heavy menstrual bleeding or pelvic pain. Though the literature regarding the safety and efficacy of IUD use in women with a history of solid organ transplant is currently limited, initial case series are reassuring. While one early case report demonstrated failure of the Cu-IUD in two renal transplant recipients, subsequent case series have reported no unintended pregnancies and no pelvic infections in transplant and HIV-infected women who received an IUD. However, it must be noted that the current literature consists of only a few case studies and observational studies with small numbers of patients. It is unlikely that randomized control trials will occur for practical and ethical reasons. In the absence of more data on IUD use from women with transplants, we have extrapolated from the apparent safety and efficacy of IUD use among women with HIV, and this evidence therefore has limitations. Based on the findings in this review, we believe that both types of IUDs can be considered in transplant patients. The ultimate decision on the particular type used should be based on patient preference and management goals, with the exception of placing an IUD in complicated patients with graft failure, rejection or cardiac allograft vasculopathy (Category 3 MEC). Finally, we have discussed with the American Society for Transplantation that they consider releasing an updated consensus statement with their recommendations for IUD use in solid organ transplant recipients.

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