# Intracytoplasmic sperm injection (ICSI) for non–male factor indications: a committee opinion

Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

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Intracytoplasmic sperm injection, while 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 2010 normative reference values. This committee opinion provides a critical review of the literature, where available, to identify situations where this may or may not be of benefit. This document replaces the previously published document of the same name, last published in 2012 (Fertil Steril 2012;98:1395–9). (Fertil Steril® 2020;114:239–45. ©2020 by American Society for Reproductive Medicine.)

**El resumen está disponible en Español al final del artículo.**



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) (4–7), studies to date support the safety and efficacy of ICSI to treat various male factor conditions. The use of ICSI for patients with borderline or even normal semen parameters has 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 non–male factor infertility (10). Data from the U.S. 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 the diagnosis of male factor in patients <35 years, and 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 non–male factor infertility cases did not improve live-birth rates. Another population-based cohort study, published in 2018, concurred with this view by demonstrating a similar cumulative live-birth rate when comparing ICSI with conventional IVF for couples with non–male factor infertility (13).

Proposed indications for the use of ICSI where there is no identifiable male factor 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 avoiding fertilization failure. When using ICSI in these settings, the likelihood of fertilization failure must be balanced against any potential risks of the procedure and its costs. 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.

## 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

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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% versus 48.1% ($P<.001$) and 61.0% versus 51.6% ($P<.001$) for the two studies, respectively (14, 15). Fertilization failure occurred more commonly in the conventional insemination groups than in the ICSI groups: 0 versus 16.7% ($P<.002$) and 0.8% versus 19.2% ($P<.001$), respectively (10, 11). Other studies have confirmed these findings (16–20). However, these studies used sibling oocytes, and the embryos transferred were a mixture from the inseminated and ICSI groups, so no information about the effect 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 (21). 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%). There were two cases of failed fertilization in the conventional insemination group. The study was limited, however, by its small sample size. Similarly, another randomized trial comparing conventional insemination with ICSI in 100 couples with unexplained infertility revealed no difference in pregnancy rates between the two treatment groups: IVF 32% and ICSI 38%; relative risk (RR) 0.83; 95% confidence interval (CI), 0.48–1.45) (22). Fertilization failure occurred in only one couple (out of 48) in the conventional insemination group.

A meta-analysis examined the fertilization rates per retrieved oocyte of couples with unexplained infertility in 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 over eight 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 (23).

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.

- ICSI for unexplained infertility without male factor infertility has been associated with increased fertilization rate 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 (24). No studies addressing whether the use of ICSI in such cases improves live birth were identified as of June 2019.

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

## ICSI FOR LOW OOCYTE YIELD

Intracytoplasmic sperm injection is commonly used in cases of 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 six or fewer oocytes to ICSI or conventional insemination (25). When comparing ICSI and conventional insemination, the mean ages of the patients (35.3 and 36.7 years, respectively) and mean number of oocytes retrieved (4.4 and 4.5 oocytes, 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%). A recent large retrospective analysis confirmed these findings (26).

When initial ART cycles in women for whom elevated levels of follicle-stimulating hormone (FSH) was the only infertility diagnosis were compiled from the Society for Assisted Reproductive Technology Clinical Outcomes Reporting System (SART-CORS) registry (2004–2011) and recently 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 versus 21.9% in cycles without ICSI, $P=.002$) (27).

Based on the limited evidence, the use of ICSI for low oocyte yield does not significantly improve fertilization rates, embryo number and quality, or live-birth rates.

- ICSI for low oocyte yield does not improve 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 (20). 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%) (28).

- ICSI for advanced maternal age does not improve live birth outcomes.

## 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% (29–31). Subsequent total failed fertilization was correlated with the number of follicles, oocytes retrieved, and mature oocytes.

In a prospective study, sister oocytes were allocated to conventional insemination versus ICSI in the IVF cycle after total failed fertilization with IVF/conventional insemination (32). In this study subsequent conventional insemination resulted in 12 (11%) of 109 oocytes fertilized by IVF/conventional insemination and 78 (48%) of 162 fertilized with IVF-ICSI. Although subsequent total failed fertilization may be related to poor oocyte quality, using IVF-ICSI may decrease the risk of subsequent poor fertilization.

- 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 the infertility has been proposed (33, 34). 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 non–male factor infertility (35). 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. Based on 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 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, 36–43). Although the risk of failed fertilization is low, it occurs with similar frequency following both conventional insemination and ICSI.

- In cases without male factor infertility or a history of prior fertilization failure, the routine use of ICSI for all oocytes is not supported by the available evidence.

## 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 polymerase chain reaction was used (44). With next generation sequencing newer molecular techniques, this is less of a concern. As expected, this report showed no difference in cleavage and quality of embryos derived from normal zygotes by the two insemination methods. Another retrospective analysis failed to show a statistically significant difference in aneuploidy rates or mosaicism when comparing fertilization methods (45), although there is a dearth of data in the literature.

- ICSI for PGT in the absence of male factor infertility should be limited to cases where contamination of extraneous sperm could affect the accuracy of test results.

## ICSI AFTER IVM

Because of potential hardening of the zona pellucida during IVM of immature oocytes (46, 47), 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 (48). Fertilization rates of matured oocytes in patients who did not receive gonadotropins were only 37.7% (229 of 608 matured 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%; $P<.05$) (33) as were the clinical pregnancy rates per embryo transfer (34.5% vs. 20.0%; $P<.05$). Trials comparing IVF with ICSI for fertilization of in vitro matured oocytes are needed.

- ICSI appears to improve fertilization rates of in vitro matured (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. This may lead to changes in the zona pellucida that could reduce fertilization rates with conventional insemination. For these reasons, ICSI has

been the preferred method of fertilizing cryopreserved oocytes. Limited data exist that compare conventional insemination with ICSI for cryopreserved oocytes (49).

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

## OTHER CONSIDERATIONS OF ICSI FOR NON–MALE FACTOR INFERTILITY

The safety of ICSI for non–male 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 non–male factor infertility patients (50–55).

One large population cohort study including over 308,000 births, with over 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 (56). 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.

- ICSI requires additional laboratory experience, resources, effort, and time. Thus, expanded use of ICSI increases the complexity and cost of IVF.

## SUMMARY

- ICSI for unexplained infertility has been associated with increased fertilization rates and decreased risk of failed fertilization in some studies but 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 and advanced maternal age does not improve 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 is not supported by the available evidence.
- ICSI for PGT in the absence of male factor infertility should be limited to cases where contamination of extraneous sperm could affect the accuracy of test results.
- ICSI appears to improve fertilization rates of in vitro matured (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 preferred method for achieving fertilization, although limited data currently exist to support this procedure.
- When considering use of ICSI in non–male factor infertility to decrease the incidence of unexpected failed fertilization, prevention of one case of unexpected fertilization failure requires more than 30 unnecessary cases of ICSI.

## CONCLUSIONS

- ICSI without male factor infertility may be of benefit for select patients undergoing IVF with preimplantation genetic testing for monogenic disease and previously cryopreserved oocytes.
- The additional cost burden of ICSI for non–male factor indications, where data on improved live-birth outcomes over conventional insemination are limited or absent, must be considered.

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**Inyección intracitoplasmática de espermatozoides (ICSI) como indicación de factor no masculino: una opinión del comité.**
**La inyección intracitoplasmática de espermatozoides, aunque generalmente es efectiva para tratar la fecundación baja o ausente en parejas con una clara anormalidad de los parámetros seminales, es frecuentemente utilizada en combinación con tecnologías de reproducción asistida para otras etiologías de infertilidad en presencia de parámetros de semen que cumplen los valores normativos de referencia de la Organización Mundial de la Salud 2010. Esta opinión del comité proporciona una revisión crítica de la literatura, en base a evidencia disponible, para identificar situaciones donde esta puede o no ser beneficiosa. Este documento reemplaza al documento publicado anteriormente con el mismo nombre, publicado por última vez en 2012.**