

Routine use of intracytoplasmic sperm injection: How much is it evidence based?

Intracytoplasmic sperm injection (ICSI) was first started in 1992 as a treatment for severe male factor infertility.^[1] More than a decade later, Jain and Gupta^[2] explored the trends in the use of ICSI compared with the proportion of those with male factor. They found that the diagnosis of a male factor had remained static over the period but the use of ICSI had increased. In data published by the Human Embryology and Fertilization Authority (HFEA, UK), about half (52.6%) of fresh *in vitro* fertilization (IVF) treatments in 2013 involved ICSI; a similar proportion to that has been seen in recent years (2012: 53.1%; 2011: 53% - HFEA trends and figures 2013). In the USA, 67% of all treatments were ICSI in 2013, although the diagnosis of male factor was again reported in a much lower proportion of treatments.

(https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?ClinicPKID=0).

It is, therefore, clear that ICSI has been used to treat other causes of infertility. In some clinics, almost 100% of IVF cases use ICSI as a method of fertilization. This raises the question whether ICSI should be used for reasons other than a male factor or even for all.

MALE FACTOR INFERTILITY

ICSI was started as a fertilization technique for those with severe male factor infertility, i.e., those with severe oligoasthenospermia and those with surgically retrieved sperm. Its use has been expanded to those with male factor infertility, but what constitutes male factor infertility is always a matter of debate. Moreover, the diagnosis of what male factor is has changed over the years with changing WHO reference ranges for acceptable semen parameters [Table 1].

In addition, morphology is determined by individual laboratories. Despite standardization, this analysis does vary widely among laboratories. Some laboratories do not rely on morphology to make decisions about ICSI since on the day of egg collection; there is no time to do appropriate morphology assessments.

As the threshold of what constitutes male factor has been lowered, the proportion of ICSI cycles should be lowered, but that is not the case.

UNEXPLAINED INFERTILITY

Although randomized controlled trials have suggested no difference in the pregnancy rates if ICSI is routinely used in cases of unexplained infertility,^[3,4] later meta-analysis of observational data suggests that fertilization rates are higher with ICSI leading to more embryos,^[5] greater utilization and hence theoretically, the possibility of higher cumulative live birth rates.

There is a wide variation in the rates quoted for total fertilization failure (TFF), 5-25%. TFF has devastating consequences. ICSI has been recommended routinely to prevent TFF. Best available evidence comes from meta-analysis of observational data,^[5] which has inherent limitations. The pooled relative risk (RR) of TFF for well-defined unexplained infertility was significantly higher with conventional insemination (RR, 8.22, 95% confidence interval [CI] 4.44-15.23). Although this is statistically significant, CIs are very wide. Given the proportion of TFF is very low, existing randomized controlled trials are not powered to answer the question.^[3] It has been calculated by the authors of this meta-analysis that one has to do five extra ICSI cycles to prevent one TFF in cases of unexplained infertility. However, ASRM Practice Committee reports 30 extra cases of ICSI are needed to be done to prevent one TFF.

Following TFF or low fertilization with IVF, ICSI is recommended. It has to be remembered that ICSI minimizes but does not eliminate the risk of TFF. The chance of TFF with ICSI is about 3%. However, that includes cases with severe male factor infertility.^[6]

Others have suggested the use of split IVF/ICSI in cases of unexplained infertility.^[7]

POLYCYSTIC OVARIAN SYNDROME

In a single-center study, sibling oocytes were randomized to be inseminated either through ICSI or IVF.^[8] There was a higher fertilization rate and lower TFF in those inseminated through ICSI. However, the unit of randomization was oocytes rather than women.

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Newer indication for ICSI

As practice of IVF has evolved, ICSI has been used for other indications:

- **Frozen eggs:** A higher proportion of women are freezing eggs due to social reasons. When they return for their treatment, it will need to be ICSI due to the stripping of the cumulus mass before freezing and zona hardening post thaw. A number of clinics are creating egg banks by freezing the donor eggs. This makes the process much simpler rather than trying to match donor and recipients. As these eggs are frozen, they will need ICSI even if sperm is entirely normal.
- **Long duration of infertility:** It is thought that one of the contributing factors of the long duration of unexplained infertility is sperm/egg interaction. Some clinics do not wish to take any risk with this and resort to ICSI to minimize the risk of TFF. The evidence supporting this in the literature is currently nonexistent.
- **Low number of eggs:** In a retrospective analysis of the 1014 patients that underwent 2819 consecutive cycles, it was suggested that ICSI may improve ongoing pregnancy rate in those who have a poor ovarian response as per ESHRE criteria.^[9] However, this has the inherent limitations of retrospective data analysis. These findings have been contraindicated in the past by some,^[10] but supported by others.^[11] Hence, the jury is still out. The American Society of Reproductive Medicine does not support its use for this indication.^[12]
- **Advanced maternal age:** A higher proportion of women are presenting at advanced maternal age, where due to limited time and suspicion of thickened zona, ICSI has started to be the preferred mode of fertilization. There is no evidence that ICSI for advanced maternal age improves outcome.^[12]
- **HIV-positive cases:** To reduce the risk of transmission ICSI is recommended in cases where the male partner is HIV-positive (even with undetectable viral load).
- **In vitro maturation:** It was initially thought that oocytes matured *in vitro* have hardened zona and will consequently need ICSI to facilitate fertilization. However, in a randomized trial of sibling oocytes, no difference was found in fertilization rates, utilization rates, and blastocyst formation rates in oocytes matured *in vitro* when either ICSI or IVF was used.^[13]

Hence, the indications of ICSI have increased from just severe male factor infertility (without appropriate evidence) to the extent that this question is repeatedly asked whether we should do ICSI for all? There are advantages and disadvantages of doing ICSI routinely [Table 2].

EMERGING TECHNIQUES

It has been argued that sperm selection is better with IVF, as it is more natural. However there have been significant developments in the sperm selection methods such as IMSI^[14] or hyaluron binding.^[15] It may mean that the argument for a better selection of sperm has swung in favor of ICSI compared to IVF, but that has yet to be proven.

COST EFFECTIVENESS

There is limited data reported in the literature to study the cost effectiveness, alongside clinical effectiveness of routine IVF versus ICSI only for nonmale factor only. ICSI does add additional

Table 1: Comparison of WHO reference range for semen parameters

Semen parameters	WHO 1992	WHO 2010
Volume (ml)	2.0	1.5
Count (million/ml)	20	15
Progressive motility (%)	50	32
Total sperm number (million/ejaculate)	40	39
Morphologically normal forms (%)	30	4

Table 2: Advantages of intracytoplasmic sperm injection and in vitro fertilization

Advantages for ICSI	Advantages of IVF
Information about maturity of oocyte is available - easy to explain to patients	Less invasive than ICSI, less chance of damage to oocyte
ICSI bypasses any potential barrier to fertilization	Natural selection in IVF
Less chance of total fertilization failure	Chance of immature oocytes (at egg collection) to mature as surrounded by zona while inseminated with sperm for IVF
Increased fertilization rate, more embryos to choose from - increased cumulative pregnancy rate	TFF is rare; hence, it does not justify the routine use of ICSI

ICSI: Intracytoplasmic sperm injection, IVF: *In vitro* fertilization, TFF: Total fertilization failure

costs over IVF. In a four center Dutch study, assessing costs of all procedures involved in IVF/ICSI, it was found that the cost of ICSI was 8.3% higher than IVF.^[16] However, no cost effectiveness was studied. A cost-effectiveness modeling exercise revealed that split IVF/ICSI becomes the preferred approach as a result of higher cumulative live birth rate as compared to all IVF and the lesser cost per live birth compared to only ICSI.^[7]

RISK OF CONGENITAL ANOMALIES

There have been suggestions that ICSI is associated with higher incidence of congenital anomalies. Unfortunately, most of this data do not segregate the ICSI done for severe male factors over other causes. Reassurance about congenital abnormalities is provided by the fact that despite the increase in the use of ICSI across the world, there are no proportionately increased risks of congenital abnormalities.

Although concerns were raised,^[17] meta-analysis did not show any difference in congenital anomalies in children born by ICSI when compared to IVF.

PATIENT PERCEPTIONS

There are no studies which have evaluated patient perceptions as to whether they would prefer to have IVF/ICSI when the diagnosis is nonmale factor and, after all, the information is given.

CONCLUSIONS

The proportion of cases using ICSI is increasing with or without supporting evidence. The definition of male factor infertility is woolly at best. The indications of ICSI have widened to more than severe male factor alone. There is no good data on clinical and

cost effectiveness of the use of ICSI for nonmale factor infertility, linked to an outcome of cumulative live birth rate.

The risk of congenital anomalies is increased in ICSI done for severe male factor cases, but there is no evidence that it is the same for nonmale factor.

Further research is needed in evaluating patient preferences and assessing long-term outcomes of children born as a result of ICSI done for nonmale factor infertility. This could be done through large registry data available in various countries. With newer methods of selecting sperm and more familiarity with ICSI techniques, an appropriately powered randomized controlled trial is needed for evaluating the clinical and cost effectiveness of ICSI for nonmale factor infertility. Outcome measures for this trial should go beyond clinical pregnancy rates and include cumulative live birth rates and long-term societal costs.

These studies are needed urgently; otherwise, we are on a slippery slope of ICSI for all, without appropriate evidence to back it up. So far, another example of changing practice in our field without evidence in an era of evidence-based medicine.

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