

Editorial

IMSI, Useful, Useless or Harmful?

Elisabetta Tosti^{1*} and Yves Ménézo²¹Stazione Zoologica, Naples, Italy²Procrelys, Lyon France and London fertility associates, 104 Harley St, London, UK

Introduction

Since the birth of the first test-tube baby in 1978, Assisted Reproduction Techniques (ART) has been performed all over the world to alleviate human infertility. In 1991 with the advent of the Intra-Cytoplasmic Sperm Injection (ICSI) technique, a reasonable rate of male infertility cases due to severe oligospermia were successfully solved. However, several concerns about the safety and impact of ICSI on the offspring have been raised due to the forced injection of putative abnormal spermatozoa [1,2].

Starting from the hypothesis that poor spermatozoa might lead to poor blastocyst formation it was well demonstrated a strong paternal effect affecting the long-term embryo development [3-5]. Semen analysis is considered as a starting point for evaluating an infertile couple. In case of severe oligospermia and when ICSI represents the only chance for the couple, the assessment of sperm morphology seems to play a critical role. Although clinical significance of sperm morphology is still matter of debate, it has been recently recognized that an accurate measurement of morphological anomalies plays a very important role in for the determination of a male's fertility potential [6]. In this respect, in recent years the selection at high magnification (>5,000 X) of best spermatozoa has been included in the programmes of ICSI in patients with terato-zoospermia in order to first identify sperm organelle morphology (MSOME; motile sperm organelle morphology examination) and then perform IMSI (intracytoplasmic morphologically selected sperm injection). Contrasting data emerge from literature: in fact some randomized studies and a low powered meta-analysis showed that IMSI procedures yielded higher significant values of fertilization, embryo development, and clinical pregnancy rates and sometime a decreased miscarriage rate [7-10], whereas other authors observed slight or almost no improvements in the clinical outcome [11-13]. There is not, for the moment clear cut evidence that IMSI brings any advantage.

Among the organelles examined by MOMSE criteria, a particular attention has been paid to the presence of vacuoles in the sperm head. These are subtle malformations described for some authors of nuclear origin, believed to be associated with altered sperm cell structure and are thought to exert a deleterious effect on embryo development. Nuclear vacuoles were also thought to be linked to sperm DNA fragmentation [14]. This was denied by others [15-17], estimating these vacuoles are rather linked to poor sperm DNA packaging i.e. decondensation. Since a normal chromatin compaction appears to be important for the very early stages of embryonic development, nuclear vacuoles might be considered as a predictive factor of sperm quality and in particular considered as negative parameter. This idea corroborated an older finding that higher percentages of vacuoles were reported in sperm head of infertile men [18]. However, this contradicts the observations of Mauri et al. [11] that MSOME has no impact on human early preimplantation embryo development before genomic activation, and also the work of Montjean [19] where no correlation can be found between vacuoles and sperm DNA packaging. *In fine* no strong correlation has been established between the presence of these vacuoles and the quality and the structure of sperm DNA.

Selection of sperm with few or no vacuoles has been intensively

promoted as a way to increase the efficiency of ICSI, especially in patients with repeated pregnancy and implantation failures [20,21,12]. Despite this general belief, very recently, Montjean et al. [19] re-evaluated the role of vacuoles attributing them a physiological role such as the participation to the acrosome reaction. In light of this previous report a following study reported that human sperm vacuoles did not negatively affect ICSI success rates, but suggested that size of vacuoles rather than their presence may discriminate normal spermatozoa to be selected [22].

A potential harmful impact was furthermore recently reported by Palermo et al. [23] who suggested that the time spent to perform IMSI may cause a delay of time of sperm injection, with a repercussion on a dangerous oocyte aging. Even more concerning is the evaluation of Tanaka et al. [22] assessing that human sperm head vacuoles is the result of a natural physiological process. Injection of sperm with vacuoles does not affect ICSI outcomes and when using sperm without vacuoles, the fertilization rate was correct (80%) but the blastocyst formation rate was severely decreased (down to 25%). *In fine*, Junca et al. [24] have reported a trend towards a higher incidence of low birth weights for IMSI infants.

Conclusion

Actually MOMSE and subsequent IMSI are aimed to mainly evaluate vacuoles in the sperm head, based on a possible degenerative character of these organelles. However, all together the contrasting data described and recent findings led to a switch from a potential improvement to a probable deleterious (hazardous) aspect in this ART technique: it argues against the idea of including IMSI in ART routine.

Useful, useless or even harmful clinical significance of MOMSE application remains still a matter for conjecture and debate. On the contrary it appears more and more that vacuoles in the sperm head may be not considered an alteration of sperm functionality but physiological structures participating to the events of sperm maturation and activation.

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*Corresponding author: Elisabetta Tosti, Animal Physiology and Evolution laboratory, Stazione Zoologica Anton Dohrn, Napoli, Italy, E-mail: tosti@szn.it

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