Efficacy and safety of intrauterine insemination and assisted reproductive technology in populations serodiscordant for human immunodeficiency virus: a systematic review and meta-analysis

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Objective: To assess procreative outcomes for HIV-positive men and women with seronegative partners.

Design: Systematic review and meta-analysis.

Setting: Not applicable.

Patient(s): Twenty-four studies with extractable data for HIV-serodiscordant couples undergoing intrauterine insemination (IUI) or in vitro fertilization (IVF).

Intervention(s): None.

Main Outcome Measure(s): Primary outcomes: HIV transmission to a seronegative partner and per cycle fecundability; secondary outcomes: analysis of multiple gestation rates, miscarriage rates, and cancellation rates.

Result(s): For serodiscordant couples, HIV-positive men or women undergoing IUI and IVF treatment had a 17%, 30%, 14%, and 16% per cycle fecundability, respectively. Multiple gestation rates were 10%, 33%, 14%, and 29%, respectively. Miscarriage rates were 19%, 25%, 13%, and 20%, respectively. No HIV transmission was observed in 8,212 IUI and 1,254 IVF cycles, resulting in 95% confidence that the true rate is 4.5 transmissions per 10,000 IUI cycles or less.

Conclusion(s): In serodiscordant couples, IUI and IVF seem effective and safe based on the literature. Evidence-based practice and social justice suggest that our field should increase access to care for HIV-serodiscordant couples. (Fertil Steril® 2014;102:424–34. ©2014 by American Society for Reproductive Medicine.)

Key Words: HIV, insemination, IUI, IVF, serodiscordant

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he controversy over whether the partners of patients infected with human immunodeficiency virus (HIV) should undergo procreative therapy was sparked in the 1980s when noninfected women were suspected to have contracted HIV through intrauterine insemination (IUI) (1, 2). Semprini et al. (3) subsequently demonstrated

safe and effective sperm-washing techniques that could minimize the risk for transmission to the negative partner in 1992 (3). Though this has resulted in increased use of sperm processing and insemination for HIV-serodiscordant couples in Europe, it still is not commonly practiced in the United States. This situation persists despite the Ethics Committee of the American Society for Reproductive Medicine meeting in 2001–2002 and addressing sperm-washing methods for HIV-serodiscordant couples as a safer way of conceiving when using their own gametes.

Couples who are HIV serodiscordant have both fertility desires and fertility needs. Infertility affects approximately 15% of the general population, and people with HIV have greater reproductive challenges secondary to sequelae from their HIV infection. Studies of the sperm quality of men with HIV who are on antiretroviral treatment have demonstrated significantly lower ejaculate volumes, lower sperm count, and lower progressive motility despite normal morphology (4-6). This is consistent with HIV-associated hypogonadism, which can occur even without highly active antiretroviral therapy (HAART). Women with HIV have lower fertility rates across the world, especially in Africa. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that the global age-specific fertility ratios for women with HIV in the reproductive-age group of 20-44 years are lower than that of women without HIV (ranging from 0.76 to 0.53) (7). These were suspected to be secondary to higher rates of gynecologic infections in women with HIV, with tubal factor infertility from pelvic inflammatory disease being an important obstacle to conception (8, 9). Many of these factors can be overcome via reproductive therapies, reproductive including insemination and assisted technology (ART). Our objective was to systematically explore fecundability (the probability of pregnancy in a given cycle) for people with HIV in serodiscordant relationships via a meta-analysis comparing the success rates between genders based on HIV serostatus as well as the degree of benefit from the techniques of IUI and in vitro fertilization (IVF). Our secondary objectives included assessment of cycle cancellation, miscarriage, and multiple gestation rates. We also assessed the rate of HIV transmission between serodiscordant couples for eligible studies.

MATERIALS AND METHODS

Two of the authors performed an independent search of the PubMed and Ovid Medline to obtain all clinical trials involving IUI and ART including HIV-infected populations through April 2013. For the purposes of this study, the definition of ART used is that of the 1992 Fertility Clinic Success Rate and Certification Act in which ART includes all fertility treatments in which both eggs and sperm are handled. We also searched for and identified studies performing IUI on HIV-serodiscordant couples. The search terms used were "HIV" AND "assisted reproduction," "assisted reproductive technology," "in vitro fertilization," "intrauterine insemination," and "artificial insemination." Abbreviations were also used as well as different configurations of the search terms such as "IVF" and "ICSI." The studies were limited to human

trials. Review studies were cross-referenced to obtain additional clinical trials. The search was not restricted by language, and applicable non-English papers were translated into English. Data extraction was performed independently by two of the authors to ensure validity, with discrepancies resolved through in-person discussion, with both authors reassessing the data simultaneously.

The inclusion criteria for selection of the studies for the meta-analysis were [1] distinct outcomes for HIV-positive patients, [2] a clearly defined ART method (including use of donor egg or fresh cycles relative to frozen cycles), [3] pregnancy per cycle data, and [4] an overall sample size of at least three patients. Studies in which fecundability was not calculable were excluded. Fecundability was calculated through the available data per cycle based on the number of women conceiving and delivering, respectively, and these were independent of the number of gestations in a given pregnancy. When compared with national metrics for IVF, 2009 Centers for Disease Control and Prevention (CDC) data were used because the vast majority of cycles used in the meta-analysis were from 2009 or earlier.

Secondary outcomes calculated were multiple gestation rates, miscarriage rates, and live-birth rates. All outcomes were analyzed separately for each reproductive technique used as well as separately for HIV-positive men and women. Seroconcordant couples were not included because transmission rates could not be assessed, and seroconcordance would obscure the etiology for issues of efficacy. We also excluded oocyte donation cycles and all frozen embryo transfer data because of the paucity of information. Multiple gestation rates were calculated as a function of live-birth rates (e.g., a vanishing twin pregnancy was treated as a "singleton" for the sake of this study). Investigators were e-mailed when contact information was available to clarify or provide input on additional data; only one investigator responded (10).

A proportion meta-analysis using a DerSimonian-Laird random-effects model was performed. The data are reported as pooled proportions (PP) in percentages with 95% confidence intervals (CI). A Q-statistic was used to assess for heterogeneity. Egger statistic and visual inspection of funnel plots are reported to assess for publication bias for all measured outcomes.

RESULTS

An initial list of 221 studies was obtained (Fig. 1). This resulted in 24 studies meeting the criteria for analysis of the primary outcome of pregnancy per cycle. The sample size of the studies included ranged from 19 to 853. Of the 24 studies that had calculable pregnancy per cycle data, 14 studies contained IUI data, and 15 studies contained ART data. Five studies included couples who underwent a trial of IUI before ART or included both methods independently, and these outcomes were stratified where possible.

Of the 14 studies with IUI data, 12 studies had data on discordant couples with HIV-positive men, and four studies looked at HIV-positive women. Of the 15 studies with ART data, 12 studies had outcomes for an HIV-positive male partner, and seven studies had outcomes for an HIV-positive

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