Treatment for couples with unexplained infertility: the female partner at the end of reproductive years

TO THE EDITOR: We are writing this letter in response to the editorial by Van Voorhis et al. (1). We thank the authors for their interest in our manuscript and their positive comments about the importance of the FORT-T trial (2). There are several points in the editorial that we address in this letter. With respect to the observation that we studied a highly selected group of patients, we would point out that all well-designed randomized clinical trials have specified inclusion and exclusion criteria. These criteria enable the study to enroll a homogeneous population with the condition of interest. Selection does not affect internal validity, although it may have ramifications for generalizability. The most common reasons for patient ineligibility in FORT-T were not heavily influenced by diminished ovarian reserve but were as follows: outside the age range (74%), not insured by a participating insurance company (6%), and prior infertility treatment (5%). The remaining ineligible patients did not have a diagnosis of infertility, were not candidates for IUI, or had severe male factor. Of the 871 patients deemed eligible after initial screening, only 13% had inadequate ovarian reserve upon testing. The remaining reasons for nonparticipation were equally distributed among biological reasons (high body mass index, pregnancy, serious medical conditions), refusal on the part of the patient or her physician, or an incomplete infertility work-up. The reasons provided most often for refusal were ambivalence about treatment or unwillingness to have treatment choice determined by random assignment.

We would also point out that broad criteria were used to define adequate ovarian reserve. Our criteria were generous enough to allow for individuals who had a reasonable chance for success. It is hard to imagine that most clinicians today would routinely consider women at this age with cycle days 3 and 10 FSH > 15 mIU/mL and cycle day 3 E2 > 100 pg/mL as reasonable candidates for IVF. Current thinking is that the best strategy for such patients may be oocyte donation. As we have stated, neither inadequate clomiphene challenge tests nor diminished ovarian reserve were common reasons for ineligibility.

With respect to age, in this randomized clinical trial we blocked on age, that is, we used a randomization scheme that maximized the opportunity to equally distribute age across the treatment arms. Sample size was sufficient for this to be successfully achieved with no significant differences observed across treatment arms for age at baseline. It was never the goal of this study to conduct subgroup analyses to examine pregnancy or live-birth rates separately for 38- to 40- and 41- to 42-year-olds, regardless of sample size.

As we state in the paper when discussing study outcomes, we chose clinical pregnancy rate as the primary outcome because it is the best indicator of treatment success given the high miscarriage rate in this population. We recognize the importance of a “take home baby” and also provide data on live-birth rates. We agree with the authors that in patients with unexplained infertility, expectant management (as evidenced by pregnancies before and between treatment cycles) may be as efficacious as controlled ovarian hyperstimulation/IUI in this age group. We believe that this is yet another reason why immediate IVF is the best treatment choice.

Finally, the authors point out that “ultimately” the three studied strategies produced similar live-birth rates and go on to say, “This suggests that couples electing to start simpler and less expensive treatment than IVF are not harming their ultimate chances of having a child.” A similar percentage of couples had a live birth in each of the arms at the end of the study because all three arms moved to IVF after the first two treatment cycles. We suggest that in this population of women, at the end of their reproductive potential, the goal is not “ultimate” success but “immediate” success.

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REFERENCES