Review Article

A Comprehensive Review of Conventional In Vitro Fertilization (IVF) versus Intracytoplasmic Sperm Injection (ICSI) in Patients Without Severe Male Factor Infertility

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Abstract: Intracytoplasmic sperm injection (ICSI) and conventional in vitro fertilization (c-IVF) are foundational techniques in assisted reproductive technology (ART), but their appropriate application has become a subject of considerable debate. While the efficacy of ICSI is undisputed for severe male factor infertility, its routine use in patients without this indication has surged globally, often without robust evidence of improved outcomes. This review synthesizes data from a recent randomized clinical trial (the INVICSI study) and other key meta-analyses and cohort studies to evaluate the comparative efficacy, safety, and long-term implications of both procedures. This report finds that for patients without severe male factor infertility, c-IVF offers comparable, if not superior, cumulative live birth rates while avoiding the increased cost and invasiveness of ICSI. The analysis delves into the psychological and economic drivers of ICSI overuse, such as the irrational fear of total fertilization failure, and discusses the nuanced, yet critical, long-term risks to offspring, including an increased likelihood of inheriting male infertility and potential associations with certain congenital anomalies. This report concludes that c-IVF should remain the preferred first-line treatment for the vast majority of patients without severe male factor infertility, with ICSI reserved for specific, evidence-based indications.

Keywords: in vitro fertilization, intracytoplasmic sperm injection, male factor infertility

1. INTRODUCTION

Since its inception, assisted reproductive technology has revolutionized the treatment of infertility, offering hope to millions of couples worldwide. Over 4 million ART treatments were performed globally between 2008 and 2010, underscoring its pivotal role in modern medicine [1]. Within ART, two primary fertilization techniques are employed: conventional in vitro fertilization (c-IVF) and intracytoplasmic sperm injection (ICSI) [2]. Initially, c-IVF was the standard of care for female and unexplained infertility, where fertilization occurs in a petri dish through the natural interaction of sperm and egg. ICSI, on the other hand, was pioneered in the early 1990s specifically for cases of severe male factor infertility, which would not be treatable with c-IVF. The technique involves a laboratory scientist injecting a single, carefully selected sperm directly into the cytoplasm of an egg using a microscopic needle [4]. A significant and concerning trend has emerged over the last few decades: the widespread application of ICSI has expanded dramatically beyond its original, evidence-based indication. In the United States, for instance, the use of ICSI in fresh IVF cycles more than doubled, increasing from 36.4% in 1996 to 76.2% in 2012 [1]. This rise was most pronounced in cycles without male factor infertility, where the rate jumped from 15.4% to 66.9% during the same period. This disparity between the procedure's original purpose and its current clinical practice is not limited to the U.S.; in some countries in the Middle East, ICSI now accounts for 100% of all fresh cycles, suggesting that factors other than severe male infertility

are driving its widespread adoption [6]. This trend of using a more invasive and costly procedure without clear evidence of benefit has become a major point of contention in reproductive medicine, with professional societies and researchers alike questioning its justification. The increasing use of ICSI for non-male factor infertility, often referred to as "empirical ICSI," has led to a critical knowledge gap in the field. The American Society for Reproductive Medicine (ASRM) has explicitly stated that the routine use of ICSI in cases without male factor infertility is not supported by available evidence [6]. To address this lack of high-quality data, large-scale randomized controlled trials (RCTs) are essential for comparing the efficacy, safety, and cost-effectiveness of ICSI versus c-IVF in this specific patient population [7]. The INVICSI study (IVF versus ICSI) was designed precisely to provide this evidence. It is a key reference point for this review, offering a robust, head-to-head comparison of the two techniques.[6] By integrating the findings of the INVICSI study with other prominent meta-analyses and cohort studies, this review aims to provide a comprehensive and nuanced perspective on the true role of ICSI in modern ART. The central objective is to move beyond the assumption of ICSI's superiority and critically evaluate whether its added invasiveness, cost, and potential risks are justified in a patient population for whom conventional IVF was traditionally the gold standard.

2. METHODOLOGY OF KEY RANDOMIZED CLINICAL TRIALS

The INVICSI study was an open-label, multicenter randomized controlled trial designed to directly compare the efficacy of ICSI and c-IVF in patients without severe male factor infertility [2]. The trial, conducted across six public fertility clinics in Denmark, enrolled patients between November 2019 and December 2022. A total of 824 women undergoing their first IVF cycle were randomized in a 1:1 ratio, with 414 allocated to the ICSI group and 410 to the c-IVF group. A critical aspect of the study's design was its patient inclusion criteria, which were meticulously defined to isolate the effects of the fertilization method. This is important for ensuring the generalizability of the findings to the specific patient population of interest. Other similar trials, such as the NSMI-ICSI study, have used specific semen parameters, such as a semen concentration of 5–15 × 10^6/mL, to define non-severe male infertility, helping to standardize the patient population across different research endeavors [9].The INVICSI study's methodological rigor, including the use of both intention-to-treat (ITT) and per-protocol (PP) analyses, ensures that the conclusions drawn are robust and account for minor protocol deviations and patient withdrawals that occurred during the trial [2]. The primary outcome measure of the INVICSI study was the cumulative live birth rate (CLBR) from a single stimulated cycle, which included all live births resulting from both fresh and frozen-thawed embryo transfers [2]. This endpoint is particularly relevant from a patient perspective, as it reflects the ultimate goal of a single IVF treatment plan rather than just the outcome of a single embryo transfer. Secondary endpoints included a comprehensive list of reproductive outcomes and safety measures. These included fertilization rates, the incidence of total fertilization failure (TFF), time to live birth, and a review of obstetric and perinatal outcomes [2]. This detailed approach allows for a more complete picture of the comparative benefits and risks beyond just the final live birth rate. The protocol for a different trial also highlights the importance of assessing maternal safety and pregnancy complications, which are crucial for a thorough evaluation of any ART procedure [1]. To evaluate the primary outcome, the INVICSI study employed standard statistical methods, reporting a risk ratio (RR) and its 95% confidence interval (CI) to compare the CLBR between the ICSI and c-IVF groups [2]. This allows for a clear interpretation of whether ICSI offers a statistically significant advantage. The use of both ITT and PP analyses is a key methodological strength. The ITT analysis includes all participants as originally randomized, preserving the benefits of randomization and providing a more conservative, real-world estimate of the treatment effect. The PP analysis, which excludes participants who deviated from the protocol, provides a clearer picture of the efficacy in a patient population that strictly adheres to the assigned treatment. The multicenter, randomized design of the INVICSI study is its greatest strength, as it provides a high-level of evidence to address the core

clinical question. The large sample size and the use of CLBR as the primary endpoint contribute to the clinical relevance and reliability of the findings. However, it is important to acknowledge the limitations inherent in such studies. One limitation in a similar study was the lack of diversity in the patient population, which was predominantly female and White, a factor that may affect the generalizability of the results to a broader global population [10]. Another challenge lies in capturing subtle, long-term health outcomes for offspring, which often requires decades of follow-up and relies on extensive registries [11]. The current data, therefore, must be interpreted in light of these limitations, and continued vigilance and long-term surveillance remain paramount.

3. EFFICACY AND REPRODUCTIVE OUTCOMES

Beyond the ultimate outcome of live birth, the study also examined intermediate endpoints. The fertilization rate, defined as the proportion of oocytes with two pronuclei (2PN), was found to be lower in the ICSI group (53.5%) compared to the c-IVF group (58.1%) [2]. This observation challenges the common assumption that injecting sperm directly into the egg would inevitably lead to higher fertilization success. Furthermore, the study addressed the clinical concern of total fertilization failure (TFF), an emotionally devastating but relatively rare event in ART. The incidence of TFF was 4.8% in the ICSI group and 3.7% in the c-IVF group, with no statistically significant difference between the two groups (RR 1.29, 95% CI 0.68–2.54).

Table 01: Comparative Efficacy and Safety of ICSI vs. c-IVF (Non-Severe Male Factor Infertility)

Study/Source	Patient Population	Cumulative Live Birth Rate (ICSI vs. c-IVF)	Risk Ratio (95% CI)	Total Fertilization Failure (ICSI vs. c-IVF)
INVICSI Study [2]	First-time IVF patients without severe male factor infertility	43.2% vs. 47.3%	0.91 (0.79–1.06)	4.8% vs. 3.7%
U.S. Observational Data [1]	Non-male factor cycles	36.5% vs. 39.2%	0.93 (0.91–0.95) (adjusted)	Not Reported
Unexplained Infertility Meta-analysis [13]	Unexplained infertility	33.3% vs. 35.2%	Not Reported	Higher rate with c-IVF in some studies

This finding is particularly important when considering the justification for ICSI overuse. While a meta-analysis in unexplained infertility did find a higher risk of TFF with c-IVF, the number of couples needed to undergo ICSI to prevent a single case of TFF was estimated to be 33, meaning 32 of those couples would undergo an unnecessary procedure [8]. This highlights a paradox: the fear of TFF, while a powerful motivator, is not a valid justification for routinely performing ICSI, which adds cost, invasiveness, and complexity without a statistically meaningful reduction in this rare outcome. The data on embryo development present a more nuanced picture. While one study found that ICSI might have beneficial effects on embryo development in specific subgroups, such as patients with polycystic ovary syndrome (PCOS) or anovulation, leading to faster development and higher KID Scores, this is not a universal finding [4].Conversely, a study on unexplained infertility found that ICSI was associated with a higher cycle cancellation rate (19.1%) compared to c-IVF (11.1%), which could indicate a negative impact on embryo quality or viability [13]. The fact that the data are not uniformly positive for ICSI, even on a metric like embryo development, suggests that a blanket recommendation for its use is inappropriate. Instead, it underscores the need for a highly personalized approach to ART. The one-

size-fits-all adoption of ICSI is misguided; a deeper understanding of patient-specific factors is necessary to identify the rare subgroups that might genuinely benefit from this technology. These conflicting findings highlight a critical area for future research to precisely define these patient profiles.

4. CLINICAL, SAFETY, AND LONG-TERM CONSIDERATIONS

ICSI is an invasive procedure that bypasses the natural selection barriers of the oocyte and requires more time and resources in the laboratory compared to c-IVF [1]. For patients, this translates to additional expense and increased financial burden.[1] While the risks associated with egg retrieval, such as ovarian hyperstimulation syndrome (OHSS), bleeding, or infection, are common to both IVF and ICSI, the microinjection process itself introduces a different set of potential complications [3]. These include the possibility of damaging the egg during the injection, which could have downstream consequences on embryonic development [12]. A significant concern in the debate over ICSI overuse centers on the long-term health and developmental outcomes of the children conceived through this procedure. Birth defects and other health issues in ART-conceived children are known to have a slightly higher risk compared to spontaneously conceived infants, but it is often debated whether this is due to the ART procedure itself or the underlying infertility of the parents [3]. The specific role of ICSI remains a subject of ongoing investigation. A meta-analysis of four prospective cohort studies found no significantly increased risk for major birth defects, including cardiovascular, musculoskeletal, or oral clefts, when comparing ICSI to c-IVF [11]. However, another meta-analysis found a higher rate of overall genitourinary congenital malformation with ICSI [18]. Historically, some studies have even blamed ICSI for an increased incidence of hypospadias, a urogenital defect [5]. However, the etiology of hypospadias is complex and multifactorial, involving genetic and hormonal influences, as well as environmental factors [19]. Therefore, a definitive causal link to ICSI remains elusive, and these associations must be interpreted with caution. On a more reassuring note, studies on long-term developmental outcomes have largely provided a positive outlook.

Table 02: Long-Term Health Outcomes in Offspring: A Comparison of ICSI vs. c-IVF

Outcome	Comparison Groups	Key Finding/Conclusion	Source
Developmental Vulnerability at School Entry	ICSI vs. c-IVF children	No causal effect on overall vulnerability	[21]
Neurodevelopment, Growth, Vision, and Hearing	ICSI vs. spontaneously conceived children	Outcomes are comparable	[22]
Male Reproductive Health (adult men)	ICSI-conceived men vs. spontaneously conceived men	Lower sperm concentration and total sperm count; 3x more likely to have sub-fertile sperm count	[25]
Infertility Inheritance	Sons of fathers with Y chromosome deletions (via ICSI)	Sons inherited the same genetic defect and will likely be infertile	[23]
Major Birth Defects	ICSI vs. standard IVF	No significantly increased risk for most major categories (e.g., cardiovascular,	[11]

		musculoskeletal, hypospadias)	
Genitourinary Congenital Malformations	ICSI vs. standard IVF	Higher rate of overall malformation with ICSI in one meta-analysis	[18]

A population-based study comparing school-age children conceived via ICSI and c-IVF found no causal effect of the procedure on overall developmental vulnerability at school entry [21]. Similarly, a comprehensive review of 24 studies concluded that neurodevelopment, growth, vision, and hearing were comparable between ICSI-conceived and spontaneously conceived children [22]. These findings offer valuable reassurance to parents and clinicians regarding the neurodevelopmental safety of the procedure. Perhaps the most profound and ethically significant concern related to ICSI is the potential to create an intergenerational cycle of infertility. By bypassing the natural barriers of sperm selection, ICSI may facilitate the transmission of genetic defects that would not have been passed on otherwise [1]. This is particularly relevant in cases where the father's infertility is due to a genetic cause, such as a Y chromosome deletion, which is the most commonly known cause of inadequate sperm production [23]. A study on young adult men conceived by ICSI for male factor infertility found that they had significantly lower sperm concentrations and total sperm counts compared to men who were spontaneously conceived. These ICSI-conceived men were nearly three times more likely to have sperm concentrations below the World Health Organization (WHO) reference value for fertility [25].This finding is supported by genetic studies that demonstrated sons of men with Y chromosome deletions who underwent ICSI inherited the same deletion and will likely also be infertile as adults [23].This intergenerational transmission of infertility represents a serious long-term consequence that is directly linked to the ICSI procedure itself, and not just the underlying parental infertility. This raises a host of ethical issues and underscores the critical importance of pre-conception genetic counseling for men undergoing ART [24].

5. DISCUSSION

The body of evidence, including the recent INVICSI study, does not support the routine use of ICSI for patients without severe male factor infertility. However, this does not mean the procedure should be abandoned entirely. There are specific, evidence-based indications where ICSI's use is justified and beneficial. These include: for fertilization of previously frozen oocytes, as the cryopreservation process can harden the zona pellucida; for preventing sperm DNA contamination in samples undergoing pre-implantation genetic testing (PGT) [8]; and in cases with a history of prior absent or low fertilization with c-IVF. In situations where clinicians want to guard against the rare possibility of total fertilization failure, a technique known as "split ICSI" can be used, where a portion of the retrieved eggs are fertilized with ICSI and the rest with c-IVF, providing a safety net without universally applying the more invasive procedure [24]. The widespread overuse of ICSI is not a purely rational, evidence-based phenomenon. It is driven by powerful psychological and behavioral factors on both the provider and patient sides. The provider's "irrational fear of total fertilization failure," while a rare event, can be emotionally devastating to witness and can lead to a state of "cognitive dissonance," where clinicians act against evidence-based guidelines to avoid this outcome. Clinicians may generate plausible but unsubstantiated rationalizations, such as "In our personal experience, ICSI leads to better outcomes" or "Patients are asking for it," to justify their deviation from standard of care [8]. This clinician behavior is reinforced by the patient's perspective. Infertility is a condition with an immense emotional and financial toll. Patients experience cycles of anticipation and disappointment, and the grief from a failed IVF cycle can be profound [28]. Faced with this emotional vulnerability, patients are naturally inclined

to accept any add-on or intervention that offers a perceived advantage, even if it is not supported by data. This combination of provider fear and patient desperation creates an environment where ICSI overuse becomes entrenched, as it is seen as a way to minimize the psychological trauma of failure, even at a higher financial cost and with a potentially more invasive procedure [8]. To address this complex issue, professional societies like the ASRM and ESHRE have issued clear guidelines against the routine use of ICSI in non-male factor cases [6]. However, simply issuing these guidelines is not enough. The analysis suggests a critical need for transparent, evidence-based counseling that empowers patients to make informed decisions. This counseling should not only detail the success rates and risks of each procedure but also explicitly address the rarity of total fertilization failure and the increased costs and invasiveness of ICSI [8]. This is essential to help patients and providers alike move from an emotionally driven decision-making process to one grounded in scientific evidence. A thorough evaluation of the male partner, including a comprehensive semen analysis and genetic testing where indicated, should also be a standard practice to identify any underlying, potentially inherited conditions that would justify the use of ICSI and to inform patients of the risks of passing on infertility to their sons [23].

6. CONCLUSION AND RECOMMENDATIONS

The INVICSI study and other large-scale reviews provide compelling evidence that ICSI does not improve cumulative live birth rates for patients without severe male factor infertility. The belief that ICSI acts as a "safety net" to prevent total fertilization failure is largely unsubstantiated, as the risk of this event is low and not meaningfully mitigated by routine ICSI. Moreover, the long-term data, while still emerging, raises a significant ethical concern about the potential for ICSI to pass on genetic male infertility to sons. The widespread overuse of ICSI is driven by a complex interplay of provider fears and patient emotional vulnerability, which together create a difficult environment for evidence-based decision-making. Based on the synthesis of current evidence, the following recommendations are put forth for clinical practice:

- Primary Recommendation: Conventional IVF should be the first-line fertilization method for all patients without severe male factor infertility.
- ICSI Indications: ICSI should be reserved for specific, evidence-based indications, including severe male factor infertility, the use of previously frozen oocytes, and cases where there is a history of total fertilization failure. Its use for pre-implantation genetic testing (PGT) to prevent sperm DNA contamination is also a valid indication.
- Counseling: Fertility providers must engage in robust, transparent counseling with all patients. This counseling should clearly articulate the comparable efficacy of c-IVF, the minimal risk of total fertilization failure, and the increased cost and invasiveness of ICSI. For men with a known genetic cause of infertility, the ethical implications of transmitting this condition to their sons via ICSI must be discussed thoroughly.
- Male Evaluation: A comprehensive evaluation of the male partner's reproductive health should be a standard component of the infertility workup, including a detailed semen analysis and genetic testing where indicated, to identify treatable conditions and inform the choice of ART procedure.

While this review clarifies the role of ICSI for non-male factor infertility, several critical questions remain. Continued research is necessary to definitively determine if the slightly increased risks of certain birth defects are a direct consequence of the ICSI procedure or are instead a manifestation of the underlying parental infertility. Larger, long-term studies with extended follow-up are also required to confirm the findings on the reproductive health of men conceived via ICSI, as current data on this topic is limited. Finally, research is needed to develop effective counseling tools and strategies that

address the psychological factors influencing both provider and patient behavior, thereby facilitating a more evidence-based and patient-centric approach to ART.

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