Intracytoplasmic sperm injection (ICSI) for non-male factor infertility: a committee opinion

The Practice Committees of the American Society for Reproductive Medicine and 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 utilized in combination with assisted reproductive technologies for other etiologies of infertility in the presence of normal semen parameters. This committee opinion provides a critical review of the literature, where available, to identify situations where this may or may not be of benefit. (Fertil Steril® 2012;98:1395–9. ©2012 by American Society for Reproductive Medicine.)

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). While 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). Proposed indications for use of ICSI include: unexplained infertility, poor-quality oocytes, low oocyte yield, advanced maternal age, prior fertilization failure with conventional insemination, routine use in all IVF cycles, preimplantation genetic testing (PGT), fertilization after in vitro maturation (IVM), and fertilization of cryopreserved oocytes. 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.

ICSI FOR UNEXPLAINED INFERTILITY

ICSI has been proposed for use in patients with unexplained infertility, since 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. Fertilization rates after ICSI, even when the immature oocytes not subjected to ICSI were included, were higher than the conventionally inseminated group: 65.3% vs. 48.1%, $P<.001$ and 61.0% vs. 51.6%, $P<.001$ for the two studies respectively (10, 11). Fertilization failure occurred more commonly in the conventional insemination groups than in the ICSI groups: 0% vs. 16.7%, $P<.002$ and 0.8% vs. 19.2%, $P<.001$ respectively (10, 11). Other studies have confirmed these findings (12–16). However, since these studies used sibling oocytes and the embryos transferred were a mixture from the inseminated and ICSI groups, no information about the effect of insemination or ICSI on clinical outcomes such as implantation, pregnancy, or live-birth rates could be ascertained from these studies.

A study of 60 women with unexplained infertility randomized patients to IVF with conventional insemination or ICSI (17). The study found no significant differences in the primary outcome (fertilization rate 77.2% vs. 82.4%) or in secondary outcomes: embryo quality, implantation rate (38.2% vs. 44.4%), clinical pregnancy rate (50% in each group), or live-birth rate

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(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 to ICSI in 100 couples with unexplained infertility revealed no difference in pregnancy rates between the two treatment groups (IVF 32%, ICSI 38%; relative risk (RR) 0·83 [95% confidence interval (CI) 0·48–1·45]) (18). Fertilization failure occurred in only one couple (out of 48) in the conventional insemination group.

Overall, the current evidence regarding the routine use of ICSI for unexplained infertility is limited and does not demonstrate improvement in clinical outcomes. Further studies are thus needed to determine the role of ICSI in this population.

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. No studies addressing whether the use of ICSI in such cases improves clinical outcomes were identified for this document.

ICSI FOR LOW OOCYTE YIELD

ICSI is commonly used in cases of low oocyte yield, in theory to increase the number of embryos achieved compared to that expected with conventional insemination. One controlled trial randomized 96 patients without male factor who had six or fewer oocytes to ICSI or conventional insemination (19). When comparing ICSI and conventional insemination, 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. ICSI provided statistically similar outcomes compared to 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 (20).

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

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 over 35 years of age using conventional insemination are similar to fertilization rates in younger women (16). No studies assessing the benefits of ICSI in this specific group of patients for any outcomes such as embryo quality or implantation rate were identified for this document.

ICSI FOR PRIOR FAILED FERTILIZATION WITH CONVENTIONAL INSEMINATION

The use of ICSI in IVF following 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 30–97% (21–23). Subsequent total failed fertilization was correlated with number of follicles, oocytes retrieved, and mature oocytes. In a prospective study, sister oocytes were allocated to conventional insemination vs. ICSI in the IVF cycle following total failed fertilization with IVF/conventional insemination (24). In this study subsequent conventional insemination resulted in 12/109 (11%) oocytes fertilized by IVF/conventional insemination and 78/162 (48%) fertilized with IVF/ICSI. Although subsequent total failed fertilization may be related to quality of the IVF stimulation, utilizing IVF/ICSI may decrease the risk of subsequent poor fertilization failure.

ICSI FOR ROUTINE USE

The routine use of ICSI for all oocytes, regardless of the etiology of the infertility, has been proposed (25, 26). The rationale is to reduce the likelihood of fertilization failure and potentially increase the number of embryos. A well-powered multi-center, randomized, controlled trial compared outcomes after conventional insemination or ICSI in 415 couples with non-male factor infertility (27). The fertilization rate per oocyte retrieved was higher with conventional insemination than with ICSI (58% vs. 47%, $P<.0001$). Fertilization failure occurred in 5% (11/206) and 2% (4/209) in the conventional insemination and ICSI groups, respectively. Based on these data, the number needed to treat (NNT) 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 non-randomized studies comparing conventional insemination to routine ICSI have found no significant differences in fertilization rate, failed fertilization, clinical pregnancy rates, or live-birth rates (28–31). Although the risk of failed fertilization is low, it occurs with similar frequency following both conventional insemination and ICSI. The emotional and financial costs of failed fertilization must be taken into consideration.

The routine use of ICSI for all oocytes does not appear to be justified in cases without male factor infertility or a history of prior fertilization failure based on available evidence.

ICSI FOR PGT

ICSI is used in cases requiring PGT of embryos. The rationale for ICSI use is to ensure monospermic fertilization and eliminate potential paternal contamination from extraneous sperm attached to the zona pellucida (32, 33). While there are no randomized, controlled trials, the concerns of inaccurate results due to extraneous sperm contamination with PGT justifies the use of ICSI in this situation.

ICSI AFTER IVM

The investigational process of IVM may lead to alterations in the zona pellucida, which reduce the fertilization potential of oocytes using conventional insemination (34, 35). One study randomly assigned mature oocytes after being denuded of their cumulus cells to conventional insemination or ICSI. Oocytes that were allowed to mature in vitro with or without their cumulus complexes had significantly lower fertilization rates with conventional insemination compared to ICSI (56.3% vs. 84.1%, $P<.01$ and 39.5% vs. 84.5%, $P<.01$, respectively) (34). An additional study similarly demonstrated conventional insemination fertilization rates of 37.7% of mature oocytes (although oocyte maturity was not assessed until the fertilization check 18 hours after insemination), compared to a 69.3% fertilization rate using ICSI of metaphase II oocytes. While pregnancy rates were similar between the conventional insemination and ICSI groups (23.8% and 17.1%, respectively, P=not significant), the implantation of oocytes fertilized with standard insemination techniques was higher than those where ICSI was used (24.2% vs. 14.8%, $P<.05$) (25). While ICSI may improve fertilization rates of in vitro matured oocytes, further studies are needed to evaluate this hypothesis.

ICSI FOR CRYOPRESERVED OOCYTES

In general, oocyte cryopreservation involves the removal of the cumulus cells prior to 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 comparing conventional insemination to ICSI for cryopreserved oocytes (36).

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. It is unknown how these risks may relate to ICSI for non-male factor patients (37–46).

One large population cohort study including over 308,000 births, with over 6100 from ART, noted that the risk of major birth defects after IVF (with or without ICSI) had an odds ratio of 1.2 (95% CI, 1.09 to 1.41) after adjustment for several potential confounders (47). 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 to 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, and is not unexpected in this study. Still, this study injects an additional note of caution into the indiscriminate 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 is a safe and effective therapy for the treatment of male factor infertility.
- ICSI can increase fertilization rates when lower than expected or failed fertilization has previously occurred with conventional insemination.
- ICSI for unexplained infertility does not improve clinical outcomes.
- ICSI for low oocyte yield and advanced maternal age does not improve clinical outcomes.
- ICSI may improve fertilization rates in a subsequent cycle following total failed fertilization in a prior IVF/conventional insemination cycle, although fertilization failure seems to correlate with poor ovarian stimulation.
- ICSI for routine use may decrease the incidence of unexpected failed fertilization; however, more than 30 couples would have to undergo ICSI unnecessarily to prevent one failed fertilization.
- ICSI may be of benefit for patients undergoing IVF with PGT, in vitro matured oocytes, and previously cryopreserved oocytes.

CONCLUSIONS

- There are no data to support the routine use of ICSI for non-male factor infertility.
- ICSI may be beneficial for patients using PGT, IVM, or cryopreserved oocytes.
- The safety and cost of ICSI in the setting of non-male factor infertility must be considered.

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