Caution: counseling patients with diminished ovarian reserve and recurrent pregnancy loss about in vitro fertilization with preimplantation genetic screening

Dr. Shahine and colleagues (1) highlight an important aspect of IVF-preimplantation genetic screening (PGS) that is often overlooked in counseling patients with diminished ovarian reserve (DOR) and recurrent miscarriage. In their article, "Higher rates of aneuploidy in blastocysts and higher risk of no embryo transfer in recurrent pregnancy loss patients with diminished ovarian reserve undergoing in vitro fertilization," they demonstrate that many patients who undergo IVF-PGS do not reach ET owing to the culmination of low embryo number and high aneuploidy rate (1). The average age of the women in this study was 36.1 for normal responders and 37.0 for DOR patients ($P=.09$). The live-birth rate per cycle with embryo biopsy was 47.5 % in the normal responding recurrent pregnancy loss (RPL) patients and 35% in the DOR-RPL patients; however, these statistics likely understate the effect of DOR on IVF-PGS outcomes as they exclude the eight DOR patients who did not make it to retrieval and the nine patients who either had no blastocysts to biopsy or opted out of PGS. The clinical miscarriage rates after euploid ET were 10% and 14%, respectively.

The main finding of this paper is that the risk of not having a euploid blastocyst available for transfer in an IVF-PGS cycle was 13% in the normal reserve group and 25% in the DOR group. Because this number does not include the eight patients with DOR who did not even make it to retrieval, we calculate the risk of no transfer for DOR patients was at least 37%. Proponents of IVF-PGS often quote high success rates and low miscarriage rates per euploid transfer in good-prognosis patients with normal ovarian reserve. Few studies have examined outcomes in a population with limited ovarian reserve. When counseling patients about success rates with IVF-PGS, it is important to quote not only success rates per transfer but also the likelihood of having a euploid blastocyst available for transfer.

An additional finding from this paper is that in women younger than 38, patients with DOR and RPL had higher aneuploidy rates than their age-matched RPL counterparts, leading to a worse than expected prognosis in this subset of RPL patients. Women over 38 years appeared to have similar aneuploidy rates in their embryos regardless of ovarian reserve testing. It is unclear but inferred from this data set that young women with DOR and RPL may have higher aneuploidy in their miscarriages. This could reflect that DOR in younger patients is more pathological, while DOR as defined by the authors in patients ages 38 and older may be physiological. If this is confirmed in additional studies, it may lead to an interesting line of investigation. Do young women in general with DOR have higher than expected aneuploidy rates? Could DOR in younger patients be a cause of recurrent miscarriage?

Having an evidence-based and realistic estimate of success is extremely important in counseling women with RPL who are considering IVF with PGS. The American Society for Reproductive Medicine recommendation for unexplained recurrent early pregnancy loss remains expectant management with supportive care (2). The prognosis for live birth with subsequent pregnancies is 60%–70% in most women with unexplained RPL, although miscarriage rates are still 30%–40% (3). Most women chose IVF-PGS in the hopes of decreasing the emotional burden of RPL and the cost and time spent on another miscarriage. Although the emotional impact of a miscarriage is well documented, there are little data on the emotional impact of a failed IVF cycle or a cycle when all embryos are determined to be aneuploid. In addition, recent data indicate that IVF-PGS does not increase the live-birth rate over expectant management in the RPL population (4).

Treatment costs increase as additional attempts are needed to reach ET. A recent cost analysis of PGS in the RPL population demonstrated that the cost per live birth was approximately $45,000, while the cost per miscarriage averted was >$100,000 (5). These numbers were calculated using published literature and are based on typical-prognosis patients. If the number of cycles needed to reach live birth is increased due to fewer blastocysts available for screening, the cost per live birth would be even higher, thus adding to the emotional burden of treatment. Time to pregnancy and live birth are extremely important to patients, particularly those with DOR. Many argue that time to a successful pregnancy is shorter with IVF-PGS; however, Murugappan et al. found that conception occurred 3.5 months faster with expectant management compared with IVF-PGS (4). The majority of fertile RPL patients will conceive within 3 months of timed intercourse, and multiple IVF-PGS attempts will typically exceed this timeline. Additional data are needed to determine whether the same is observed with time to live birth, a more important metric.

It is important to note that the authors of this paper define DOR as FSH> 10 IU/mL or antimüllerian hormone (AMH) < 1.0 ng/mL. In this population the average number of oocytes retrieved was eight, and the mean number of blastocysts biopsied was 3.6. Although this was lower than their age-matched RPL controls, it still is a reasonable number to proceed with IVF-PGS. Some patients with severe DOR will have even fewer oocytes and blastocysts. It is likely that in this retrospective analysis, patients with the poorest prognosis were counseled against initiating IVF and therefore this study underestimates the impact of DOR on IVF-PGS outcomes. The highest maternal age in this study was 41 and the lowest AMH was 0.4 ng/mL. More severe DOR patients would have a higher incidence of no transfer due to lower blastocyst number or higher likelihood of no blastocyst formation. Patients and providers should be aware that the prognosis quoted in this paper would not apply to patients with AMH < 0.5 or

fewer than four developing follicles, as these patients will likely have an even higher risk of not having an embryo available for transfer.

Although ovarian reserve is clearly tied to IVF-PGS success rates, it is unclear whether women with DOR and RPL have a worse prognosis with expectant management. We cannot rely on the assumption that just because IVF success rates are decreased in DOR patients that spontaneous pregnancy rates are also decreased. Studies are needed to determine whether or not expectant management would outperform IVF-PGS. To date, there is no prospective study comparing IVF-PGS with expectant management for RPL patients. Without this data, we must counsel patients based on retrospective data and all their inherent limitations. Prospective data on IVF-PGS as well as expectant management examining the prognostic impact of ovarian reserve testing on subsequent miscarriage and live-birth rate in an otherwise unexplained RPL population will be essential to counsel patients on which option would provide the highest success rate.

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REFERENCES

1. Shahine LK, Marshall L, Lamb JD, Hickok LR. Higher rates of aneuploidy in blastocysts and higher risk of no embryo transfer in recurrent pregnancy loss patients with diminished ovarian reserve undergoing in vitro fertilization. Fertil Steril 2016;106:1124–8.
2. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril 2012;98:1103–11.
3. Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Hum Reprod 1999;14:2868–71.
4. Murugappan G, Shahine LK, Perfetto CO, Hickok LR, Lathi RB. Intent to treat analysis of in vitro fertilization and preimplantation genetic screening versus expectant management in patients with recurrent pregnancy loss. Hum Reprod 2016;31:1668–74.
5. Murugappan G, Ohno MS, Lathi RB. Cost-effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained recurrent pregnancy loss. Fertil Steril 2015;103:1215–20.