Delayed treatment or deferred treatment: What's intended? A commentary on national oocyte thaw outcomes data

The long-awaited national summary of oocyte thaw outcomes is finally available (1). In keeping with the mission of the Society for Assisted Reproductive Technology (SART) to set standards for fertility care, the release of this data establishes a much-anticipated and desperately needed benchmark for providers of oocyte thaw procedures. The authors of the report are to be commended for undertaking the analysis of the outcomes of oocyte cryopreservation at a national level. For too long, counseling patients about the expectations for thawed oocytes has been limited to data from individual clinics and reference to small series publications, disaggregated and decentralized experiences subject to the idiosyncrasies of patient population and provider preference. Before now, publication bias and a reluctance to publish disappointing results might have provided overly optimistic and unintentionally misleading assessments of expectations for success. The results of small samples are too easily skewed by limited-run data, whereas large, successful programs with good results may have been more willing to share outcome reports that might not have been representative of the general experience in this venture.

Despite the steady rise in the utilization of oocyte cryopreservation, possibly from increased patient awareness, availability of services and insurance coverage, a relatively low fraction of oocyte thaw cycles have been attempted, possibly from continued delay of family building, natural fertility obviating the need to employ previously cryopreserved oocytes, and utilization of other infertility treatment options. The pooled data of the national experience provides a gauge of demographic data, utilization rates, and outcomes experience.

What is already known about human reproductive aging is that oocyte age is a primary predictor of success, and it comes as no surprise that this maxim includes the use of cryopreserved oocytes. Given the historical laboratory challenges presented by oocyte cryopreservation, it is also not surprising that the accumulated results of oocyte thaw so far do not exceed the success rates of in vitro fertilization (IVF) treatment. However, similar pregnancy rates per transfer between frozen-thawed oocytes and IVF treatments using fresh oocytes are encouraging for the promise of delayed pregnancy, but they also raise an important question: why do the frozen oocytes of presumably fertile patients, when thawed, perform only approximately as well as, but not better than, fresh oocytes of their infertile peers undergoing IVF? According to the data, presumably fertile patients at the time of oocyte cryopreservation are transformed into infertile versions of their younger selves at the time of oocyte thaw. This does not negate the value of oocyte cryopreservation, which lies in age-shifting infertile patients to younger oocyte age categories. Because of the impact of reproductive aging, employing younger cryopreserved oocytes may still represent a statistically significant advantage over retrieving fresh oocytes. However, we must still be concerned about why the success rate of cryopreserved oocytes from presumably fertile patients fails to exceed the success rate of fresh oocytes from their infertile, age-at-time-of-collection-matched peers; we must not consider only the improvement in outcome when using previously cryopreserved oocytes for the treatment of infertility at a patient's current chronological age.

Cryopreservation of oocytes stops short of the essential prerequisite of successful infertility treatment: an embryo. Because of the obvious need of infertile patients to have embryos with which to establish pregnancies, oocyte cryopreservation has generally been utilized as a fertility preservation procedure. In view of this limitation, oocyte cryopreservation has not generally been considered a first-line treatment for pre-existing infertility. Unless cryopreservation of oocytes provides some benefit for the treatment of existing infertility, there would be few reasons to justify cryopreservation before the creation of embryos for these patients.

The most concerning result revealed in the national data analysis is that the average duration of cryopreservation was initially 15.7 months (1.3 years) and rose to 29.4 months (2.5 years) for the average patient, who was 35.4 years old at the time of the first cryopreservation cycle. The duration of cryopreservation is surprisingly short, especially if the use of previously cryopreserved oocytes is reserved as a last resort to start or expand families. Presumably, the chronologically youngest oocytes would have the highest probability of creating euploid embryos. Patients undergoing infertility treatment would probably be best served by reserving these oocytes for final efforts and using fresh oocytes as first-line treatment unless a surfeit of oocytes was available or only one pregnancy was desired. What cannot be determined from these data is the reason for thaw: patients seeking to avoid initiating new ovarian stimulation cycles may be doing so because of cost, concern about repeated exposure to infertility treatment, or desire to achieve only one pregnancy from these oocytes. The large standard deviations of the duration of storage at both the beginning (19.7 months) and the end (28.1 months) of the study period suggest that the duration of cryopreservation is not normally distributed, which is to be expected when the purpose of oocyte cryopreservation before the diagnosis of infertility is to preserve future fertility and/or postpone family building. Longer durations of cryopreservation can be predicted for younger patients because they have the longest timeline for natural fertility and attempts at family building, and therefore data from these patients would be predicted to skew the distribution toward longer periods of cryopreservation. Additionally, because there is no strictly defined upper limit for the use of these oocytes, patients can delay their use indefinitely. Therefore, a non-normal distribution of data with a long tail skewed toward longer durations of cryopreservation could be anticipated.

However, according to the data presented, nearly half of all oocyte thaw cycles (47.6%) were performed *within one*

year of oocyte cryopreservation. The short duration of cryopreservation represents a small interval of reproductive time-shifting and largely fails to take advantage of the value of cryopreservation, which is to mitigate the effect of reproductive aging; for many patients, the timeline presented would not have amounted to a change in SART age classification. In some cases, such as the sudden and unanticipated unavailability of sperm, unplanned oocyte cryopreservation may have served to rescue the efforts of patients and their physicians, but cases of previously undiagnosed azoospermia lacking cryopreserved sperm backup would be expected to be few; other patients may have refused donor insemination as a treatment alternative. Another subset of patients may have been disinclined to have embryos cryopreserved for personal or ethical reasons. However, what about the other patients? If a patient is seeking infertility treatment, why cryopreserve oocytes? If a patient is seeking fertility preservation, why thaw oocytes after such a short time? Unfortunately, these questions cannot be answered with the available data.

Because SART uses the "intent" to fertilize cryopreserved oocytes within one year after retrieval as the determinant for categorization of ART data, these cryopreservation-thaw cycles may pass unnoticed. "Unintended" short-term storage would be missing from topline IVF data in the current reports and would be lost in the less carefully scrutinized oocyte cryopreservation-thaw outcomes. Even if this data is subsequently revised and reported in future years, the greatest interest will always lie in the most current clinic data.

SART is to be praised for trying to detail the nuances of infertility treatment outcomes, but the clinic report is not patient-friendly and uses complex definitions. Patients may suffer from information overload, and small corrections to previous-year reports are likely to go unnoticed. Additionally, patients evaluating clinic performance by referring to traditional IVF success rates might be expected to exclude the results of oocyte thaw cycles, since they are already perceived as a technically more complicated treatment with anticipated lower results. They may also presume that this data does not apply to them, since patients undergoing oocyte cryopreservation are generally assumed to have done so for fertility preservation, not after the diagnosis of infertility has been made. However, if so-called "short-term" oocyte cryopreservation is surreptitiously performed as a mode of infertility treatment rather than for fertility preservation, these assumptions are wrong and misleading. Misclassification of this data would do a disservice both to patients seeking oocyte cryopreservation for future family building and to patients seeking IVF for infertility treatment.

Is the statistic for duration of cryopreservation a limitation of the timeline, and can we expect that the duration of cryopreservation will continue to increase as more years of experience are accumulated? For example, if this study had been performed after data on oocyte cryopreservation were only available for one year, all of the outcome data would have been accumulated from oocytes stored for less than one year. At what time can we assume that the duration of availability of these services no longer biases this aspect of the results? Is that time now?

The most important contribution of this study is to report the number of oocytes needed for successful treatment, a benchmark that has serious implications for patients seeking elective services. Unsurprisingly, the average number of cryopreserved oocytes needed to achieve a successful live birth increases with advancing reproductive age; the number needed to thaw to achieve a live birth, however, is staggering. However, if short-term cryopreservation is performed for treatment of pre-existing infertility, the data fails to apply to presumably-fertile patients seeking fertility preservation.

Accordingly, there is no substitute for good quality assurance assessment of laboratory outcomes. Unfortunately, when patients are to be counseled regarding their proposed treatment, the current dataset can be misused as a substitute for real experience. The rise of commercial oocyte freezing-only programs, while ostensibly in place to "disrupt the marketplace" for the benefit of "clients," is lacking in accountability. In the absence of clinic-specific results, nationally aggregated data might be substituted to counsel clients regarding expectations. Given the paucity of outcome data for programs that do not thaw oocytes, patients may encounter another hurdle when seeking infertility treatment: a program willing to accept extramural cryopreserved oocytes. The existence of the SART database, an important safeguard for patients, provides a disincentive for member clinics to import oocytes with unknown performance characteristics; member clinics are required to report the outcomes of these cycles as if they had been responsible for the entire treatment, whereas the program of origin is not required to report outcomes that they did not generate, a neat loophole. Given the lack of transparency when oocytes are transferred between clinics, future SART reporting should include the provenance of cryopreserved oocytes so that the outcome of thaw can be attributed to the originating clinic. The lack of cycle tracking leaves a critical information gap that hopefully can be corrected in future reports.

The national data analysis of oocyte thaw outcomes provides much-needed data that broadens our understanding of the utilization and success of cryopreserved oocytes. The data challenges presumptions about the use of cryopreserved oocytes and their outcomes and informs our counseling about expectations. The data also enlightens us to new, unanswered questions and the challenges that remain.

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