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LETTER TO EDITOR

# Comparison of in vitro fertilization/intracytoplasmic sperm injection on live birth rates in couples with non-male factor infertility and advanced maternal age: overlooked details

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We read with interest the recent publication named "Comparison of in vitro fertilisation/intracytoplasmic sperm injection on live birth rates in couples with non-male factor infertility and advanced maternal age" [1]. The study included a total of 577 fresh cycles within 10 years of retrospective data.

When comparing conventional in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) outcomes in couples with advanced maternal age and non-male factor infertility, fertilization, embryo utilization, blastocyst for embryo transfer, and miscarriage rates were found to be comparable. On the contrary, IVF insemination appears to increase the chance of live birth compared with ICSI.

ICSI is an invasive procedure that incurs additional costs, and the potential risks from ICSI in the absence of any clear advantage in improving live birth outcomes should be considered. Understanding the relative effectiveness of ICSI compared with IVF cycles can help providers and patients to make informed decisions about its applications. The study's findings are welcomed by us in terms of discouraging the overuse of ICSI for the treatment of non-male factor infertility.

However, when examining the publication, it is seen that there appear to be some critical flaws.

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One of the largest studies to examine whether ICSI is of value for older women with non-male factor infertility on the decision regarding the insemination method reflects the practice dilemma care providers face [2]. Here, older patients with decreased fertility potential were mostly fertilized, performing ICSI to "ensure" maximal fertilization. On the other hand, patients with secondary infertility were mostly fertilized via IVF, probably due to the method's "proven" fertilization success. The McPherson study included only the first treatment cycles, but the infertility status (primary vs secondary) and the insemination method's decision criteria were not addressed. There appears to be a common practice in the field to avoid fertilization failures after IVF, as secondary infertility patients with proven fertilization success are more blindly assigned to conventional insemination. As the decision criteria were absent, it will be inevitable that such biases will arise. The study's length (≈ 10 years) introduces practices that have changed over the years, i.e., increase in blastocyst transfers and freeze-all cycles, which can also create potential bias.

In the current study, infertility diagnoses were classified as tubal, endometrial, unexplained, and others. However, ovulation disorders are present in more than 25% of infertile female partners, and the majority of these women have polycystic ovary syndrome [3]. We believe that, at best, the missing ovulation disorders category should have been placed within the "other" category, as it is unrealistic that a patient cohort of female infertility is free of ovulation disorders. In this context, we understand that we are dealing with a critical flaw. Patients with "other female infertility" etiology and with a higher body mass index (BMI) were more common in the ICSI group. Accordingly, the ICSI group seems to be assembled with more patients with ovulation disorders but only those who do not develop an ovarian hyperstimulation syndrome (OHSS), which points out a poor to moderate ovarian response. The reproductive outcome of these women may be

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influenced by BMI [4], as different endometrial gene expression patterns during the window of implantation have been described in obese patients, particularly in those with polycystic ovaries [5]. Besides, since freeze-all and OHSS patients were excluded and patients with good to hyper response did not receive an embryo transfer, the patients in the ICSI group with high pregnancy and live birth expectations were not inevitably available in the study. This might create bias in favor of the IVF group.

The other issue is that cycles with immature oocytes collected at oocyte pick-up (OPU) were excluded from the study. As we all know, for IVF inseminations, oocyte maturity cannot be identified, as the insemination procedure is performed before denudation. The appearance of the cumulus-oocyte complex is mainly used to predict oocyte maturity, but this does not guarantee a definite identification. Therefore, some patients with mature oocytes in the IVF group might be excluded from the study. Meanwhile, if the maturity of IVF oocytes were evaluated post-fertilization, which is supposed to be predominantly late day 0 or early day 1, then some immature oocytes would have matured in vitro during the fertilization process. Therefore, oocyte maturity was inevitably assessed at different times in the two insemination methods, making the comparison of oocyte maturity, fertilization, blastocyst development, and embryo utilization rates uninterpretable.

In this study, it is seen that there are potential differences between the characteristics of both groups. We believe that the abovementioned details will be useful for future research.

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## Declarations

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**Conflict of interest** The authors declare that they have no conflicts of interest.

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