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Women's Health Science Journal
ISSN: 2639-2526

Clinical Intracytoplasmic Sperm Injection in Human Assisted Reproduction: Guidelines for Customization and Best Practice of the Procedure

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Opinion

Volume 2 Issue 3

Received Date: September 19, 2018

Published Date: September 27, 2018

DOI: 10.23880/whsj-16000120

Abstract

Clinical ICSI is the most frequently used procedure in modern human assisted reproduction. Despite the technique was firstly applied almost three decades ago, the quest for the highest fertilization and pregnancy rates after ICSI still continues. The present article examines some key events of ICSI suggesting specific means and processes in order to develop and offer a customized and highly efficient ICSI to our patients. This tailor-made approach should be the gold goal of every clinical embryologist worldwide and the correct path of modern clinical embryology.

Keywords: Intracytoplasmic Sperm Injection; Oocyte Denudation; Oocyte Degeneration; Artificial Oocyte activation; Fertilization Failure

Abbreviations: ICSI: Intracytoplasmic Sperm Injection; SUZI: Sub-Zonal Insemination; IVF: In Vitro Fertilization; FSH: Follicular Stimulating Hormone; HCG: Human Chorionic Gonadotropin; ZP: Zona Pellucida; COC: Cumulus Oocyte Complex; MI: Metaphase I; MII: Metaphase II; AOA: Artificial Oocyte Activation.

Introduction

Since the beginning of the IVF era in 1978 with the birth of Louise Brown, there was a major issue surrounding male infertility and how to overcome it. Several attempts had been made either by inseminating the oocytes in very low volumes of culture medium, or by other techniques such as sub-zonal insemination (SUZI). The outcome of those attempts was not optimal with adverse events in some cases such as fertilization of the ova with more than one spermatozoa, a phenomenon known as polyspermy.

The efforts of Palermo, et al. [1] to directly inject the spermatozoa into the cytoplasm of the oocytes, a technique known as intracytoplasmic sperm injection (ICSI), unveiled a whole new horizon in assisted reproduction: the treatment of male and severe male infertility. A real breakthrough that allowed many men with poor sperm parameters to enjoy fatherhood.

After the passing of more than 20 years since the first ICSI procedure, the technique has remained unchanged and clinical embryologists need to master the skills the technique demands in order to achieve fertilization rates of more than 70%, with excellent implantation and live birth rates after ICSI.

As with every procedure in human IVF, ICSI demands a high hand eye coordination, a strong focus and a strong technical skill by the clinical embryologist. Apart from these, there are some fine elements surrounding the technique that if followed, can lead to optimal results. Below we analyze some of these key factors.

Oocyte Denudation Process

Oocyte denudation process i.e. the removal of any cumulus or corona cells surrounding the oocyte, is mandatory before the ICSI procedure. The process combines chemical and mechanical means, such as the use of the enzyme hyaluronidase and mechanical pipetting of the cumulus-oocyte-complexes (COC) by the embryologist. Two key factors in this process may influence the ICSI result. Firstly, the hyaluronidase used need to be recombinant and not bovine-derived. Evison, et al. [2] found that the use of recombinant hyaluronidase in COC denudation significantly decreased oocyte degeneration compared to the bovine-derived one. Secondly, a complete denudation of the ova from the surrounding cells may increase oocyte survival after ICSI, since Ebner, et al. [3] reported that incomplete oocyte denudation produced a significantly higher degeneration rate.

Oocyte Degeneration after ICSI

The major problem puzzling all embryologists performing ICSI, is the reduction of the percentage of degenerated/destroyed oocytes due to the invasiveness of the procedure. The biological basis of oocyte degeneration after ICSI is not that clear. Oocyte maturity at ICSI time, day 3 Follicular Stimulating Hormone (FSH) levels and estradiol levels on hCG triggering day, have been shown to be predictors of degeneration rate [4]. Other factors include excessive manipulation and movements of the injecting pipette while inside the ooplasm and thick/hard zona pellucida (ZP). The latter results in oocyte deformation during injection that eventually causes the cytoplasm to lyse. Careful hormonal monitoring of the stimulation cycle, increased oocyte maturity level and correct microsurgical treatment of the ovum by the operating embryologist are the key factors of reducing oocyte degeneration post-ICSI. In the last case-scenario of thick/hard ZP the best option is to pre-treat the ova with 1.48μm diode Laser creating a small opening of about 5μm on the ZP. The technique is known as Laser-Assisted ICSI and has been shown to significantly reduce oocyte degeneration rate, while increases fertilization, embryo quality, blastulation and clinical pregnancy rates [5]. Finally, the use of ultra-thin injection micropipette with 4.5μm internal diameter could significantly reduce oocyte degeneration resulting in higher survival and fertilization rates (personal data, not shown).

Immature Metaphase I ova: To inject or not?

Quite often the ICSI embryologist has to face the problem of a high incidence nuclear immaturity in the oocytes of a patient. These Metaphase I (MI) oocytes are known to maintain meiotic arrest. The use of MI oocytes could be advantageous especially in patients with low oocyte yield after oocyte retrieval. The intervention here would be a short culture (2-3 hours) of these oocytes in the commercial culture medium used by each clinic, in order these ova to achieve nuclear maturation and extrude the first polar body. A recent study [6] revealed, in concordance with previous studies, that the use of *in vitro* cultured MI oocytes for ICSI resulted in very poor fertilization rates (37%), while the transfer of embryos derived from such ova did not produce any clinical pregnancies at all. The chromosomal status of embryos produced by MI-MII *in vitro* matured oocytes has been found to be highly abnormal (80.6%) [7], posing the question of introducing high percentage of culture-derived aneuploidies if such embryos are to be used in embryo transfers. Based on the available literature, the widespread use of MI oocytes should be avoided in ICSI and if it is deemed necessary such as in cases of no other option, aneuploidy screening by preimplantation genetic diagnosis employing embryo biopsy is mandatory before any clinical use of the embryos created.

Time to ICSI after Oocyte Retrieval

Another major factor that can affect ICSI outcome is considered to be the best time to perform ICSI after oocyte collection. It is important to mention that the oocytes biologically are characterized by the nuclear maturation evidenced by the presence of the first polar body in their perivitelline space and the cytoplasmic maturation that involves reorganization of cytoplasmic organelles in the cytoskeleton, and the synthesis of maternal mRNAs and proteins [8]. Both types of maturation are necessary to occur in order to achieve normal fertilization. In stimulated cycles though these two types of maturation appear to be asynchronous [9]. In

order to achieve the maximum ICSI results, oocyte denudation needs to be performed 1 hour post-oocyte retrieval, while ICSI needs to performed between 37 and 39 hours post-hCG administration [10].

ICSI and Fertilization Failure

Fertilization failure post-ICSI is a rare phenomenon present in about 1-3% of ICSI cases, even in the presence of normal spermatozoa [11]. The main reason contributing substantially in fertilization failure is oocyte activation deficiency (40-70% of failed ICSI cases) [12].

In order to salvage such cases, artificial oocyte activation (AOA) mostly by exposing the oocytes in calcium ionophores immediately after ICSI has been proposed as a rescue technique. The use of calcium ionophore could restore fertilization in otherwise known failed fertilization ICSI outcomes in azoospermic or cryptozoospermic men [13] or in globozoospermia cases [14].

Interestingly, calcium ionophore A23187 has been used to rescue fertilization failure of unexpected cases of aged unfertilized oocytes 18 hours post-ICSI [15]. In such cases the combination of calcium ionophore A23187 and granulocyte-macrophage colony-stimulating factor (GM-CSF) could restore fertilization, while the producing embryos could develop into euploid morphologically nice blastocysts with potential clinical use.

Conclusion

There have been almost three decades after ICSI implementation in clinical embryology practice and the guidelines for good ICSI practice consist the Holy Grail of contemporary IVF laboratory. Nowadays, personalization of IVF practice by clinical embryologists is more than a necessity. ICSI is currently the most commonly used assisted reproductive technology, accounting for 70-80% of the cycles performed, while the fertilization rate should be estimated at more than 75% of the ova injected if a satisfactory ICSI procedure has been performed.

The abovementioned methodologies are being suggested as means towards good ICSI practice by the clinical embryologist trying to achieve high fertilization and pregnancy rates after performing the procedure. Laser-assisted ICSI, the use of ultra-thin injection micropipette, the use of recombinant hyaluronidase and the complete denudation of the ova from the surrounding cells, the avoidance of injecting *in vitro* matured MI oocytes, the use of AOA techniques if fertilization failure is being suspected and the performance of ICSI 37-39 hours post-hCG administration are the key factors to achieve the abovementioned fertilization rate. The need for personalized IVF in our modern times, oblige the clinical embryologists worldwide to offer the best practices to the patients and one of those is to perform tailor-made ICSI. The application of the abovementioned guidelines is a significant step towards this direction.

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