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ORIGINAL ARTICLE

A systematic review on sperm DNA fragmentation in male factor infertility: Laboratory assessment

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KEYWORDS

Sperm DNA fragmentation (SDF);
Terminal deoxynucleotidyl transferased UTP nick-end labelling (TUNEL);
DNA damage;
Sperm DNA fragmentation (SDF) assay

ABBREVIATIONS

AO, acridine orange;
ART, assisted reproductive technology;
CMA3, chromomysin A3;

Abstract ***Objective:*** To review sperm DNA fragmentation (SDF) testing as an important sperm function test in addition to conventional semen analysis. High SDF is negatively associated with semen quality, the fertilisation process, embryo quality, and pregnancy outcome. Over recent decades, different SDF assays have been developed and reviewed extensively to assess their applicability and accuracy as advanced sperm function tests. Amongst them, the standardisation of the terminal deoxynucleotidyl transferased UTP nick-end labelling (TUNEL) assay with a bench top flow cytometer in clinical practice deserves special mention with a threshold value of 16.8% to differentiate infertile men with DNA damage from fertile men.

Materials and methods: A systematic literature search was performed through the PubMed, Medline, and ScienceDirect databases using the keywords 'sperm DNA fragmentation' and 'laboratory assessment'. Non-English articles were excluded and studies related to humans were only included.

Results: Of the 618 identified, 87 studies (original research and reviews) and in addition eight book chapters meeting the selection criteria were included in this review. In all, 366 articles were rejected in the preliminary screening and a further 165 articles related to non-human subjects were excluded.

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dsDNA, double-stranded DNA;
dUTP, 2′-deoxyuridine 5′-triphosphate;
DFI, DNA fragmentation index;
FITC, Fluorescein isothiocyanate;
ICSI, intracytoplasmic sperm injection;
IUI, intrauterine insemination;
IVF, *in vitro* fertilisation;
PI, propidium iodide;
ROS, reactive oxygen species;
SDF, sperm DNA fragmentation;
ssDNA, single-strand DNA;
TdT, terminal deoxynucleotidyl transferase;
TUNEL, terminal deoxynucleotidyl transferased UTP nick-end labelling;
SCD, sperm chromatin dispersion;
SCSA, sperm chromatin structure assay

Conclusion: There are pros and cons to all the available SDF assays. TUNEL is a reliable technique with greater accuracy and as an additional diagnostic test in Andrology laboratories along with basic semen analysis can predict fertility outcome, and thus direct the choice of an assisted reproductive technology procedure for infertile couples. Also, the TUNEL assay can be used as a prognostic test and results are beneficial in deciding personalised treatment for infertile men.

Introduction

Infertility is prevalent in 9% of couples of reproductive age and is described as the inability to establish pregnancy within 12 consecutive months of unprotected intercourse. Amongst infertile couples, ~20% is contributed by male factors alone [1]. Continuous decline in male fertility over time, which cannot be attributed to any specific cause, results in idiopathic infertility [2]. Various factors underlying male infertility include varicocele, oxidative stress, genetic abnormalities, systemic disease and infections, altered lifestyle, and exposure to xenobiotics [3,4]. All these factors can influence sperm DNA fragmentation (SDF), which acts as potential mediator for establishing an infertility status in men. Apart from these factors, the reproductive time line in men is one of the factors affecting semen parameters. Decline in the semen quality and increase in the SDF is observed after the ages of 35 and 40 years, respectively [5–7].

In current practice, male fertility status is evaluated indirectly based on the individual's semen parameters. Conventional semen analysis is the first step in the assessment of infertile men and it reflects the overall functioning of all male reproductive organs [8]. In general, semen volume, pH, sperm concentration, motility, vitality, and morphology are determined according to the WHO 2010 guidelines [9]. Even though basic semen analysis is considered as the key investigation in all Andrology laboratories worldwide, it cannot accurately differentiate fertile from infertile men. Nearly 15% of infertile men have normal sperm parameters according to the WHO 2010 [10]. This clearly indicates the presence of other subcellular and nuclear factors that have a major contribution towards male infertility that may not be identified by conventional semen analysis.

The nuclear component of the spermatozoa, especially sperm DNA integrity, is essential for normal fertilisation, implantation, pregnancy, and foetal development [11,12]. As a consequence of the high incidence of SDF in the men with idiopathic infertility [13], recent research has focussed more on determining the clinical value of assessing SDF in male infertility and using SDF as an advanced sperm function test along with the conventional tests to evaluate the fertility status of the individual. The importance of the SDF assay has also been recognised in the latest AUA and European Association of Urology guidelines on male infertility [14].

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