



Perspective

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Semen features for conventional IVF: Need for a simple universal index

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Conventional *in-vitro* fertilization (C-IVF) and intracytoplasmic sperm injection (ICSI) are the two existing insemination methods presently in use in contemporary medically assisted reproduction treatments. While C-IVF refers to co-incubation of a cumulus-oocyte complex (COC) with a certain concentration of sperm suspension, ICSI is defined as the injection of a single spermatozoon directly into the ooplasm of a denuded oocyte. Although the balance of the literature is motivating enough to prefer C-IVF as the insemination method in non-male factor infertility cases, real world data reflect that majority of the practitioners are far from being convinced to do so[1].

There are conceivable reasons from the practitioners' point of view for preferring ICSI in their practices, the most important of which is "the fear of total fertilisation failure". Actually, several studies[2] and guidelines of the international societies[3,4] clearly show the similarity of both techniques regarding the probability of total fertilisation failure. Anyhow, it is a quite stressful situation for the practitioner to explain C-IVF related total fertilisation failure to a patient who has already been under the influence of mass media promoting ICSI as the state of the art practice for almost all etiologic subgroups of the infertile population.

Another reason for preferring ICSI is the sophisticated misbelief that "the technique promises higher fertilisation rate". The fact is: if the fertilisation rate is calculated per inseminated oocyte [number of two pronuclei (2PN) oocytes/number of inseminated oocytes ×100], ICSI may yield higher fertilisation rate compared to C-IVF as expected since immature oocytes have already been discarded after denudation and only mature oocytes are enrolled in the ICSI procedure. On the other hand, if the denominator of the equation is changed as all collected COCs (number of 2PN oocytes/all collected COCs ×100), then C-IVF is reported to result in either similar or higher fertilisation rate[5]. With no doubt, the latter equation provides a better index regarding the total number of embryos obtained.

Considering that ICSI is currently used as the routine insemination technique in the Middle East and in most of the Balkan countries[1], another crucial but not much pronounced point for the tendency towards ICSI use is that the young practitioners stepping in the field of medically assisted reproduction in these geographical

regions start their professional life with ICSI as the only available insemination method without having the chance of training or even observing C-IVF as an alternative.

Which features should spermatozoa possess to ensure successful C-IVF? In other words, what should be the lowest state of semen quality for not preferring C-IVF? The aim of this paper is to draw attention to this point. Apart from the debatable issues stated above, difficulty to define the suitable semen quality can be regarded as an additional hesitancy for the practitioners to proceed to C-IVF. Medical practices are not uniform and cannot always be put into mathematical frames because of the variation of biological systems *e.g.* great diversity may be observed between analyses of consecutive semen samples of the same individual and there may be heterogeneity among evaluation reports of the same semen sample by different andrologists. Furthermore, neither ESHRE Special Interest Group of Embryology nor Alpha Scientists in Reproductive Medicine present strict semen criteria for preferring C-IVF. Instead, it is recommended that while choosing the insemination method, laboratories should develop and apply their own criteria depending on their laboratory data and clinical experience[6]. Despite the above mentioned variations, clarification of this elusive point about eligibility criteria would have great contribution to create a useful algorithm for triage of cases regarding insemination method.

A recent systematic review and meta-analysis searched available literature dating between 1992 and 2020 to investigate the efficacy of ICSI in couples diagnosed with non-male factor infertility. Among nearly 1600 studies, four randomised controlled trials and 22 cohort studies were found to be eligible for analysis. Based upon these 26 publications it can be deducted that studies in the

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existing literature either did not mention any criteria or used World Health Organisation (WHO) reference values or certain criteria compatible with these references in order to define non-male factor and to prefer C-IVF[7].

When WHO reference values are regarded as the eligibility criteria for C-IVF, then each individual parameter in the semen analysis report must be $\geq$ defined reference value by rule, which means ICSI should be preferred in all other occasions. In other words, if the reference values proposed by the WHO[8] are considered as the mainstay of triage, then shall we prefer ICSI if any of the semen parameters outliers the reference values? Such an approach may be misleading in certain circumstances. For instance, what if the semen sample reveals subnormal value(s) for one or two parameters but much higher than the reference values for the rest? With an analytic approach it can clearly be claimed that any higher parameter(s) may possibly compensate subnormal parameter(s) hence keeping the entire semen quality eligible for C-IVF. As an example, if the volume or the motility is low but the sperm concentration is very high, it can easily be deducted that ignoring C-IVF with such a sample suspension will not be prudent as far as the high concentration compensates for the relatively low volume or motility and providing an optimum overall sperm quality.

As an opposite example, what if all semen parameters are above reference values in a couple with high ovarian response where the normal volume of the semen sample is not enough for inseminating the very high number of COCs via C-IVF?

Since each of the four functional variables of semen analysis (namely volume, concentration, motility and morphology) may have a certain contribution to the fertilisation potential, then a question comes up: wouldn't it be very useful and comfortable for the practitioners to have a definite semen index -taking into account all four of these variables- for the sake of simplicity? To the best of our knowledge there is neither a universally accepted nor a proposed semen index so far.

Exactly based on this crucial point, as a clinic practicing C-IVF for nearly fifteen years and applying C-IVF in more than half of all medically assisted reproduction cycles for the last couple of years; based on our clinical experience, we defined a C-IVF index which has been used in our clinical protocol since 2015. A signed informed consent giving detailed information about the insemination techniques is obtained from all patients before enrolment in assisted reproductive technology treatment. Eligibility of a patient to be enrolled in C-IVF is based on this cut off index (namely "Antalya C-IVF index") defined as total progressively motile sperm with normal morphology count ≥ 100000 . C-IVF is used as the method of insemination in all cases achieving this threshold or above unless the patient has a history of prior total fertilisation failure. ICSI is preferred for couples with an index below this limit. This index is calculated by simply multiplying the four basic semen parameters [volume (cc) $\times$ concentration (million) $\times$ progressive motility (%) $\times$ morphology (%)]. Regarding progressive motility, both straight

line or curvilinear motility are taken into consideration. Recently, we have published the results of a randomised controlled study comparing the laboratory and clinical outcome of ICSI with those of C-IVF in non-male factor cases[9]. This was followed by a retrospective study comparing both methods for patients with poor ovarian response[10] in order to clarify if lower number of oocytes would be a determinant for choosing the insemination method. Both studies revealed similar fertilisation rates and similar clinical outcome in C-IVF cases compared with those of ICSI.

We propose that using such a C-IVF index will provide the following crucial advantages in medically assisted reproduction practice: 1) It will create a consensus among the medically assisted reproduction team while deciding the method of fertilisation. 2) Any new member joining an existing team will adapt to the clinical C-IVF decision criteria right away without any hesitation. 3) It will prevent the overuse of ICSI particularly for patients with some outlier semen parameter(s) where other semen parameters are high enough to compensate for the lower one (s). 4) It will provide a standardisation for multicentre studies or systematic reviews.

Last but not the least, such a standardisation will help convince many practitioners to switch back to C-IVF in non-male factor infertility cases and place C-IVF again in the right position it deserves. In conclusion, a universal semen index for deciding the method of fertilisation has utmost importance. We propose our Antalya C-IVF index as a model to create awareness of this point. Future studies using such an index will further contribute to improvement for optimum usefulness.

Conflict of interest statement

Author declares no conflicts of interest in this study.

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Author's contributions

Mete Isikoglu contributed to conception, design, drafting the article and also revising it critically and final approval of the version to be published.

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