

Should I opt for intracytoplasmic sperm injection or should I not: high-tech no matter what?



Intracytoplasmic sperm injection (ICSI) stands out as a groundbreaking innovation in the realm of treating male infertility, and there is unanimous consensus on this fact. Having technology that is so successful, particularly in severe cases of male infertility, without obvious short- and long-term side effects is powerful and is an almost surreal advancement in the field of medicine. Nonetheless, as with any advanced treatment, it is important that we exercise caution, and approach it with a keen awareness of its potential unknown consequences.

It is pondered frequently whether applying a highly effective technology to all cases might enhance outcomes even in situations where there is no clear indication for its use—why not explore this possibility? As a testament to this notion, the use of ICSI in the United States surged from 36.4% in 1996 to 51.7% in 2000 to 77.4% in 2020, as indicated in the Centers for Disease Control and Prevention national assisted reproductive technology summary report (<https://www.cdc.gov/art/reports/2020/index.html>). However, there has been no substantial increase reported in the rate of male infertility. Similar trends have been observed in European countries, as highlighted by the European in vitro fertilization (IVF)-monitoring consortium for the European Society of Human Reproduction and Embryology (1).

Two predominant practices have emerged globally: one involves the selective use of ICSI on the basis of specific indications (such as male factor infertility, poor or failed fertilization, the use of preimplantation genetic testing of Mendelian disorders, or frozen eggs), whereas the other entails using ICSI for all patients, regardless of their clinical situation and characteristics.

There are logically two main reasons for the tendency to increase ICSI use: first, the hopeful belief to achieve perfect fertilization rates in all patients, regardless of the presence of male factor infertility, and second, streamlining the IVF laboratory and clinic workflow. The decision feels comfortable given the data on seemingly reassuring health outcomes in ICSI offspring. Or is it?

Indeed, perinatal outcomes were comparable between conventional insemination (CI) and ICSI, as indicated by the results of retrospective studies, meta-analyses, and a recent randomized controlled trial (RCT) involving over 1,000 patients (1, 2). The slightly elevated occurrence of genitourinary abnormalities in male offspring is believed to be linked to paternal characteristics in cases of severe male factor infertility. Because of the long-term health assessment of children conceived through ICSI, it was demonstrated that their neurodevelopment, growth, vision, and hearing are on par with those of spontaneously conceived children (1). Consequently, the technique has been deemed safe for more widespread adoption.

The most recent report from this year, using large patient databases from Nordic European countries, once again evalu-

ated the risk of congenital malformations in live-born singletons conceived with ICSI vs. CI (3). They compared 32,484 ICSI-conceived newborns with 4,804,844 spontaneously conceived and 47,178 CI-conceived newborns and found a slightly but significantly increased risk of major malformations in fresh ICSI cycles compared with fresh CI cycles, 6% vs. 5.3%, compared with 4.2% among spontaneously conceived children. This extensive dataset revealed some noteworthy findings, such as that in cases of male factor infertility, it was observed that hypospadias was the prevailing malformation, confirming prior reports. However, when considering the overall ICSI group, it displayed higher rates of respiratory and chromosomal malformations in contrast to the CI group. Additionally, children conceived through ICSI exhibited a heightened risk of major malformations across various organ systems when compared with children conceived naturally, indicating a potential association between ICSI and increased congenital malformation risk (3). There was no difference in the risk of stillbirth between the ICSI or CI groups.

Interestingly, several studies conducted in the United States and elsewhere, including RCTs and meta-analyses, have revealed that employing ICSI in clinical scenarios such as poor ovarian response, low egg yield, advanced maternal age, preimplantation genetic testing for aneuploidy use, and even the use of frozen donor sperm, did not yield improved outcomes in IVF cycles (2). In fact, recent European Society of Human Reproduction and Embryology guidelines advise against the use of ICSI in cases of nonmale factor infertility (1). The American Society for Reproductive Medicine (ASRM) guidelines from 2020, although perhaps slightly less specific, continue to advocate a cautious approach to the use of ICSI outside of specific indications such as male factor infertility, preimplantation genetic testing of Mendelian disorders, use of frozen oocytes, or instances of prior failed fertilization.

A large retrospective study from a single, academically affiliated fertility center in the US analyzed their data for the effect of ICSI vs. CI on blastocyst ploidy rate in cases with a total motile sperm count >4 million in 3,554 patients undergoing 4,897 IVF cycles and showed a strong tendency for a lower fertilization rate and a lower euploidy rate when ICSI was performed in the setting of nonmale factor infertility (4).

The article authored by Gingold et al. (5), being published in this issue of *F&S Reports*, sets out to address the question of the effectiveness of nonindicated ICSI with a large dataset from Society for Assisted Reproductive Technology member clinics using cycles conducted between 2014 and 2017. The investigators undertook a comprehensive analysis of these cycles by applying the recommendations set forth by the ASRM Practice Committee in 2012 and 2020. Out of the total of 318,930 cycles, 18% used CI, and 82% used ICSI. Notably, the analysis revealed that 151,627 cycles (58%) adhered to the ICSI indication as per the 2012 recommendations, although a mere 41.7% of cycles met the ICSI indication in accordance with the 2020 ASRM guidelines. This suggests that a substantial proportion of cycles involved the nonindicated use of ICSI, signifying an overuse of this technology.

Furthermore, employing multivariate models for analysis, the investigators demonstrated that the nonindicated use of ICSI was associated with a diminished availability of blastocysts for transfer compared with CI, resulting in lower live birth rates. When comparing the outcomes of frozen embryo transfer cycles subsequent to nonindicated ICSI, with or without preimplantation genetic testing for aneuploidy, the success rates in terms of lower birth rate and clinical pregnancy rate were found to be comparable (5).

Although this study does not unveil entirely new findings, it does offer a recent reaffirmation of prior reports. Using data from all Society for Assisted Reproductive Technology-reporting clinics within the US National Database underscores the need for a thoughtful reevaluation of the use of ICSI technology in assisted reproductive procedures.

What about costs? The expenses associated with ICSI are notably higher compared with CI. These increased costs stem from the need for specialized personnel, extended personnel hours, and the use of more advanced equipment. Consequently, this raises the financial burden on patients and health care systems alike. Given that the use of ICSI for indications other than male factor infertility does not necessarily lead to improved success rates and instead incurs additional costs and unnecessary manipulation of embryos, it raises a pertinent question: why has there been such widespread overuse of this technique?

When discussing the ICSI procedure with patients, we are faced inevitably with inquiries about potential risks to offspring and the associated financial implications. It prompts us to reflect on whether pursuing this technique is justified, especially when ample evidence suggests that nonindicated ICSI may not significantly enhance cycle outcomes. It is essential for us to approach the micromanipulation of human gametes with humility, considering the potential for unforeseen issues that may arise from what has become a seemingly routine and commonplace procedure. The ongoing debate concerning the possible long-term effects of ICSI on the

health of offspring, beyond congenital anomalies, underscores the need for continued research and cautious consideration of its application.

At this point, in my opinion, it should be evident to all well-intentioned professionals in our field that there is no apparent benefit or advantage to employing ICSI technology in all IVF cycles. As a result, it is crucial that we establish and follow clear criteria when formulating treatment plans.

CRediT Authorship Contribution Statement

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