

Is sperm chromatin packaging relevant for IVF success?

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Spermiogenesis is the last phase of the process that give rise to a mature and competent spermatozoon. It occurs from a dramatic morphological and structural change of the spermatid, in particular replacement of DNA-linked histones by protamines leading to a highly compact chromatin structure consisting of DNA and heterogeneous nucleoproteins. The target of a fertilizing spermatozoon is to deliver into the oocyte the paternal genome and regulatory factors that are required for proper embryonic development [1]. To do this the sperm must be capable of undergoing decondensation at a peculiar moment of the fertilization process.

Increasing evidence on the strong paternal effect on preimplantation embryo development [2] focus on the importance to identify a reliable sperm quality parameter. Although many different causes may give rise to male infertility [3], traditionally in IVF centres, routine laboratory investigations evaluate seminal parameters such as concentration, motility and morphology in order to assess semen quality prior to undergo assisted reproduction. Recent acquisitions correlate poor chromatin condensation to a failure in fertilization, embryo development and repeated miscarriages indicating even that sperm DNA damage over 30% impedes natural pregnancy [4-11].

Although it is described that oocytes and early embryos are able to repair sperm DNA damage [12], this seems to not occur in presence of an extensive percentage of damaged DNA in the sperm [13].

The aim of this editorial is to give readers a basis upon which to form an opinion on:

- i) the relationship between sperm chromatin condensation status and conventional semen parameters; ii) the need to include the chromatin condensation test as a new diagnostic tool in the routine spermogram; iii) the predictive value of this investigation in assessing fertility and outcome of pregnancy.
- i) in order to assess male factor for infertility, the main parameters investigated have been the sperm concentration, motility and morphology. Additional tests such as hypo-osmotic swelling test and sperm-mucus interaction have been used to corroborate the full diagnosis. However in the recent publication of WHO manual, a series of functional tests have been reported to be aimed at assessing the competence of human spermatozoa and it has been emphasized the importance of nuclear sperm chromatin structure assay. Literature reports contradictory results showing from no correlation between chromatin condensation and any of the parameters used for sperm analysis [14] to an high correlation with severe abnormal morphology [15-17] and a negative correlation between normal sperm head morphology and loosely packaged chromatin [7,18]. Similarly, oligospermic ejaculates appeared to be not correlated [19] with chromatin integrity, but our recent findings showed that low number of spermatozoa may also reflect their immaturity [20].
- ii) conventional semen analysis includes parameters such as concentration, motility and morphology assuming that sperm population falling within the standard values are also genetically adequate [21]. In particular it has been highlighted that sperm morphology represents one of the best discriminators for the fertilization potential of human spermatozoa [22]. At present

these parameters appear of limited value in determining the embryotropic potential of spermatozoa [16]. The need to use new markers of sperm function is of recent acquisition [17,23,24] especially in the case of morphologically normal sperm that posses a limited fertilizing ability if it is accompanied by a low packaging quality.

In the last decade [15] it was claimed to consider chromatin integrity one of the complementary tests of semen analysis for the clinical assays of sperm quality; at present this view is reinforced by the evidence that sperm DNA damage analysis may reveal hidden abnormalities in men showing apparently normal standard semen parameters [10,25-27].

- iii) the whole purpose of performing a diagnostic test to assist couples with fertility problems and especially in case of idiopathic infertility is to identify a threshold above and below which the test may exhibit a predictive value. Contrasting data exist in literature if the sperm chromatin integrity may predict fertility potential prior to ART. Starting from the late 90' many authors supported the utility of using the sperm chromatin structure as a diagnostic and prognostic tool in predicting fertilization and pregnancy rates following IVF [28-30]. They suggested in fact that optimal sperm chromatin packaging was necessary for full expression of the male fertility potential and that abnormal chromatin structure in semen, appeared to be potentially useful as predictor of fertilizing ability or pregnancy outcome [31,32]. More recently, apart a few exceptions claiming the limited value of sperm chromatin decondensation in assessing fertilization and pregnancy rates [6] it is advocated that this examination should be carried out in all cases of long-standing, unexplained male infertility before embarking upon IVF programmes.

Conclusions

Abnormal chromatin condensation reflects sperm immaturity and may have a highly diversified aetiology such as age, smoke, pollution and oxidative stress [16,33,34]. In the latter case it has been shown that changes in chromatin structure may be amplified by the sperm preparation techniques for ART procedures [23] and cryopreservation [20].

In this editorial we have reported the increasing concern for the adverse impact of chromatin damage on male fertility potential and the following pregnancy outcomes. Nonetheless controversial data, literature reveals how is now of critical importance to develop new objective markers of sperm function to accompany and/or even to oppose to the standard semen analysis. The latter is in fact

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Received December 12, 2011; **Accepted** December 15, 2011; **Published** December 17, 2011

Citation: Tosti E, Fortunato A (2011) Is sperm chromatin packaging relevant for IVF success? J Fertiliz In Vitro 1:e107. doi:[10.4172/2165-7491.1000e107](https://doi.org/10.4172/2165-7491.1000e107)

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considered not representative of the many biological properties of the spermatozoon and furthermore subjected to the observer variability.

We can *bone fide* conclude that especially in absence of pathophysiological diagnosis, chromatin decondensation test represents a modern tool for the assessment of male subfertility and a major predictor of reproductive outcomes in couples with suspected fertility problems [35].

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