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Is intracytoplasmic sperm injection an add-on to conventional in vitro fertilisation for infertility without severe male factors?

Since the birth of the first in vitro fertilisation (IVF) baby in 1978, there have been over 12 million babies born from IVF globally.¹ The first IVF baby in mainland China was born at Peking University Third Hospital in 1988, nowadays, more than 300 thousand IVF babies are born in China per year. Intracytoplasmic sperm injection (ICSI) was introduced in 1992 in which conventional IVF (c-IVF) had failed in severe male infertile couples (Figure 1).² Over the past 30 years, the use of ICSI has increased and now accounts for nearly two-thirds of IVF cycles worldwide, including 70% in Europe and North America, and nearly 100% in some low-income and middle-income countries.³ However, the male factor solely or partly contributes to 30~50% of couples with infertility,^{4,5} with severe male factor only affecting up to 30% of those with male infertility.^{6,7} The current utilization of ICSI is far beyond the proportion of severe male factors among infertile couples.⁸ In addition, fewer applications of ICSI in China didn't result in a low fertility rate for infertile patients without severe male factors, which would give raise to controversy about ICSI or conventional IVF for fertilization during ART in these population.

A multicentre randomised clinical trial⁹ was implemented and published in *The Lancet* recently. Between April 2018 and November 2021, 2,387 couples from 10 reproductive medicine centres in China were randomised to the ICSI group (n=1,184) and the c-IVF (n=1,203) group. After excluding couples who were ineligible, randomised twice, or withdrew consent, 2,329 couples were included in the primary analysis (1,154 in the ICSI group and 1,175 in the c-IVF group). Live birth after the first embryo transfer occurred in 390 couples (33.8%) in the ICSI group and 430 couples (36.6%) in the c-IVF group (adjusted risk ratio [aRR] 0.92; 95% confidence interval [CI]: 0.83 to 1.03). Total fertilization failure rates were not statistically significantly different between groups (42 [3.6%] vs 56 [4.8%], aRR 0.77, 95% CI: 0.52 to 1.14). Compared with the c-IVF group, the ICSI group had fewer available embryos on day 3 (4 [2, 8] vs 5 [2, 9], adjusted p=0.0009), and a lower implantation rate (564/1642 [34.3%] vs 620/1644 [37.7%], RR 0.91, 95% CI: 0.83 to 1.00). The incidences of maternal and neonatal complications were comparable. Post-hoc analysis of cumulative pregnancy outcomes showed that the cumulative live birth rate of embryos transferred within 12 months after randomisation in the ICSI group was lower than that of the c-IVF group (514 [44.5%] vs 598 [50.9%]; aRR 0.88, 95% CI: 0.81 to 0.96). As of August 31, 2023, the cumulative live birth rate in the ICSI group remained lower than in the c-IVF group (539 [46.7%] vs 618 [52.6%]; aRR 0.89, 95% CI: 0.82 to 0.97). The Kaplan-Meier survival curve also showed that the cumulative ongoing pregnancy rate leading to live birth in the ICSI group was lower than that of the c-IVF group (log-rank p=0.0073; aHR 0.86, 95% CI: 0.76 to 0.96).

This randomised trial⁹ showed that in infertile couples with non-severe male factors, ICSI does not improve live birth rates compared to c-IVF. A similar trial from Viet

Nam published in *The Lancet*¹⁰ also affirmed the equivalence of conventional IVF and ICSI in couples with female infertility factors and male partners with basic semen parameters (ie, sperm concentration and motility) within the WHO reference ranges. Since ICSI is a more invasive procedure, associated with additional costs and a potential increased risk to offspring health, c-IVF should be recommended as the choice of treatment for infertile couples with non-severe male factors.

Health issues in infants are key focus of assisted reproductive technology (ART), both in c-IVF and ICSI. Data in this randomised trial⁹ comparing health outcomes based on fertilisation methods remain insufficient. A Nordic study¹¹ from the CoNARTaS group found the risk of major malformations in live-born singletons to be slightly higher after fresh ICSI compared with fresh IVF. These findings should be considered when choosing the assisted reproductive technology method for couples without male factor infertility. Another big data cohort study¹² showed the rates of congenital malformations in c-IVF and ICSI were comparable, as indicated by the adjusted odds ratio of 1.098 (95% confidence interval 0.787, 1.532). The rates of specific malformations based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) were also comparable between ICSI and IVF. It is evident that additional trials and studies are needed to address these gaps in data on infant health after ART.

These research findings will provide the best evidence-based basis for international guidelines, further standardize the indications of ICSI technology, avoid abuse of ICSI technology, and improve the standardization and safety of assisted reproductive technology. Meanwhile, appropriate choice will reduce the cost of infertility treatment, and help to benefit more infertile couples and families.

The *Lancet* invited Professor Sandro C. Esteves from Androfert Reproductive Center in Campinas, Brazil, and Professor Peter Humaidan, a reproductive endocrinologist from Fertility Clinic at Skive Regional Hospital of Aarhus University in Denmark, to write a comment¹³ to provide in-depth interpretation of the results of the study⁹ and the utilization of ICSI in ART. It is pointed out that this study provides Level 1 evidence for reproductive medicine practitioners in the treatment of non-severe male infertility by conducting a large-scale, multicenter randomized controlled trial. It is also pointed out that with the rapid development of emerging technologies, the conventional semen analysis methods widely adopted globally and recommended by the World Health Organization, as well as the evaluation methods for male infertility, need to be further innovated. Factors such as sperm DNA or epigenetic defects, endocrine parameters, lifestyle, environmental exposure, medication, and anatomical pathology need to be considered.

Funding Statement

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Ethics Approval Statement

Ethics Approval Not Applicable.

Competing Interest Statement

There are no competing interests for any author.

Contributorship statement

Li R planned, conducted and modified this article. Yang R was in charge of preparing and modifying the manuscript.

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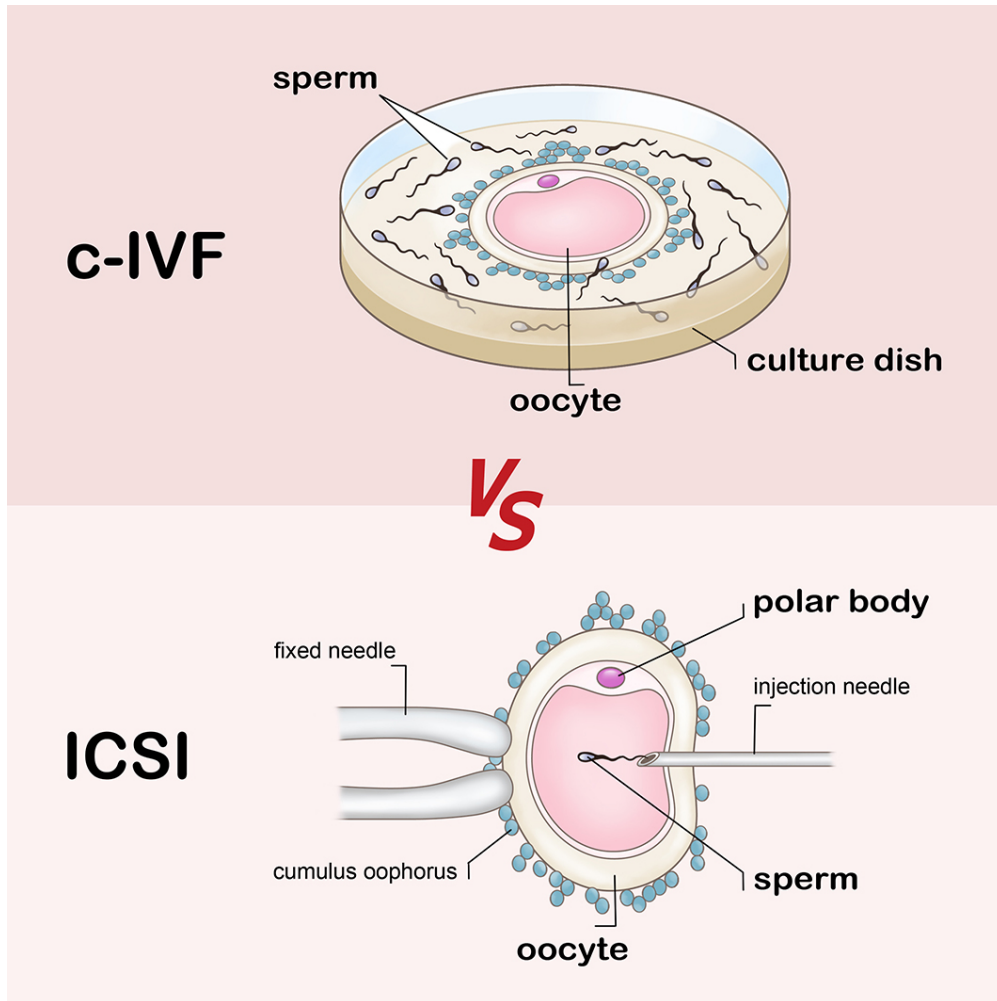
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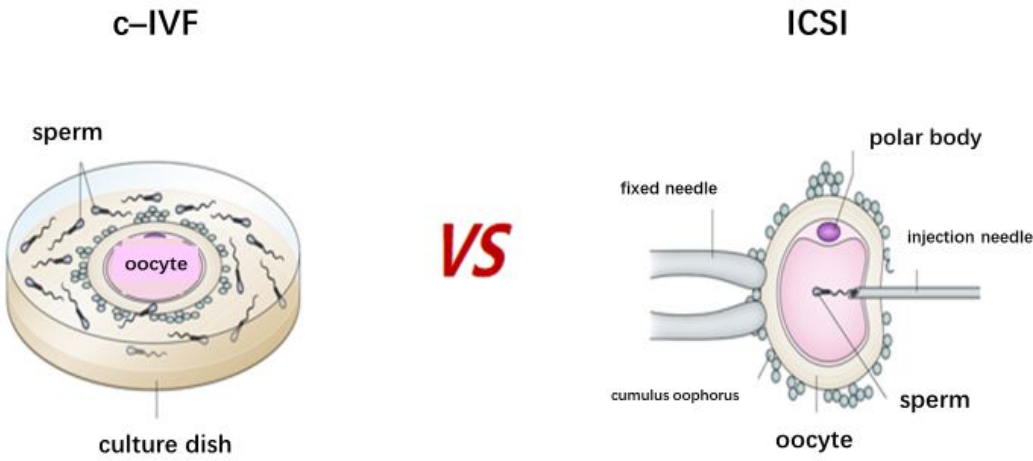


Figure 1: Sketch Map of c-IVF and ICSI fertilisation procedures

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