

# Advances in the management of male infertility

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## Abstract

Male infertility can be treated by surgical procedures (e.g., varicocelectomy) or by administration of drugs if causal factors (e.g., seminal tract infections) are detected. In more severe cases, methods of assisted fertilization often have to be applied, but even these have only a limited success rate. Recent studies have demonstrated that disturbances of sperm DNA integrity (determined by the acridine orange test) can explain certain cases of fertilization failure and failure to achieve pregnancy following *in vitro* fertilisation with intracytoplasmic sperm injection. The evaluation of DNA integrity should be considered when diagnosing male infertility as it has been shown to be an independent factor and can be used as a supplement to standard semen analysis. Analysis of DNA integrity may, therefore, provide further information about altered male fertility and lead to administration of more appropriate therapy.

## Introduction and context

DNA integrity is a prerequisite, not only for the fertilization of an oocyte, but also for oocyte activation and achievement of an ongoing pregnancy [1]. It has been documented that there is a negative correlation between defective sperm chromatin structure (DNA breaks) and fertility, *in vivo* and *in vitro* [2]. Several studies have demonstrated that disturbed DNA integrity reduces fertilization and pregnancy rate during *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) treatment, and also increases the risk of early miscarriage [3,4].

DNA integrity can be assessed by the sperm chromatin structure assay (SCSA), by terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling (TUNEL), and more recently, the sperm chromatin dispersion assay. Special consideration should be made when comparing these methods, however, because they are each measuring different parameters. The SCSA is considered an indirect indicator of DNA damage. It is based on exposing sperm nuclei to acid then staining them with acridine orange (the acid exposure causes denaturation of double-stranded DNA in sperm with

impaired chromatin structure). The stain will attach to the ends of the broken DNA only, enabling evaluation of the proportion of single- and double-stranded DNA in the sample. The sperm chromatin dispersion assay also measures the susceptibility of sperm DNA to acid denaturation, but in a different way. The SCSA is based on the metachromatic property of the stain acridine orange, where intact DNA are characterized by a green fluorescence and disturbed DNA by orange fluorescence. The evaluation is carried out by flow cytometry; therefore a high number of cells (about 10,000) can be studied. The sperm chromatin dispersion test is performed using conventional bright field microscopy and analyses dispersed DNA loop halos. Between 300 and 500 spermatozoa can be evaluated during this test. The TUNEL assay uses fluorescein-dUTP to label single- and double-stranded DNA breaks.[5–7].

## Recent advances

In most recent studies, no correlation between DNA integrity and conventional semen parameters has been found; therefore, DNA integrity can be considered as a sperm function that is independent from sperm count, motility, and morphology [7,8].

Disturbances in sperm DNA integrity have been described in patients with varicoceles, testicular tumours, genital tract infections/inflammations, and patients with 'idiopathic' infertility [1,9,10]. Disturbances of DNA integrity occur predominately at the post-testicular level, which is why a recent study suggested testicular sperm extraction with subsequent ICSI as a possible treatment [11].

Research by different groups suggests that extrinsic oxidative stress, including environmental or industrial toxins or smoking, seems to be the major cause of sperm DNA damage rather than apoptosis [5], and a recent study showed that treatment with antioxidants has positive effects on implantation and pregnancy rates after ICSI [12].

Regarding further treatment options for disturbed DNA integrity, it is fortunate that a considerable number of recent studies have focused on the correlation between disturbed DNA integrity and genital tract inflammations and infections, respectively. It was shown that DNA integrity was impaired in leukocytospermic semen samples [13,14], and in patients with less than 1 million leukocytes per ml and high levels of reactive oxygen species [5]. In the last scenario, disturbed DNA integrity may still allow oocyte fertilization and formation of the 2-pronuclei stage, but when the paternal genes are 'switched on' at the 4-cell stage, further embryonic development stops because of oxidation and fragmentation of the paternal DNA, even after blastocyst formation [5].

Another recent advance is the demonstration that DNA integrity is improved after antibiotic treatment in patients infected with *Chlamydia trachomatis* [15]. Another recent study demonstrated that, compared with men without varicocele, men with varicocele have a higher percentage of sperm cells with DNA fragmentation. Thus, evaluation of sperm DNA fragmentation could be an important factor in deciding treatment options for men with varicocele [9]. This is supported by further studies, including a small one in which 10 of 11 patients with varicocele showed a significant decrease in sperm DNA fragmentation after varicocele repair, and an earlier, larger study of 37 patients [16,17].

### Implications for the clinical practice

The evaluation of DNA integrity should be considered when diagnosing male infertility. However, the different DNA integrity tests can often draw different conclusions and sometimes even the same test can yield different results (most probably due to low study populations), therefore, interpretations of test results in clinical practice have to be made with some caution. A greater quantity of

larger studies is needed for validation of such tests before they are ready to be used in general clinical practice. Despite these limitations, this is an interesting and promising field that may offer new tools for andrological diagnostic work-up and may finally lead to more diagnosis-related instead of symptoms-related treatment of male infertility.

### Abbreviations

ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilisation; SCSA, sperm chromatin structure assay; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling.

### Competing interests

The author declares that he has no competing interests.

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