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Review

Effectivity of conventional *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) when male factor is absent: a perspective point of view

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ABSTRACT

An objective and individualized approach of *in vitro* fertilization techniques tends to decrease costs and improve the experience of infertile couples during treatment. The use of available technologies to diagnose and treat infertility based on scientific evidence seems to be the best practice, which is the guideline that motivates this review on the available techniques for laboratory oocyte insemination. Conventional IVF, the pioneering technique, was initially used in the treatment of tubal obstruction infertility, successfully expanding the treatment of infertile couples presenting with several other factors. However, it was less effective in cases of severe male factor infertility. Intracytoplasmic sperm injection, which was developed in 1992, proved to be the method of choice for treating couples with severe male factor infertility. Since then, it has been increasingly used regardless of the infertility factor. This review discusses the effectiveness of conventional *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) when the male factor is absent in all aspects, as technical and clinical outcomes, associated risks, adjustments for using with other technologies and costs. Finally we discuss the advantages and disadvantages of each one, with all aspects reviewed.

Keywords: conventional IVF, ICSI, success rates, assisted reproduction

INTRODUCTION

Infertility is defined by the failure of conception within 12 months of unprotected regular sexual intercourse (Practice Committee of the American Society for Reproductive Medicine, 2020). Although infertility affects around 10% of couples in reproductive age, couples usually do not consider the possibility of having difficulties in getting pregnant. Experiencing infertility and undergoing treatments using assisted reproduction techniques (ART) to finally getting pregnant can cause psychological and financial discomfort and a significant rate of treatment dropouts. Facing this scenario, an individualized approach tends to result in higher success, decreased costs and improves the couples' experience during treatment. Among the available technologies for the diagnosis and treatment of infertility, a number of choices are possible and the rational use of them, based on scientific evidence, seems to be the best practice.

The choice of oocyte insemination techniques available, conventional *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have been discussed in the literature about indications and efficiency. This study was conducted to address the advantages and disadvantages of each technique and discuss efficiency and efficacy.

IN VITRO FERTILIZATION TECHNIQUES

The possibility of collecting male and female gametes, submitting them to *in vitro* fertilization and the transfer an embryo in an early development stage has transformed the world we live in. Conventional IVF is the pioneering technique, and was initially used in the treatment of tubal obstruction infertility (Steptoe & Edwards, 1976). Since then, it has been widely and successfully used to treat infertile couples presenting with several factors, such as endometriosis, ovulatory dysfunction, and infertility without apparent cause (Taylor *et al*., 2019). However, IVF has shown lower fertilization and pregnancy rates when treating infertility due to severe male factor, compared to treating infertility due to other conditions (Cohen *et al*., 1988; Ng *et al*., 1988; Iritani, 1991).

Palermo *et al*. (1992) developed the ICSI technique, which was a significant milestone in ART evolution, and proved to be the method of choice in couples with severe male factor infertility. Furthermore, ICSI enables men with azoospermia to have their own biological children, if associated with surgical epididymis or testicular sperm harvesting methods (Palermo *et al*., 2015; Esteves *et al*., 2018; Halpern & Schlegel, 2018). Following the implementation of that technology in ART laboratories, the use of ICSI has expanded to other situations beyond its specific indication, such as decreased ovarian reserve, women of advanced age and idiopathic infertility (van der Westerlaken *et al*., 2005; Komsky-Elbaz *et al*., 2013; Vitek *et al*., 2013; Tannus *et al*., 2017).

Currently, ICSI is estimated to be used in 85% of all treatment cycles in Latin America, and in almost 100% of the cycles in the Middle East (Dyer *et al*., 2016). In Australia, the use of ICSI increased from 57.8% in 2005 to 67.5% in 2014, while the proportion of infertility attributed to male factor remained relatively stable over the same period (Fitzgerald *et al*., 2018). In the USA, the use of ICSI increased from 36.4% in 1996 to 76.2% in 2012, with the highest relative increase (15.4% to 66.9%) in unchanged male factor cycles (Boulet *et al*., 2015). The records on the use of ART worldwide generated by the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) between 2008 and 2010 showed that the use of ICSI expanded, becoming the most common oocyte insemination technique in the world, being used in 67% of treatment cycles (Dyer *et al*., 2016). These data show the use of ICSI regardless of the assigned infertility factor.

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Several studies have compared IVF and ICSI results for oocyte fertilization in recent decades. Fishel *et al*. (2000) conducted a study in which oocytes from the same patient were randomly shared between these two fertilization modalities. The ICSI technique resulted in a higher fertilization rate, more embryos developed and less risk of total fertilization failure (TFF) in male factor cases. On the other hand, the results were similar in patients without the male factor, leading the authors to recommend ICSI in all IVF cases. Other authors follow the same rationale, recommending the use of ICSI in all high-complexity treatment cycles regardless of the infertility factor. The motivation for this approach based on the fact that ICSI allows direct visualization of the degree of oocyte maturity, allows to eliminate oocyte membrane physical barriers for sperm penetration, decreases TFF, and provides more embryos for transfer (Abu-Hassan & Al-Hasani, 2003). In contrast, Li *et al*. (2018) showed that in couples without the male factor, oocyte fertilization results are superior with conventional IVF than with ICSI. However, these studies did not analyze positive clinical outcomes such as pregnancy success and live births.

Prospective studies in women with low ovarian response and no male factor reported similar results between groups for fertilization rates, embryo quality, implantation and pregnancy rates (Moreno *et al*., 1998; van Rumste *et al*., 2003; Luna *et al*., 2011). These data show that the use of ICSI for couples without the male factor is not inferior compared with conventional IVF (Kahyaoglu *et al*., 2014). The largest study published so far evaluated 569,605 ART cycles retrospectively to compare the reproductive outcomes of conventional IVF and ICSI in women with a low response to ovarian stimulation and normal seminal parameters. There were no advantages in cumulative pregnancy or live birth rates for couples without the male factor, comparing ICSI to conventional IVF (Supramaniam *et al*., 2020).

However, these studies consider only cases involving embryo transfer, i.e., studies with TFF were excluded. Also, cumulative pregnancy rates were not evaluated and the outcomes considered only the first embryo transfer. Then, since the available evidence shown similar clinical outcomes after the first embryo transfer, the TFF could be a more useful measure of conventional IVF *versus* ICSI comparison, than the fertilization rate. TFF is defined by the failure to fertilize all oocytes, which occur in 5 to 10% of conventional IVF cycles, even in the absence of the male factor (Mahutte & Arici, 2003; Kahyaoglu *et al*., 2014). Its occurrence is mostly unpredictable and can be associated with low amounts of collected oocytes, primary oocyte maturation deficiency, sperm function defects, among others (Liu & Baker, 2000; Hariprashad *et al*., 2002). Thus, patients who had TFF with conventional IVF benefit from the use of ICSI in the subsequent cycle (Ruiz *et al*., 1997; Bhattacharya *et al*., 2001). In ICSI, TFF occurs in a smaller proportion of treatment cycles, about 2 to 3% (Palermo *et al*., 1992), and may be related to oocyte activation deficiency or intrinsic sperm competence changes (Tucker *et al*., 2001). These data suggest that the use of ICSI in couples without the male factor is not related to a higher pregnancy rates, but can be used to prevent oocyte TFF - which has unpredictable occurrence. Moreover, greater embryo availability for transfer associated with cryopreservation can increase cumulative pregnancy rates.

Newborn Risks Associated with ICSI

The incidence of congenital malformations in people born by ART has always been a subject of interest. The invasive nature of ICSI, which overrides the natural mechanisms of sperm selection for fertilization and artificially transpose the physical barrier of the oocyte has always raised questions about the welfare of infants born through this technique. A few studies suggest that ART leads to a higher incidence of congenital malformations compared to natural conception (Hansen *et al*., 2013; Qin *et al*., 2015). But it is not possible to ascertain weather it is related to the technique or couple's background, and it makes sense to consider two risk variables in ICSI. The first is related to gametes from men with abnormal semen, which may carry genetic abnormalities or structural defects with no capacity to fertilize the oocyte naturally, but can be injected with ICSI. The second is related to the intracytoplasmic injection procedure, which can damage meiotic spindles, inducing aneuploidies, generating poor oocyte activation, affecting sperm chromatin decompaction, or inadvertently inject contaminant substances (Belva *et al*., 2016). Conversely, the risk of malformations and chromosomal disorders seem to be more associated with parental genetic defects in the sperm of men affected by errors in either spermatogenesis or mitosis rather than with oocyte fertilization technique (Thornhill *et al*., 2005; Agarwal *et al*., 2016). Cognitive developmental anomalies do not seem to be different in children born by conventional IVF or ICSI, at least in the first years of development (Miranda-Ribeiro *et al*., 2019).

Therefore, couples with subfertility should be advised about the increasing incidence of congenital malformations regardless of the type of oocyte fertilization procedure. This risk is not only related to the subfertility condition, but also to conditions inherent to the treatment procedure, such as ovarian stimulation, embryo culture environment, and occurrence of multiple pregnancies, which may increase the incidence of congenital malformations (ESHRE Task Force on Ethics and Law *et al*., 2012; Ehrbar *et al*., 2016).

Fertilization Method and New Technologies

A number of new technologies has been incorporated to ART during the last decades. Preimplantation genetic test (PGT) for aneuploidies or monogenic diseases, oocyte cryopreservation, time-lapse monitoring of embryo development are some of them. ICSI is the preferred oocyte fertilization method when PGT is performed. The main reason for this indication is the certainty that only one sperm will fertilize the oocyte, eliminating the possibility of contamination by additional sperm adherence to the zona pellucida (Gook & Edgar, 2007). On the other hand, a study involving a cohort of 927 patients showed that the accuracy of PGT with biopsy on the third day of embryo development is similar in conventional IVF and ICSI cycles, as the prevalence of parental contamination (Bouwmans *et al*., 2008). More recently, the risk of sperm contamination seems to be even lower due to biopsy being performed in blastocysts instead of cleavage embryos (De Munck *et al*., 2020). Moreover, during the DNA amplification technique, the sperm DNA is not regularly amplified, since additional steps would be necessary for sperm genetic material decondensation (Kazem *et al*., 1995; Casillas *et al*., 2018).

The impact of conventional IVF or ICSI on embryo euploidy is also a subject of interest, but few studies are available. Couples with recurrent miscarriages were evaluated and similar fertilization rates, number of biopsied blastocysts and rates of euploid blastocysts were seen according to oocyte insemination methods (Practice Committees of the American Society for Reproductive, 2012).

A more recent and widely used technology is oocyte cryopreservation, used for fertility preservation in women undergoing cancer treatment (Zagadailov *et al*., 2020), or social fertility preservation. Although oocyte vitrification is a safe technique with excellent thawing results, the process affects the zona pellucida, decreasing conventional IVF fertilization rates (Zagadailov *et al*., 2018). Thus, for

vitrified oocytes, better results are obtained using ICSI (Awtani *et al*., 2017). Although no controlled studies have compared conventional IVF and ICSI results in cryopreserved oocytes, ICSI has been the preferred fertilization method. Currently, embryonic development monitoring by time-lapse imaging (TLI) is a non-invasive method used to evaluate embryo morphokinetics. This new technology improved the understanding of the early stages of embryogenesis. However, the value of this knowledge in improving clinical outcomes still needs to be better determined (Gleicher *et al*., 2019). Considering the technical differences between conventional IVF and ICSI, it is important to establish whether there is consequences for initial embryonic kinetics. An analysis of 1,203 embryos obtained from oocyte donors and normal seminal samples were observed via TLI. When pronuclear fading [PNF] was established as a reference, embryonic development were similar for ICSI compared to conventional IVF (Cruz *et al*., 2013).

Cost Analysis

An issue frequently raised in clinical practice is the cost analyses of the techniques used in IVF laboratories. Details of treatment cost analyses for each procedure are not easy to compile. Therefore, it is common for human reproduction centers to analyze fixed treatment costs based on the individual clinic perception. Conversely, scientific issues and additional costs involved in the treatment protocol technology used should be considered since high-complexity ART has a high cost for most couples. The effects of technical add-ons in high-complexity treatment need to be considered as technology advances and may influence therapy decisions in favor of techniques that may not reflect the best results in live births (Gleicher *et al*., 2019).

Compared to conventional IVF, ICSI is more complex and requires professional training to be performed. Bouwmans *et al*. (2008) reported a detailed treatment cost analysis of conventional IVF and ICSI, estimating the weight of each stage of the treatment process, concerning the total cost, excluding cases with surgical procedures as testicle or epididymis sperm extraction. The ovarian stimulation corresponds to most of costs (68%). About the oocyte insemination method, conventional IVF corresponds to 12% of the cost, while ICSI corresponds to 20%. The conventional IVF *versus* ICSI costs differences is due to the higher work intensity required from embryologists, supplies and equipment required for gamete micromanipulation in ICSI. The embryo transfer and possible complications are responsible for the remaining costs. Other authors performing similar analyses reported that the cost of ICSI was 11-30% higher than that of conventional IVF (ASRM, 2020).

According to the American Society of Reproductive Medicine (ASRM), the mean cost of an IVF cycle in the United States in 2017 was USD 12,400 and ICSI can add approximately USD 1,500 to this expense (Jain & Gupta, 2007). Even though the percentage of ICSI cycles in the USA has increased since its introduction, despite of no variation in the incidence of male factor (Dieke *et al*., 2018), or improvements in clinical outcomes, such as live birth rate (Zagadailov *et al*., 2018). This is also the reality in Europe upon analysis of the results of the European IVF Monitoring, with ICSI being the predominant method over conventional IVF, regardless of the presence of male factor (De Geyter *et al*., 2018). ICSI represents around 75% of the cycles in the USA and Europe (Zagadailov *et al*., 2018; ASRM, 2020; ESHRE, 2020).

On the other hand, the source of payment for treatment directly influences the choice of the oocyte insemination method. Currently, 14 American states have partial health insurance or state coverage for infertility diagnosis and treatment. Treatment cycles for patients younger than 35 years with health insurance coverage are associated with decreased use of ICSI, regardless of the presence of male factor infertility, increased elective single embryo transfers, and better pregnancy and birth rates compared to the states with no health insurance coverage (Zagadailov *et al*., 2020).

DISCUSSION

Precision, assertiveness, and the definition of individualized strategies for the best results in infertility treatments are a challenge, and discussions regarding the use of conventional IVF and ICSI are inserted in these choices. The successful use of ICSI in infertility due to severe male factor is associated with the incorporation of more advanced technologies and encourages its use to treat couples even in the absence of this factor, since there are no losses related to the technique. Also, a lower TFF incidence, higher oocyte fertilization rate, and possibly more embryos, outweighs the fear of the inherent risk of a more invasive process than conventional IVF. The fact that a higher number of embryos obtained by ICSI provides a greater chance of embryos reaching the blastocyst stage, enabling fresh transfer and the vitrification of surplus embryos, and thus providing the possibility of increasing the cumulative chance of pregnancy is the rationale for its worldwide use. However, the efficiency of a treatment includes not only one aspect but also the association of all factors involved, including cost and accessibility. Thus, it is necessary to consider not only laboratory and clinical outcomes, but also the technical capacity of the professionals involved in the procedures and the associated costs.

Since 2008, the ASRM opinion committee indicated the use of ICSI in cases with no male factor infertility (Practice Committee of American Society for Reproductive, 2008). More recently, the third update of the ASRM opinion committee was published. These documents progressively show that the most important outcome to be evaluated is live birth rate, not other laboratory treatment indicators. ICSI is indicated in male factor infertility cases and not in cases of low ovarian reserve or idiopathic infertility, since the studies showed no increased live birth rates. They also advise on the need for further studies to investigate whether ICSI increases the live birth rate in the presence of low-quality oocytes, and cycles without the male factor having the higher cost of ICSI should be considered (ASRM, 2020). Immediately after the last ASRM publication, the European Society of Human Reproduction and Embryology (ESHRE) also issued comments on its online portal, corroborating the ASRM recommendations. They explain that "ICSI continues to be the preferential fertilization method around the world, even in the absence of the male factor. Current guidelines still cannot justify this tendency" (ESHRE, 2020).

From a technical point of view, ICSI goes beyond fertilization physiology mechanisms and can hurt the principle of non-maleficence when used in the treatment of couples with no male factor. On the other hand, conventional IVF does not offer maximum fertilization potential, since better fertilization rate and a lower chance of TFF are observed with ICSI. It is worth suggesting that tests should be conducted to assess functional capacity and identify other sperm function defects in patients with normal semen, which may discourage the use of conventional IVF. Besides that, it is not consistent to expect significant increase in the live births rates in ICSI cycles when it is indicated for couples without the male factor compared to conventional IVF. Studies evaluating clinical outcomes have failed to answer this question as they only evaluate transfer cycles, not considering TFF cases. Most of them only evaluate the

first transfer without analyzing cumulative results, including the transfer of surplus cryopreserved embryos. In such cases, it would be reasonable to expect comparable results provided that ICSI is performed using the correct technique and ideal technical conditions. Hence, the evidence of any superiority of ICSI over conventional IVF for live birth rates, is weak.

In countries where the treatment is subsidized by the government or by health insurance plans, conventional IVF is the preferred oocyte insemination method, due to lower costs in a range of USD 1,500s per cycle compared to ICSI. However, this is not the economic scenario of many countries, including Brazil, where ART is mostly self-financed by the patients. Then, the highest chance of having transferred embryos and possibly freezing for further transfers, which would supposedly increase the final chances of success in one cycle, is an important point and makes generalized ICSI use in most clinics. The treatments in these countries are conducted in private clinics with no possibility to deny the existence of "economic competition" between human reproduction centers. The high pregnancy rates associated with very low TFF rates, which are fully funded by the patients, serve as quality indicators of the center. It is still worth considering that economic and psychological factors associated with repeat treatment cycles is a worry in the private clinics and other treatment indicators that are less clinically important, but certainly economically relevant, may be prioritized.

In summary, the cost-effectiveness for using conventional IVF or ICSI for oocyte insemination in the absence of the male factor, must didactically be split into two factors: the technical outcome (efficacy) and the accessibility/financial burden (efficiency). Together, both will result in the cost-effectiveness of the procedure. About the efficacy of the techniques, further studies are needed to compare the clinical outcomes of ART cycles after conventional IVF or ICSI considering all initiated cycles, total fertilization failure, cumulative clinical pregnancy outcomes and having the live birth rate per initiated cycle as the primary outcome. The past studies evaluating the clinical outcomes of conventional IVF and ICSI did not consider the improvement of pregnancy rates after frozen-thawed embryo transfers by the vitrification technique. With the implementation of this technology in recent years, the results of cumulative clinical pregnancy can have a positive impact and new studies are necessary.

On the other hand, the efficiency of those technologies does not consider just the technical success but, they must also take into account the financial burden. That is the motivation for the spread use of ICSI, due to supposed higher fertilization rates and lower total fertilization failure, which in the bottom line would result in higher numbers of embryos to be transferred in one stimulation cycle. Literature evidences until now do not support the technical superiority of ICSI over conventional IVF, but the higher fertilization rates, and consequently higher number of embryos per ovarian stimulation cycle obtained with ICSI, encourage the spread use of ICSI around the world.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest in the submitting manuscript.

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