

DEVELOPMENTAL SPERM CONTRIBUTIONS: FERTILIZATION AND BEYOND

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Male fertility potential is extremely difficult to predict on the basis of a single sperm variable. Clearly, there are many male and female factors contributing to the successful establishment of a viable pregnancy including: (i) a variety of attributes of sperm quality (competence for acquisition and maintenance of capacitation and progressive motility, zona pellucida recognition, binding and penetration, acrosomal exocytosis, oocyte fusion and activation, and pronuclei formation); (ii) oocyte quality, including the capacity of this cell to protect itself from oxidative stress as well as its potential for DNA repair; (iii) embryo quality, including a timely embryonic gene activation and ability of the embryo's apoptotic machinery to delete defective blastomeres; and (iv) the structural and functional competence of the receptive endometrium supportive of implantation.

The role of the various spermatozoal components suspected of actively participating in early human development is being re-evaluated. The contributions of the fertilizing spermatozoon to the oocyte include, as a minimum, the delivery of the DNA/chromatin, a putative oocyte-activating factor, and a centriole; spermatozoa may also provide the zygote with a unique suite of paternal mRNAs and some transcripts might be crucial for early and late embryonic development. Furthermore, elaborate non-random organization of human sperm chromosomes at different structural levels, starting from the DNA packing by protamines up to the higher-order chromosome configuration and nuclear positioning of chromosome territories, suggest the existence of several layers of genetic/epigenetic information.

The advent of IVF and its augmentation with ICSI has allowed a large number of couples suffering from moderate-severe male infertility, to achieve their reproductive dreams. Notwithstanding the existence of fundamental questions about the pathophysiological mechanisms leading to sperm dysfunction(s), and still unanswered concerns about health risks following ICSI, it appears that overall ICSI is safe and is here to stay. While on one hand ICSI possible hampered advances of the knowledge in some areas of gamete biology and interaction, on the other it definitely gave impulse to studies designed to unveil the sperm contributions during and beyond fertilization, including the normalcy of the DNA/chromatin as well as molecular mechanisms of genetic/epigenetic control and nuclear organization status. In all, almost entering the fourth decade of ART, we should continue monitoring the safety of the technique and long term development of offspring, while at the same time prioritizing areas of research addressing these fundamental questions.

Sperm nuclear factors that may have implications on reproductive outcome have been described, including DNA strand breaks, numerical and structural chromosomal abnormalities, Y chromosome microdeletions, and alterations in the epigenetic regulation of paternal genome. Recently, the focus has shifted to the analysis of sperm DNA damage. Within the ART setting, the type and degree of DNA damage experienced by the spermatozoa (presence of adducts, degree of single and double stranded DNA fragmentation, associated or not with genetic and/or epigenetic defects), whether the result of direct oxidative damage, apoptosis, or other cause, can have a profound impact on clinical outcomes. Therefore, the use of sperm cells with "invisible" damage should be prevented in the ART setting. To date, it is not possible to assess DNA integrity in the spermatozoa to be injected during ICSI, and current sperm separation techniques are only efficient in a limited fashion.

Recently, we reported that highly motile and morphologically normal sperm (examined by strict criteria) may have DNA fragmentation. This finding was extremely significant in infertile men with severe teratozoospermia (where all studied patients had some degree of DNA fragmentation ranging from 20-60% affected cells), and even present, albeit in much lower proportions, in subfertile patients with borderline to normal semen parameters (25% of those men had some degree of DNA damage in morphologically normal spermatozoa). On the other hand, none of the fertile men (donors) examined as controls had any morphologically normal spermatozoa with DNA damage.

Even more clinically significant was the subsequent finding that the presence of an increased proportion of normal spermatozoa with damaged DNA was negatively associated with embryo quality and also pregnancy outcome after ICSI. Because typically only motile and morphologically normal sperm are selected for ICSI, the selection and injection of morphologically abnormal spermatozoa is less likely to occur. In consequence, we postulate that the evaluation of DNA fragmentation in the total sperm population (normal and abnormal) is not the best way to assess the possibility of success with ICSI. Instead, the evaluation of DNA integrity in morphologically normal spermatozoa after sperm selection is a better approach to examine sperm DNA fragmentation and any potential impact on the ICSI procedure.

We propose that the evaluation of DNA integrity in morphologically normal spermatozoa after sperm selection is a better approach to evaluate the impact of sperm DNA fragmentation on ICSI outcome than the assessment of the total sperm population. It will be important to establish the exact nature of the DNA lesions as well as their intensities. This new way to evaluation may guide the development of improved methods of selection of spermatozoa with intact DNA.