

Editorial

IVF: The Gold Standard for Assisted Reproduction Treatment

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Introduction

A variety of clinical procedures have been utilised for the alleviation of infertility including intra-cervical insemination, intra-uterine insemination (IUI), *in vitro* fertilization (IVF), high-insemination concentration IVF (HIC-IVF), short-insemination IVF, intra-cytoplasmic sperm injection (ICSI) and intra-cytoplasmic morphologically selected sperm injection. Though IUI may be considered a low cost, non-invasive first line of treatment, clinical pregnancy rates are usually in the range, 15-20%, even when combined with ovulation induction. Therefore, it is a less suitable approach for patients of advanced maternal age (AMA) for whom achieving a pregnancy in the shortest time possible is of prime importance. Furthermore, when IUI fails it is impossible to diagnose the cause of failure, whether due to problems in sperm transport, sperm binding to the *zonapellucida*, fertilization, embryogenesis or implantation. In comparison, clinical pregnancy rates following various modifications of IVF or ICSI are usually in the range, 30-40%, so these two insemination techniques are twice as effective as IUI and benefit from the fact that, up to the stage at which embryos are transferred to the uterus, the cause of any failure is usually self-evident. However, which of the two, IVF or ICSI, should be considered the gold standard for assisted reproduction treatment (ART)?

Semen Analysis & Treatment Allocation

Semen analysis is the cornerstone of male fertility investigations. It has long been accepted that male factor infertility is estimated to account for approximately one third of all couples that fail to conceive. In fact, revision of the lower reference limits for the normality of a semen sample in the latest edition of the World Health Organisation's laboratory manual for the examination and processing of human semen suggests that this may be an over-estimate [1]. Hence, by definition, the majority of patients should have a relatively normal semen analysis and need only require treatment with IUI or IVF. Therefore, if >50% of patients are being allocated to treatment with ICSI, then semen analysis and treatment allocation policies and procedures probably need to be subjected to more rigorous quality control and quality assurance. For example, it may be that just a single semen analysis is requested prior to treatment allocation, which is notoriously unreliable due to the known variation in semen

quality from day to day. Hence, with a view to choosing the most appropriate form of treatment, various factors should be taken into consideration during analysis of the raw ejaculate including the total motile count (TMC), the quality of sperm progression (more so than the percentage of motile spermatozoa) and the percentage of morphologically normal spermatozoa present, before and after sperm preparation on the day of treatment. In this respect, the TMC has been shown to be the most reliable predictor of IVF treatment outcome, whereas sperm morphology is the least reliable predictor [2]. Each IVF unit should determine their own evidence-based semen analysis parameter criteria for determining the most appropriate allocation of treatment (a simple example is shown in Table 1).

Discussion

The concept of IVF as a gold standard for ART is well supported by the available evidence. Based purely upon the observed incidence of male factor infertility, IVF should be the treatment of choice for the majority of patients seeking ART. Indeed, one of the cornerstones of evidence-based medicine, Cochrane Reviews, reported no superiority of ICSI over IVF in pregnancy rates for couples with non-male factor infertility [3]. This is consistent with our own retrospective analysis of data from >3000 cycles of treatment from 2004-2007 where only 40% of all patients were allocated to treatment with ICSI [4]. Fertilisation and clinical pregnancy rates were 70.9% and 30% for IVF, and 65.6% and 32.5% for ICSI, respectively, and the failed fertilisation rate for all patients was only 3%. In this respect, IVF and ICSI fertilisation should be compared per egg collected rather than per egg inseminated, which otherwise always skews the data in favour of ICSI since not all eggs are injected whereas all eggs are inseminated with conventional IVF. Similar studies have been recently reviewed, demonstrating that ICSI does not improve clinical outcomes for unexplained infertility, low egg yield and AMA, concluding that there is no data to support the routine use of ICSI for non-male factor infertility [5]. Furthermore, **Table 1:** Semen analysis parameters and treatment allocation.

CATEGORY	PARAMETERS	TREATMENT
ICSI only	TMC < 10 million Or Motility < 25% Or Morphology < 1%	ICSI
Split treatment	TMC < 20 million And Motility ≥ 25% And Morphology < 4%	HIC-IVF and/or ICSI
IVF only	TMC ≥ 20 million And Motility ≥ 25% And Morphology ≥ 4%	IVF

Abbreviations: ICSI: Intra-Cytoplasmic Sperm Injection; IVF: *In vitro* Fertilization; HIC-IVF: High Insemination Concentration IVF; Morphology: Normal Sperm Morphology; Motility: Progressive Motility; TMC: Total Motile Count

data from the Human Fertilization & Embryology Authority (HFEA) shows that those centres that use ICSI more frequently fail to achieve an increased live birth rate [6].

Increased success rates over the past decade have resulted primarily from the development of improvements in culture media and a culture environment that more accurately mimics the *in vivo* environment provided within the fallopian tube and uterus. Other than IUI, fertilization by IVF most closely replicates the natural process within the fallopian tube in that the maturity and quality of the oocyte-cumulus complex (OCC) largely determines whether the oocyte is capable of being fertilized – in this respect, clinical skill with controlled ovarian hyper-stimulation is just as important as scientific skill with sperm preparation and insemination. The biological interaction of the gametes during IVF is permitted to proceed relatively non-invasively and with minimal disturbance of the culture environment. Trans-zonal processes between the nutritive cumulus cells and the oocyte that they encompass are maintained for the appropriate period of time, without any exposure to exogenous enzymes. Importantly, the integrity and long-term viability of the OCC is not subjected to the risk of iatrogenic damage and any physiologically incompetent spermatozoa that may carry defective DNA are not forcibly injected into the oocyte. Ultimately, those oocytes that fail to fertilize may well not have had the developmental competence to support embryogenesis and implantation in any case. Indeed, one of the advantages of IVF is that such incompetence in oocyte viability is more likely to be exposed through fertilization failure. From a purely biological perspective, therefore, IVF is the gold standard for ART.

There are also compelling economic arguments in favour of IVF over ICSI. IVF is a less costly process to the patient, the IVF centre and the Department of Health [7]. In comparison, some concern over the

long-term safety of ICSI has been raised recently [8]. Hence, a benefit/risk/cost analysis would almost certainly demonstrate IVF to be the better option for the majority of patients. We all want our patients to have a healthy baby using the most appropriate and safest means at our disposal, without it costing them or the taxpayer any more than necessary. For these reasons alone, IVF is the gold standard for ART.

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