

Intracytoplasmic sperm injection for nonmale factor indications: a Committee opinion

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Intracytoplasmic sperm injection, although typically effective for overcoming low or absent fertilization in couples with a clear abnormality of semen parameters, is frequently used in combination with assisted reproductive technologies for other etiologies of infertility in the presence of semen parameters that meet the World Health Organization normative reference values. This committee opinion provides a critical review of the literature, where available, to identify situations in which this may or may not be beneficial. This document replaces the previously published document of the same name, last published in 2020 (Fertil Steril 2020;114:239–45). (Fertil Steril® 2026;126:49–56. ©2026 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: ICSI, fertilization, male infertility, ovarian reserve, IVF

Intracytoplasmic sperm injection (ICSI) was introduced in 1992 to improve fertilization in couples with male factor infertility, undergoing in vitro fertilization (IVF), or in couples with fertilization failure in a prior IVF cycle without detectable abnormalities of semen parameters (1–3). Although the diagnostic criteria used to identify male factor infertility fail to predict with perfect accuracy, poor or absent fertilization in assisted reproductive technology (ART), studies to date support the safety and efficacy of ICSI to treat various male factor conditions (4–7). The use of ICSI for patients with borderline or even normal semen parameters has increasingly become more common (8, 9).

In the United States, the use of ICSI for all indications increased from 36.4% in 1996 to 76.2% in 2012, with the largest increase (from 15.4% to 66.9%) occurring in cycles with nonmale factor infertility (10). Many centers utilized ICSI for 100% of cases.

Data from the US Centers for Disease Control and Prevention (CDC) on the percentage of fresh nondonor oocyte retrievals that used ICSI for diagnosed male factor in 2016 ranged from 87% to 94% across all age groups, and ICSI in cases without male factor ranged from 68% to 72% (11). A cohort study published in 2018 using CDC data demonstrated that increased use of ICSI did not correlate with an increase in male-factor diagnoses in patients <35 years and showed only a modest increase in live-birth rates per cycle over the study period (2000–2014) (12). This suggests that the increasing use of ICSI for nonmale factor infertility cases did not improve live-birth rates. Other population-based studies have concurred with this view by demonstrating a similar cumulative live-birth rate when comparing ICSI with conventional IVF for couples with nonmale factor infertility (13, 14).

Notably, two large population-based studies suggest that ICSI for non-

male factor infertility may be associated with worse outcomes. A 2024 study using Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) data analyzed >400,000 fresh autologous IVF cycles and found that nonindicated ICSI was associated with lower odds of reaching blastocyst-stage transfer and lower odds of live birth (15). This study demonstrated that even after adjusting for confounders, use of ICSI in the absence of male factor infertility resulted in significantly reduced reproductive efficiency. Additionally, a study analyzing CDC data from 317,996 fresh IVF cycles without male factor infertility found that ICSI use was associated with lower implantation rates (23.0% vs. 25.2%; adjusted risk ratio [RR], 0.93; 95% confidence interval [CI], 0.91–0.95) and live birth rates (36.5% vs. 39.2%; adjusted RR, 0.95; 95% CI, 0.93–0.97) compared with conventional IVF (10). Taken together, these findings suggest that routine use of ICSI in fresh IVF cycles without male factor may not only lack benefit but may also reduce the chance of live birth.

Proposed indications for the use of ICSI, where no identifiable male factor

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is present, now include unexplained infertility, poor-quality oocytes, low oocyte yield, advanced maternal age, prior fertilization failure with conventional insemination, preimplantation genetic testing (PGT), fertilization after in vitro maturation (IVM), and fertilization of cryopreserved oocytes. Some practitioners have even proposed routine use of ICSI in all IVF cases without an indication. The rationale for all these indications, with the exception of PGT, is to avoid fertilization failure.

When using ICSI in these settings, the likelihood of fertilization failure must be weighed against the potential risks and costs of the procedure. ICSI requires additional laboratory experience, resources, effort, and time. Thus, expanded use of ICSI increases the complexity and cost of IVF. It should be recognized that the goal of treatment, thus the outcome of interest, is live birth. Studies of surrogate outcomes, such as fertilization failure, may not correlate with live birth (16–19).

ICSI FOR UNEXPLAINED INFERTILITY

Intracytoplasmic sperm injection has been proposed for use in patients with unexplained infertility because its use may bypass potential fertilization barriers that could be the cause of the unexplained infertility. Two studies in patients with unexplained infertility compared conventional insemination with ICSI using sibling oocytes. The fertilization rates after ICSI, even when the immature oocytes not subjected to ICSI were included, were higher than those of the conventionally inseminated group: 65.3% vs. 48.1% ($P < .001$) and 61.0% vs. 51.6% ($P < .001$) for the two studies, respectively (20, 21). Fertilization failure occurred more commonly in the conventional insemination groups than in the ICSI groups: 16.7% vs. 0% ($P < .002$) and 19.2% vs. 0.8% ($P < .001$), respectively. Other studies have confirmed these findings (19, 22–25). However, these studies used sibling oocytes, and the embryos transferred were a mixture of those from the inseminated and ICSI groups, so no information about the effects of insemination or ICSI on clinical outcomes, such as implantation, pregnancy, or live-birth rates, could be ascertained.

A study of 60 women with unexplained infertility randomized patients to IVF with conventional insemination or ICSI. The study found no statistically significant differences in the primary outcome (fertilization rate 77.2% vs. 82.4%) or in the secondary outcomes of embryo quality, implantation rate (38.2% vs. 44.4%), clinical pregnancy rate (50% in each group), or live-birth rate (46.7% vs. 50%) (26). In a different study, including patients with endometriosis without male factor infertility, there was no significant difference in fertilization and live birth rates between using conventional insemination vs. ICSI (27).

A meta-analysis examined fertilization rates per retrieved oocyte in patients with unexplained infertility across 11 randomized controlled studies. In five of these studies, sibling oocytes were specifically assigned to ICSI or conventional IVF before assessment of maturity, and no relevant information was presented in the others. An almost 30% higher fertilization rate was observed in ICSI-fertilized oocytes (RR 1.27;

95% CI, 1.02–1.58). Fertilization failure was >8 times more likely in cycles that used conventional insemination compared with ICSI (RR 8.22; 95% CI, 4.44–15.23). An important concern with this meta-analysis was that the failed fertilization rate was 21.5% (194 of 901) in the conventional fertilization group, much higher than the presumed background rate in an unexplained infertility population (28).

Overall, the current evidence regarding the benefits of the routine use of ICSI for unexplained infertility is limited. The limited evidence suggests that ICSI may be associated with a decreased occurrence of fertilization failure but does not demonstrate an improvement in live birth. Further studies are, thus, needed to determine the role of ICSI in this population.

Summary statement

- *ICSI for unexplained infertility without male factor infertility has been associated with increased fertilization rates in some studies. However, it has not been shown to improve live birth outcomes.*

ICSI FOR POOR-QUALITY OOCYTES

Morphologically abnormal oocytes (with either nuclear, cytoplasmic, or zona pellucida abnormalities) in the presence of normal semen parameters create a clinical challenge (29). No well-designed studies have been identified that address whether the use of ICSI in such cases improves live birth rates.

Summary statement

- *There are no studies addressing whether ICSI of poor-quality oocytes improves live birth rates.*

ICSI FOR DIMINISHED OVARIAN RESERVE

ICSI is commonly used in cases of diminished ovarian reserve or low oocyte yield, in theory, to increase the number of embryos achieved compared with the number expected with conventional insemination. One controlled trial randomized 96 patients without male factor infertility who had <6 oocytes to ICSI or conventional insemination (30). Comparing ICSI and conventional insemination, the mean patient age (35.3 and 36.7 years, respectively) and the mean number of oocytes retrieved (4.4 and 4.5, respectively) were similar. The study found that ICSI provided statistically similar outcomes compared with conventional insemination in terms of fertilization rates (77.7% vs. 70.2%), fertilization failure (11.5% vs. 11.5%), embryo quality, mean embryos per patient (2.5 vs. 2.2), clinical pregnancy rates (17.3% vs. 21.1%), and miscarriage rates (33.3% vs. 36.4%). Other more recent retrospective studies confirmed these findings (31, 32).

A large European multicenter study investigated whether ICSI offered any benefit over conventional IVF for women with nonmale factor infertility, considering different ovarian response categories (33). Analyzing 4,891 first IVF cycle patients across 15 hospitals, the study found that mean fertilization rates, embryo utilization, and both fresh and

cumulative live birth rates did not differ significantly between ICSI and conventional IVF, regardless of the number of oocytes retrieved. The results indicated that the number of eggs collected did not influence the relative effectiveness of ICSI vs. IVF in such cases.

When initial ART cycles in women with elevated follicle-stimulating hormone, as the only infertility diagnosis were compiled from the SART CORS registry (2004–2011) and analyzed, ICSI did not improve the odds of live birth. In those cycles, meeting the SART criteria for diminished ovarian reserve (a composite diagnosis that considers age, ovarian reserve biomarkers, and other clinical factors), ICSI was associated with a lower live-birth rate compared with cycles using conventional IVF, showing an absolute decrease of 1.5% (20.4% LBR in ICSI vs. 21.9% in cycles without ICSI, $P=.002$) (34).

On the basis of the limited evidence, the use of ICSI for diminished ovarian reserve does not improve fertilization rates, embryo number and quality, or live-birth rates.

Summary statement

- *ICSI for low oocyte yield, diminished ovarian reserve, and advanced maternal age does not improve fertilization or live birth outcomes.*

ICSI FOR ADVANCED MATERNAL AGE

Oocytes retrieved from older women have been theorized to have structural defects of the zona pellucida or cytoplasm that might reduce the fertilization rate with conventional insemination. In practice, oocyte fertilization rates in women older than 35 years using conventional insemination are similar to the fertilization rates of younger women (19). One retrospective study attempted to address this question, demonstrating similar fertilization rates (64% vs. 67%), clinical pregnancy rates (21.1% vs. 16.7%), and live-birth rates between women who had oocytes fertilized by conventional fertilization and those who had ICSI (11.9% vs. 9.6%) (35).

ICSI FOR PRIOR FAILED FERTILIZATION WITH CONVENTIONAL INSEMINATION

The use of ICSI in IVF after prior total failed fertilization with normal semen analysis in a prior IVF cycle is advocated to reduce the risk of subsequent failed fertilization. Retrospective studies have shown that in cycles where there was total fertilization failure in IVF/conventional insemination, subsequent fertilization rates using IVF/conventional insemination again ranged from 30% to 97% (36–38). Subsequent total failed fertilization was correlated with the number of follicles, oocytes retrieved, and mature oocytes.

In a prospective study, sibling oocytes were allocated to conventional insemination vs. ICSI in the IVF cycle after total failed fertilization with IVF/conventional insemination (39). In this study, 12 (11%) of 109 oocytes were subsequently fertilized by IVF/conventional insemination, and 78 (48%) of 162 were subsequently fertilized with IVF-ICSI. This study also examined patients with a history of low fertilization (< 25%) with IVF/conventional insemination. The

study found that 16 (22%) of 72 oocytes were subsequently fertilized by IVF/conventional insemination, and 58 (60%) of 97 oocytes were subsequently fertilized with IVF-ICSI. Another prospective study also examined sibling oocyte fertilization rates in a subsequent cycle after total failed fertilization with IVF/conventional insemination (2). In this study, 0 (0%) of 89 oocytes fertilized with IVF/conventional insemination and 90 (62.9%) of 143 oocytes fertilized with IVF/ICSI. Although subsequent low or failed fertilization may be related to poor oocyte quality, using IVF-ICSI may decrease the risk of subsequent low fertilization. Of note, there is no established cutoff to define low fertilization rates for the subsequent use of ICSI.

Summary statement

- *ICSI can increase fertilization rates when lower than expected or failed fertilization has previously occurred with conventional insemination.*

ICSI FOR ROUTINE USE

The routine use of ICSI for all oocytes, regardless of the etiology of infertility, has been proposed (40, 41). The rationale is to reduce the likelihood of fertilization failure and potentially increase the number of embryos. A well-powered multicenter, randomized, controlled trial compared outcomes after conventional insemination or ICSI in 415 couples with nonmale factor infertility (16). The fertilization rate per oocyte retrieved was higher with conventional insemination than with ICSI (58% vs. 47%, $P<.0001$). Fertilization failure occurred in 11 (5%) of 206 and 4 (2%) of 209 in the conventional insemination and ICSI groups, respectively. On the basis of these data, the number needed to treat with ICSI to prevent one case of fertilization failure with conventional insemination is 33.

Additionally, this study reported similar clinical pregnancy rates with conventional insemination and ICSI (33% vs. 26%; RR 1.27; 95% CI, 0.95–1.72). The study concluded that the use of ICSI should be reserved only for male-factor infertility. Other nonrandomized studies comparing conventional insemination with routine ICSI have found no statistically significant differences in fertilization rate, failed fertilization, clinical pregnancy rates, or live-birth rates (10, 42–49). Although the risk of failed fertilization is low, it occurs with similar frequency following both conventional insemination and ICSI.

Several randomized controlled trials (RCTs) and systematic reviews have provided compelling evidence that routine use of ICSI does not improve reproductive outcomes in couples without male factor infertility and may even be associated with worse outcomes (10, 15).

In a randomized trial, 1,064 infertile couples with normal sperm count and motility were randomized to ICSI or conventional IVF. The study found no significant difference in live-birth rates (IVF 32.7% vs. ICSI 33.6%) or cumulative ongoing pregnancy rates, suggesting no benefit of ICSI in this population (50). A 2023 Cochrane meta-analysis

similarly concluded that ICSI in couples without severe male factor does not improve live-birth or clinical pregnancy rates compared with conventional IVF (51). In 2024, a large, multicenter RCT across 10 centers in China involving 2,387 couples with nonsevere male factor infertility undergoing IVF, found that live birth occurred in 33.8% of couples in the ICSI group and 36.6% in the conventional IVF group (adjusted RR 0.92, 95% CI, 0.83–1.03; $P = .16$), indicating no statistically significant difference (52). Neonatal outcomes, including neonatal death rates, were also similar between groups. Furthermore, in a multicenter RCT of 1,064 couples with infertility and men with abnormal morphology (the median sperm morphology was 3% in both groups), but otherwise normal sperm count and motility, ICSI did not significantly improve outcomes compared with conventional IVF (53). Live birth rates were 34.6% for ICSI and 31.2% for conventional IVF (RR 1.11, 95% CI, 0.9–1.37), with no statistically significant interaction between sperm morphology and the effect of ICSI vs. conventional IVF on live birth, ongoing pregnancy, clinical pregnancy, or total fertilization failure ($P = .27, .38, .33$, and $.60$, respectively). Most recently, a multicenter RCT compared conventional IVF and ICSI in 824 women undergoing their first IVF cycle without severe male factor infertility across six Danish fertility clinics. The primary outcome, cumulative live birth rate after one stimulated cycle (including all fresh and frozen embryo transfers), was 43.2% in the ICSI group and 47.3% in the conventional IVF group (RR 0.91, 95% CI, 0.79–1.06), showing no statistically significant difference. Secondary outcomes, including fertilization rates, ongoing pregnancy rates, and neonatal outcomes, were also similar between groups (54).

Summary statement

- *In cases without male factor infertility or a history of prior fertilization failure, the routine use of ICSI for all oocytes does not improve live birth rates.*

ICSI FOR PGT

Intracytoplasmic sperm injection had been recommended for cases requiring PGT of embryos. The rationale for ICSI use was to ensure monospermic fertilization and eliminate the possibility of contamination from extraneous sperm attached to the zona pellucida in cases where a polymerase chain reaction was used (55). With newer, next-generation sequencing molecular techniques, this is less of a concern. In cases of PGT-A, studies have not shown any benefit of ICSI over IVF in terms of numbers of embryos, euploidy rates, or live birth rates (13, 56). In the case of PGT-M, however, ICSI is typically recommended to minimize contamination from cumulus cells and extraneous sperm to reduce the chance of misdiagnosis.

Summary statement

- *In the absence of male factor infertility, the use of ICSI for PGT-A does not improve live birth rates, euploidy rates, or numbers of embryos.*

- *The use of ICSI for PGT-M may be appropriate to reduce the chance of contamination of extraneous sperm, which could affect the accuracy of test results.*

ICSI AFTER IVM

Because of the potential hardening of the zona pellucida during in vitro maturation (IVM) of immature oocytes (57, 58), ICSI has been advocated as the preferred method for fertilization. Although the fertilization rates appear to be increased using ICSI for IVM oocytes, developmental competence may be impaired, as demonstrated in one comparative trial (59). Fertilization rates of mature oocytes in patients who did not receive gonadotropins were only 37.7% (229 of 608 mature oocytes) with conventional IVF compared with 69.3% (318 of 459 mature oocytes) when ICSI was used as the insemination technique. Despite lower fertilization results, the implantation rate was statistically significantly higher in embryos derived from oocytes fertilized with conventional IVF compared with ICSI (24.2% vs. 14.8%; $P < .05$), as were the clinical pregnancy rates per embryo transfer (34.5% vs. 20.0%; $P < .05$) (41). Further trials comparing IVF with ICSI for fertilization of in vitro matured oocytes are needed.

Summary statement

- *ICSI appears to improve fertilization rates of IVM oocytes, although implantation and clinical pregnancy rates appear higher in IVM oocytes inseminated conventionally. Caution should be exercised in the interpretation of these data due to the lack of data on live-birth rates.*

ICSI FOR CRYOPRESERVED OOCYTES

In general, oocyte cryopreservation involves the removal of the cumulus cells before freezing. Although limited data exist, it is thought that cryopreservation may alter the oolemma and/or zona pellucida, potentially reducing fertilization rates or increasing polyspermy rates with conventional insemination. This question, however, has been poorly studied, with one study indicating that retaining the cumulus for vitrification of oocytes may improve fertilization rates after conventional insemination compared with ICSI (60). Largely due to the clinical preference to vitrify oocytes that are metaphase II, ICSI has been the preferred method of fertilizing cryopreserved oocytes. Limited data exist that compare conventional insemination with ICSI for cryopreserved oocytes (61).

Summary statement

- *ICSI on cryopreserved oocytes is the most established method for achieving fertilization, although limited data currently exist to support this procedure.*

OTHER CONSIDERATIONS OF ICSI FOR NONMALE FACTOR INFERTILITY

The safety of ICSI for nonmale factor infertility has not been evaluated. However, in studies of male factor infertility, ICSI

has been associated with a small increased risk of adverse outcomes in offspring. These risks are generally attributed to the underlying male factor infertility. It is unknown how these risks may relate to ICSI for nonmale factor infertility patients (62–68).

One large population cohort study, including over 308,000 births, with >6,100 from ART, noted that the risk of major birth defects after IVF (with or without ICSI) had an odds ratio of 1.24 (95% CI, 1.09–1.41) after adjustment for several potential confounders (69). When the women undergoing IVF alone were separated from those also undergoing ICSI, only those undergoing ICSI still had an increased odds ratio for birth defects (1.57; 95% CI, 1.30–1.90). However, this study included men with and without normal sperm counts. The increased rate of birth defects after IVF in men with abnormal semen analyses is well recognized, given the known chromosomal abnormalities in such men, which may have impacted the results of this study. Still, this study injects an additional note of caution into the unindicated use of ICSI in all IVF cycles.

A multicenter RCT of 824 women across six Danish fertility clinics specifically evaluated birth defect outcomes among patients without severe male factor infertility undergoing conventional IVF vs. ICSI (54). The study found no statistically significant difference in the rate of congenital anomalies between children conceived by conventional IVF vs. ICSI (4.2% vs. 3.4%, respectively, $P=.68$).

A 2025 study used a population-based cohort of 3,656 singleton children conceived via IVF in Australia, to compare school-entry developmental outcomes between children (age 4–6 years) conceived by ICSI (without severe male factor infertility) and those conceived by conventional IVF (70). The primary outcome was developmental vulnerability at school entry, defined as scoring below the 10th percentile in two or more domains of the Australian Early Development Census. The study found no causal effect of ICSI on the risk of developmental vulnerability at school entry compared with conventional IVF. The adjusted risk difference was –1.11% (95% CI –4.23 to 2.01%), and the adjusted RR was 0.90 (95% CI, 0.68–1.21).

Summary statement

- *ICSI has been associated with a small increased risk of birth defects in offspring. It is unclear whether this risk extends to the use of ICSI for nonmale factor indications.*

SUMMARY

- ICSI for unexplained infertility without male factor infertility has been associated with increased fertilization rates in some studies. However, it has not been shown to improve live-birth outcomes.
- There are no studies addressing whether ICSI of poor-quality oocytes improves live-birth rates.
- ICSI for low oocyte yield, diminished ovarian reserve, and advanced maternal age does not improve fertilization or live-birth outcomes.

- ICSI can increase fertilization rates when lower than expected or failed fertilization has previously occurred with conventional insemination.
- In cases without male factor infertility or a history of prior fertilization failure, the routine use of ICSI for all oocytes does not improve live birth rates.
- In the absence of male factor infertility, the use of ICSI for PGT-A does not improve live birth rates, euploidy rates, or numbers of embryos.
- The use of ICSI for PGT-M may be appropriate to reduce the chance of contamination of extraneous sperm, which could affect the accuracy of test results.
- ICSI appears to improve fertilization rates of in IVM oocytes, although implantation and clinical pregnancy rates appear higher in IVM oocytes inseminated conventionally. Caution should be exercised in the interpretation of these data due to the lack of data on live-birth rates.
- ICSI on cryopreserved oocytes is the most established method for achieving fertilization, although limited data currently exist to support this procedure.
- ICSI has been associated with a small increased risk of birth defects in offspring. It is unclear whether this risk extends to the use of ICSI for nonmale factor indications.

CONCLUSIONS

- Routine use of ICSI for nonmale factor infertility is not recommended.
- For patients without male factor infertility, ICSI is not recommended for unexplained infertility, low oocyte yield, diminished ovarian reserve, advanced maternal age, or PGT-A.
- ICSI without male factor infertility may be of benefit for select patients undergoing IVF with PGT-M, prior poor/no fertilization with conventional insemination, or previously cryopreserved oocytes.
- The additional cost burden of ICSI for nonmale factor indications, where data on improved live-birth outcomes over conventional insemination are limited or absent, must be considered.

Disclaimers

This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine (ASRM) as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report. This document was reviewed by ASRM members, and their input was considered in the preparation of the final document.

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Inyección intracitoplasmática de espermatozoides (ICSI) para indicaciones que no se deben al factor masculino: opinión de un comité

La inyección intracitoplasmática de espermatozoides, aunque típicamente es efectiva para superar la fertilización baja o ausente en parejas con una anomalía clara en los parámetros del semen, se utiliza con frecuencia en combinación con tecnologías de reproducción asistida para otras etiologías de infertilidad en presencia de parámetros seminales presentados en los valores de referencia normativos de la Organización Mundial de la Salud. Esta opinión de comité ofrece una revisión crítica de la literatura, cuando está disponible, para identificar situaciones en las que esto puede o no ser beneficioso. Este documento reemplaza al documento previamente publicado con el mismo nombre, publicado por última vez en 2020 (Fertil Steril 2020;114:239–45).