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EDITOR'S COMMENTARY

When ONE is the not-so-loneliest number!

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Big things come in small packages—so the saying goes—but what about when they arrive in small numbers as well? The numbers game is at the heart of what we do in the field of human ARTs. With exception to a healthy semen sample harboring many millions of sperm, the vital ingredients that bring babies to our patients—oocytes and embryos—are generally in short supply. Controlled ovarian hyperstimulation (COH) marshaled in an era when multiple oocytes were availed during the course a single retrieval. And the introduction of ICSI overcame the shortcomings associated with traditional IVF by increasing the number of embryos that could be transferred or frozen. Even the adoption of SET illustrates the value of having that ONE embryo. Yet, and as has received more attention of late, having more embryos at hand does not equate to more babies, as several retrospective studies have now concluded. The so-called live baby rate, when calculated on the basis of the number of oocytes retrieved and embryos produced, remains small—much to the chagrin of our patients. For human ARTs, numbers do indeed matter!

Consider the case of patients with severe azoospermia. For them and their partners, the popular hit song of the early 1970s, "One Is the Loneliest Number," by 3 Dog Night, rings a somber note with respect to their prospects for becoming parents. This may not be the case much longer. Our lead article, this month, comes from the laboratory of Nina Desai. Her team's Technical Innovation paper promises hope for male patients for whom sperm numbers become the limiting factor underscoring their infertility.

The journey from the seminiferous tubules upon the completion of meiosis, through the rete testis, and onto the epididymis, is long and arduous. While typically made by the many that are called to serve in the race to be the chosen one, for patients afflicted with disorders that limit meiotic progression and sperm production, this serpentine hallway of anticipation is void of sperm. For them, the prospects for having a child are dim.

The paper by Desai and colleagues from the Cleveland Clinic (Cryopreservation of individually selected sperm: Methodology and case report of a clinical pregnancy) breaks new ground for the treatment of male factor due to non-obstructive azoospermia. The study is much more than a case report and details a journey from testicular aspirates to embryo production that again, is of the long and arduous variety. The pursuit and selection of motile sperm from 6 patients with severe forms of azoospermia required as many as four hours of screening of testicular aspirates, and when the rare candidates were identified, they were moved into a 1 μL drop of cryopreservation medium, in preparation for storage after slow freeze cryopreservation. The search, in these cases, required an observational skill set aided by darkfield stereo microscopy (deploying maximal illumination), in order to locate and track sperm bearing normal head morphology and some degree of motility. Anyone who has taken on such a challenge knows well that the detection of a small cell in a forest of debris is difficult enough, let alone the additional obstacles to imaging in a highly refractive medium containing cryoprotectant!

Once equilibrated, a single or few sperm were placed in sealed containers and plunged into liquid nitrogen, now safely stored in their "cryo-condos." But the challenges

Capsule Using a single cryopreserved sperm from an azoospermic patient to achieve a term pregnancy required the confluence of technology and determined embryologists.

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continue after the big chill. For the case involving a live birth, 2-3 embryologists searched for a total of 9 h to find the chosen one. With a 33–100% recovery rate, clear evidence of motility was ascertained prior to performing ICSI. Thus, this work brings to our readership a roadmap of detailed technology that can be built upon as a treatment strategy for patients of this kind.

As with any notable achievement, concerns remain regarding the clinical acceptance of new procedures. While seemingly adding another feather in the cap of proponents of slow-freeze cryopreservation, relative to the *vitrificationists* in the audience (an unreasonably contentious debate, as I have previously discussed in this column), much work remains to optimize single sperm cryopreservation for general applicability. We dwell at times on the application of cryopreservation in ARTs without fully acknowledging that drawbacks exist. Among these, the poor recovery rates for eggs or sperm after thawing emphasize again that our methods are less than optimal despite opinions to the contrary.

And proof of the pudding in contemporary settings must await the demonstration of a live birth/term pregnancy as an acceptable outcome. But being ready for prime time implores us to validate safety, efficiency, and reproducibility for any new technology derived from global initiatives generating solid data bases from enough cases to bring it into the realm of the credible and the broadly translatable. Identifying the highest quality sperm, eggs, and embryos has been a daunting task, owing to our inabilities to recognize sentinels consistent with genetic, epigenetic and developmental integrity. For sperm, this means much more than having a good head and good motility (see paper by Agarwal this issue). We must bear in mind that encouraging the use of such technologies to alleviate infertility in patients with disorders of a genetic kind, as may be the case here, confers upon offspring the same pathophsyiology for which treatment is sought presently. Uncovering the inner secrets of what lies within remains the goal of new ARTs and is at the heart of the drive to improve patient care by concretizing the scientific foundations of reproductive medicine.