The great debate: fresh vs frozen, epididymal vs testicular—Does it matter?

The debate regarding the role of sperm source in outcomes following intracytoplasmic sperm injection (ICSI) has raged for quite some time. Fresh versus frozen, epididymal vs. testicular, Lewin et al. (1) attempt to shed light on this issue using aggregate ICSI data from the United Kingdom (UK) over the last decade. Through a query of more than 200,000 ICSI cycles from the UK Human Fertilisation and Embryology Authority, the regulatory registry for all fertility treatments in the UK, the authors arrived at two main conclusions. First, live birth outcomes were similar among cycles using fresh versus frozen sperm, regardless of sperm source (ejaculated vs surgically retrieved). Second, among cycles involving surgical sperm retrieval (SSR), those using epididymal sperm had a higher per-cycle live birth rate than those using testicular sperm (1).

These conclusions are limited by several analytic constraints, many of which are acknowledged by the authors. Because of the use of aggregate data, there was no ability to control for potential confounders such as male and female age, comorbidities, stimulation protocols, and many other factors that likely drive ICSI outcomes. There was also no distinction made between couples with obstructive azoospermia (OA) and nonobstructive azoospermia (NOA), which certainly impacts sperm quality, treatment choices, and outcomes. Likewise, comparison of ejaculated vs SSR sperm may be biased insofar as men undergoing ICSI with ejaculated sperm likely have an element of impaired spermatogenesis, whereas men undergoing SSR may be obstructed.

Despite these limitations, the finding of equivalent outcomes between fresh and frozen sperm is consistent with the existing literature. Karacan et al. (2) reported equivalent pregnancy and live birth rates among couples who underwent fresh versus frozen testicular sperm extraction (TESE) in a cohort of men with both OA and NOA. Even considering only those men with NOA, the cohort for which it has been suggested that fresh sperm may be most advantageous, several recent meta-analyses found no difference in outcomes (3, 4). The aggregate data from Lewin et al. (1) are mostly consistent with these prior findings: although there was a significantly higher implantation rate in the fresh vs frozen groups (67.3% vs. 59.7%; OR, 1.392; $P<.001$), this did not translate into a difference in clinical pregnancy or live birth rates. The study could not distinguish between men with OA and NOA, and it is the latter group that has impaired spermatogenesis and is therefore more likely to experience a potential benefit from avoiding cryopreservation (1). Because of the nature of the data source, the study included only those SSR cycles that resulted in ICSI; it is possible that several men with NOA underwent successful SSR and cryopreservation, only to find that sperm were not recovered after the freeze-thaw process and ICSI was not possible. These men are inherently excluded from most of the literature on this topic, and until we have better data, it is still unclear if we should pursue fresh SSR in men with NOA on this basis alone.

The authors also found higher pregnancy and birth rates in cycles using epididymal sperm compared to testicular sperm. Again, the lack of distinction between OA and NOA is a limitation, as testicular sperm quality in men with NOA is incomparable to higher-quality sperm in men with OA, who likely comprise the epididymal cohort. Furthermore, the study lacks granularity about couples' prior reproductive histories (e.g., recurrent pregnancy loss and recurrent in vitro fertilization failure). For these couples, when the male partner is found to have elevated sperm DNA fragmentation (DFI), testicular sperm is associated with better pregnancy and live birth rates, along with lower miscarriage rates (5). These findings suggest that it is possible that men with elevated DFI, and not OA or NOA, may also be included in the SSR cohort presented by Lewin et al (1). The inability to distinguish these nonazoospermic couples undergoing SSR from the aggregate data presented herein thereby further limits the generalizability of these findings.

So, what sperm should be used for ICSI? Does the source matter? Like many clinical scenarios, there is no clear, one-size-fits-all answer. Certain situations may call for particular sperm sources. Ultimately, providers should treat each couple on an individualized basis according to their unique reproductive history, etiology of azoospermia, sperm DFI, and a variety of other clinical and practical considerations.

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