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Clinical Guidelines for Sperm DNA Fragmentation (SDF) is Associated with Male Infertility from Reactive Oxygen Species (ROS)

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ABSTRACT

Sperm DNA fragmentation is common in infertile male. Besides, sperm DNA integrity is essential for fertilization and healthy offspring development. Numerous genetic and environmental elements are associated with impacting sperm DNA integrity negatively. Such as lifestyle, ageing, industrial toxins, and infection. The mechanisms behind SDF are many, but apoptosis and reactive oxygen species are considered the main SDF mechanisms. The management of male infertility has led to the desire for more advanced SDF diagnostic tools to diagnose sperm DNA. Numerous sperm DNA damage assays such as terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labelling (TUNEL) assay and in situ nick translation (ISNT) are available to enhance SDF diagnosing and ultimately to better SDF management. Clinical SDF can lead to a low pregnancy rate, defects in embryo development and impaired offspring health. Moreover, SDF can impact the effectiveness of assisted reproductive technology through transfer genetics impartment to the embryo b in vitro fertilization or intracytoplasmic sperm injection. SDF can be mange through lifestyle changing, treating existing infection in the male reproductive tract and reactive oxygen species.

Keywords

Sperm DNA Fragmentation Causes, Reactive oxygen species, Clinical guidelines for SDF, Management strategies for SDF.

Abbreviations

sperm DNA fragmentation: (SDF); in vitro fertilization: (IVF); intracytoplasmic sperm injection: (ICSI); in situ nick translation: (ISNT); mitochondrial membrane potential: (MMP); Reactive oxygen species: (ROS); triphosphate nick-end labelling: (TUNEL); sperm chromatin dispersion: (SCD); sperm chromatin structure assay: (SCSA); density gradient centrifugation: (DGC); intrauterine insemination: (IUI); Intracytoplasmic morphologically selected sperm injection: (IMSI); physiological intracytoplasmic sperm injection: (PICSI).

Introduction

Healthy embryo development arises from fertilization of healthy sperm and oocyte; thus, the genetic components of a new born are a combination of oocyte and sperm DNA information, and it can be intact for embryo and fetal development, which will lead to healthy offspring. However, several DNAL damages can present in the DNA of male or female gametes that can point to an arrest of the reproductive process and result in unhealthy embryo development [1].

One of the top common DNA damages is the reproductive gametes are sperm DNA fragmentation, which can potentially cause paternal DNA anomaly transmission to progeny and is seen in a vast rate of spermatozoa from sub fertile and infertile men [1]. This article will be discussing sperm DNA fragmentation, causes of sperm DNA fragmentation, clinical Guidelines for sperm DNA fragmentation, and the management of sperm DNA fragmentation.

Sperm DNA Fragmentation Causes

Sperm DNA fragmentation SDF is a genetic abnormality that can lead to male infertility, represented by DNA breaks. SDF can affect both natural and assisted reproduction, and its consider one of the most common genetic irregularities detected in ejaculated human spermatozoa. Generally, several factors can induce SDF, such as lifestyle habits, diseases, infections, ageing, medication, infections and exposure to pollutants (Figure 1).

Figure 1: Factors inducing sperm DNA fragmentation in male.

Sperm DNA fragmentation increases in aging male, because of an increase in oxidative stress over time, and it's confirmed by animal models that present decreased epididymal antioxidant function with increasing age. Also, in Comar et al. study confirmed that age increases DNA fragmentation through testing physiologic processes, such as disulphide bond formation, chromatin condense, DNA denaturation, and fragmentation [2] Besides, the study data proved a positive relationship linking mitochondrial membrane potential (MMP) and age ($p<0.001$), since ROS increase with age, which change mitochondrial membrane permeability and drive the loss of MMP, ending with DNA fragmentation and cell death of spermatozoa [2].

Molecular mechanism of sperm DNA fragmentation

Sperm DNA fragmentation is induced through various mechanisms such as apoptosis, defects in chromatin remodelling throughout spermiogenesis, and oxygen radical-induced DNA damage.

Apoptosis

Through spermiogenesis, apoptosis control sperm overproduction of sperm cell and the removal of abnormal cells by enabling the monitoring of the germ cell population sustained by Sertoli cells. Apoptosis produces cell membrane disruption, cytoskeletal rearrangement, nuclear condensation and intranucleosomal DNA fragmentation in repeated and numerous fragments ≥ 185 bp. This

method is induced through fas proteins, which are phagocytized and removed by Sertoli cells to which these are associated. Although, some of the defective germ cells undergo the sperm remodelling process through spermiogenesis to be pushed into the ejaculate, presenting normal morphology with altered genetics materials [1]. Moreover, the huge cytoplasmic remodelling of the last stage of spermatogenesis can also disturb the functional apoptotic process before spermiogenesis. Accordingly, a defective sperm population will be produced that have left programmed cell death and display different apoptotic markers, a procedure named 'abortive apoptosis'. Therefore, detecting defective spermatozoa in the ejaculate can be s results of the irregularities in repairing the DNA breaks which arise in spermatids and enhanced apoptosis during early spermatogenesis.

Chromatin packing

DNA fragmentation can be induced from incomplete strand breaks produced through the normal process of spermiogenesis to reduce the torsional stresses required sperm DNA packaging into the tiny sperm head. Eventually, the sperm chromatin structure has a complex DNA and sperm nuclear protein arrangement with different compaction levels to shrink the atomic volume and head size.

Reactive oxygen species

ROS generates highly reactive molecules such as hydroxyl ion [OH], superoxide ion [O_{2-}], nitric oxide [NO], peroxyl [RO_2]. These ROS can potentially influence the chromatin in the sperm nucleus, which are vulnerable to oxidative damage, pointing to base modifications and DNA fragmentation.

Studies showed that electromagnetic radiation causes ROS production, ending in DNA damage and reduced motility and vitality in human spermatozoa. Further, various structural substances like benzene, methylene chloride, hexane, toluene, trichloroethane, styrene, heptane, and phthalates, release toxins and ultimately increase ROS production in the testes, damaging the spermatogenesis process and influencing sperm DNA fragmentation. In addition, tobacco and alcohol consumption points to more extensive rates of ROS production and high levels of DNA strand breaks, and fragmentation.

There are two types of sperm DNA fragmentation double DNA strand break and single DNA strand break. Double strand break is considered to be more harmful as they have altered genetics arrangements, also they are the consequences of the single strand break [3]. While single strand breaks are generated mostly from reactive oxygen species that can be produced from exogenous sources like as environmental toxicants, smoking, alcohol, diet, radiation. Also, it can be produced from endogenous sources like high leukocytes rate, presence of varicocele or ROS generation by mitochondria for the movement of sperm cell [4]. All the above mechanism lead to male infertility and can negatively influence embryo development, implantation rates, pregnancy rate and can cause to recurrent miscarriage.

SDF testing

Several methods are applied to detect sperm DNS damage snd fragmentation, mostly common method is sperm nuclear DNA integrity test and irregular sperm chromatin packaging test. Direct sperm DNA integrity assessments such as terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labelling (TUNEL) assay and in situ nick translation (ISNT) tests. Indirect sperm DNA integrity assessments are sperm chromatin structure assay (SCSA) and the sperm chromatin dispersion (SCD) assay, which detects DNA damage by protein denaturation in an acidic solution. Sperm chromatin packaging test utilises methyl green staining, aniline blue, toluidine blue, and chromomycin A3 (Table 1) [5].

Table 1: The table above illustrates the methods used in sperm DNA fragmentation to detect any defect in the DNA integrity and structure [5].

Method Name	Method Type	Description
Transferase-mediated deoxyuridine triphosphate nick-end labelling (TUNEL)	Direct	In this method DNA ends are detected and it measures the presence of DNA fragments
In situ nick translation (ISNT)	Direct	ISNT is a subtype of TUNEL and it only can detect and measure single-strand breaks.
Sperm chromatin structure assay (SCSA)	Indirect	This method detects and measure the denaturation DNA in the sample.
Sperm chromatin dispersion (SCD)	Indirect	SCD detect highly damaged DNA which has small halo.

Moreover, another method is Comet assay which can detect sperm DNA single strand and double strands break visually using electrophoresis, where the higher the level of DNA impairment, the brighter and longer the comet tail. Also, DNA nucleus diameters, olive tail moment, and comet length have been applied to develop the efficiency of the assay (Figure 2) [5].

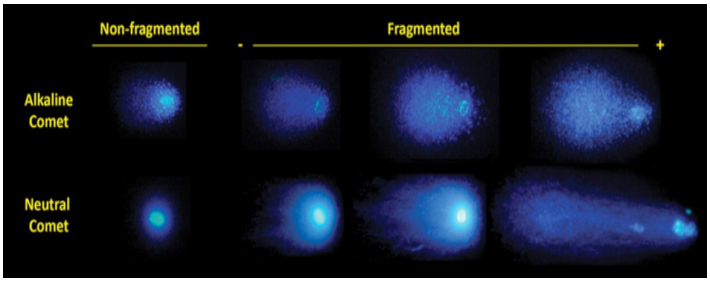


Figure 2: Fragmentation and non-fragmented sperms in alkaline and neutral comet assays. Different levels of (SDF) are shown for fragmented spermatozoa [6].

Clinical guidelines for SDF

Numerous researches attempted to recognise clinical SDF cut-offs to the prediction of natural or ART-related pregnancy. However, no standard value on a specific cut-off value of SDF has been decided; different SDF values are reported for pregnancy prediction in natural conception or assisted reproductive technology such as in-vitro fertilisation [IVF], intracytoplasmic sperm injection [ICSI],

or both) through examining native semen, sperm preparation by swim-up or density gradient centrifugation (DGC), and sperm donor cases [3]. In most cases, the TUNEL assay is most generally applied as it is accurate and reliable. At the same time, it can be beneficial to have a globally accepted assay with a solid predictive value which all clinics make. Still, the SDF assay selection in clinics usually relies on instrumentation availability and the cost of the assay to be performed in terms of reagents and run-time [3].

On the other hand, there are some clinical indications that lead to the diagnosing of SDF, such as varicocele, natural conception and assisted reproductive technology outcomes, recurrent pregnancy loss, and unexplained male infertility.

Varicocele is a clinical condition that has a harmful effect on semen parameters and the overall pregnancy percentage. It is common in up to 20% of the adult male population; still, many affected men can conceive without difficulties. An understanding of the varicocele mechanism can reveal the occurrence of SDF. Several underlying mechanisms of varicocele have been proposed, which explains the harmful effects of varicocele on testicular function, such as testicular hyperthermia [7]. Testicular temperature is highly regulated as it can affect spermatogenesis. Multiple enzymes used in DNA synthesis are temperature-dependent in the testis, mainly preferring temperatures lower than the average body temperature. In addition, the anatomic position of the testis in the scrotal sac and the countercurrent cooling mechanism provided by the pampiniform plexus of veins can regulate testicular temperature. The blood stasis with a varicocele interrupts the countercurrent cooling mechanism, making the testicular temperature rise, ending in abnormal DNA synthesis and defective spermatogenesis [7].

Moreover, another mechanism of the occurrence of DNA damage in men with varicocele is intratesticular blood stasis. The irregular dilatation of the pampiniform plexus of veins decrease testicular blood influx pointing in hypoxia and oxidative stress. It is commonly known, as mentioned earlier that oxidative stress is the most significant intermediary state in the development of irregular spermatogenesis and DNA damage [7].

As surgery is the corer treatment for varicocele, many studies have been made to look for laboratory tests which can enhance patient selection and recognise those who would benefit most after surgery. Attention in SDF testing start after a significantly positive correlation with varicocele was identified in early reports [7]. Few information is acknowledged about the influence of varicocele grade on SDF, as most of the researches that looks into the association between DNA damage and varicocele failed to inspect this link amongst different stages. Grade 3 varicocele has been found to have statistically significant reduction in SDF after surgery in patients with varicocele. Moreover, it has reported a substantial reduction in the protamine-1/2 mRNA ratio in grade 3 varicocele and a significant reduction of DNA fragmentation in grades 2 and 3 after surgery [7].

Assisted reproductive technology has now been widely applied to treat male infertility, as male infertility is now increasing due to environmental and genetic factors. ART treatment particularly intracytoplasmic sperm injection ICSI, can now give the hope and chances to couples who suffer from impaired sperm to obtain a pregnancy, while a few years ago, these couples were asked to use sperm donation to obtain their child [8]. Amongst all possible causes of failure of obtaining embryos or pregnancies, the impaired sperm genome is often implicated. Several reports investigating the predictive role of SDF on ART outcomes have reported contradictory results [8]. The sperm chromatin integrity function through ICSI is essential as this process avoids multiple unnecessary mechanisms that have developed to guarantee the selection of high-quality sperm cells for fertilisation. ICSI can allow spermatozoa with severe DNA damage to undergo nuclear decondensation and pronucleus formation. Developmental irregularities arising from such chromatin damage can't be recognised till the post implantation stages [9]. Researches have paid attention to the correlation between sperm DNA fragmentation and the pregnancy rate of intrauterine insemination (IUI) treatment due to the key function of sperm DNA integrity in embryonic development. A meta-analysis has been performed to validate the precise relationship within sperm DNA fragmentation and the pregnancy rate of IUI, by analysing the results of ten studies, where it has been found that high sperm DNA fragmentation can have a harmful influence on reproductive outcome after IUI [10].

Children born through ART, can get influenced by the sperm DNA on the short- and long-term, specifically ICSI, have a higher rate of disorder than those conceived naturally [11]. As instance, sperm nuclear DNA fragmentation thresholds significantly projected negative pregnancy results in couples going into ART treatment, also around 12 ART studies investigating SDF and ART outcomes found out that in 113 IVF and IVF-ICSI cases, there were no clinical pregnancies if the SDF index of the sample used in the ART procedure was 27% [12]. Still, fertilization rate was not correlated with sperm DNA fragmentation or high DNA stainability, which shows that high-quality DNA is not necessary for normal fertilization in the paternal genome [12].

Moreover, the degree of SDF was also examined on how it can influence ART treatment; the live birth rate was not significantly different within the low-DFI group and high-SDF group (56.03% [172/307] vs 65.31% [32/49]; $p > 0.05$). Still, the percentage of good-quality embryos in the low-SDF group was significantly higher than that in the high-SDF group (84.35% [7,328/8,688] vs 41.20% [510/1,238]; $p < 0.05$) [13]. Also, it has been found that high-SDF had a significantly higher miscarriage rate than in those in the low-DFI group. In addition, they have found that that the miscarriage percentage was significantly higher in the high-SDF group than in the low-DFI group in the IVF subgroup and ICSI subgroup but not significantly different in IVF/ICSI subgroup. In addition, they have found that that the miscarriage percentage was significantly higher in the high-SDF group than in the low-DFI group in the IVF subgroup and ICSI subgroup but not significantly

different in IVF/ICSI subgroup; besides, various SDF tests were examined to evaluate the strongest association between SDF and miscarriage, and it has been observed that e miscarriage association was strongest when using the TUNEL assay [13]. Regarding the embryo quality Dang et al., found that the in high-SDF group good-quality embryos was significantly lower than in the low-SDF group. Subgroup examines indicated that the good-quality embryo rate of the high-SDF group was lower than that of the low-DFI group in IVF subgroup [13].

In another study, short- and long-term influences of fragmented DNA sperm cells have been evaluated through analysing the level of development, implantation, and DNA methylation of embryos and adult animal health and behaviour. The mRNA expression of epigenetic regulated genes was observed if sperm DNA fragmentation can alter the epigenetically regulated genes in mouse embryos at the blastocyst stage produced by ICSI. The expression was significantly changed in retrotransposons, in the X-linked gene, and three imprinting genes, showing an ICSI-dependent epigenetic defect at the blastocyst stage [9].

Moreover, liver and lungs of females fertilized by ICSI were bigger than those of in vivo- fertilized animals. Also, there was an increase in the rate of pneumonia 40% of ICSI cases vs. 13% of control. Furthermore, mice produced by ICSI, and had SDF died between 3 and 5 months of age without any external symptoms. When ICSI generated mice with SDF were biopsied, some of them displayed hemothorax, whereas in others, pulmonary hemorrhage was obvious, suggesting fatal hemorrhagic pneumonia. Moreover, 25% of surviving mice obtained an "aged" appearance starting at approximately 3 months of age [9]. Additionally, ICSI generated mice with DFS produced had skin symptoms of aging; mice had brittle hair, earlier and more frequent hair depigmentation, and reduced fitness. Also, skeletal irregularities such as curvature of the spinal column (lordokyphosis) were detectable between 12 and 14 months of age in these animals (Figure 3) [9].

Management strategies for SDF

SDF can result in a low pregnancy rate and high miscarriage rate in male through IVF or IVF and ICSI; consequently, techniques for improving sperm DNA damage before ART procedures and selecting sperm with better chromatin are recommended for better ART outcomes [5].

Firstly, lifestyle change would be the easiest and most fundamental, essential, and simple way to enhance sperm quality. For example, men with poor sperm quality should stop smoking and drinking; start exercising and managing their weight; wear loose underwear; try to avoid environments with high temperatures and high-temperature workspaces, and ejaculate for an appropriate duration [5]. Secondly as SDF can be caused through ROS, when a vast amount of reactive oxygen species is generated, the sperm DNA is damaged by oxidative stress, pointing out infection in the whole reproductive tract, which should be treated. Antibiotic treatment can be successful in reducing the rate of SDF, and it might improve pregnancy rates [14]. Likewise, leukocytospermia empirical antibiotic treatment can enhance natural pregnancy percentage, as instance patient under doxycycline antibiotics had higher pregnancy rate (15 of 32 [47%]) than among the controls (5 of 25 [20%]) [15].

Secondly, mentioned previously, varicocele can be a potential cause of SDF; thus, varicocele treatment will improve sperm

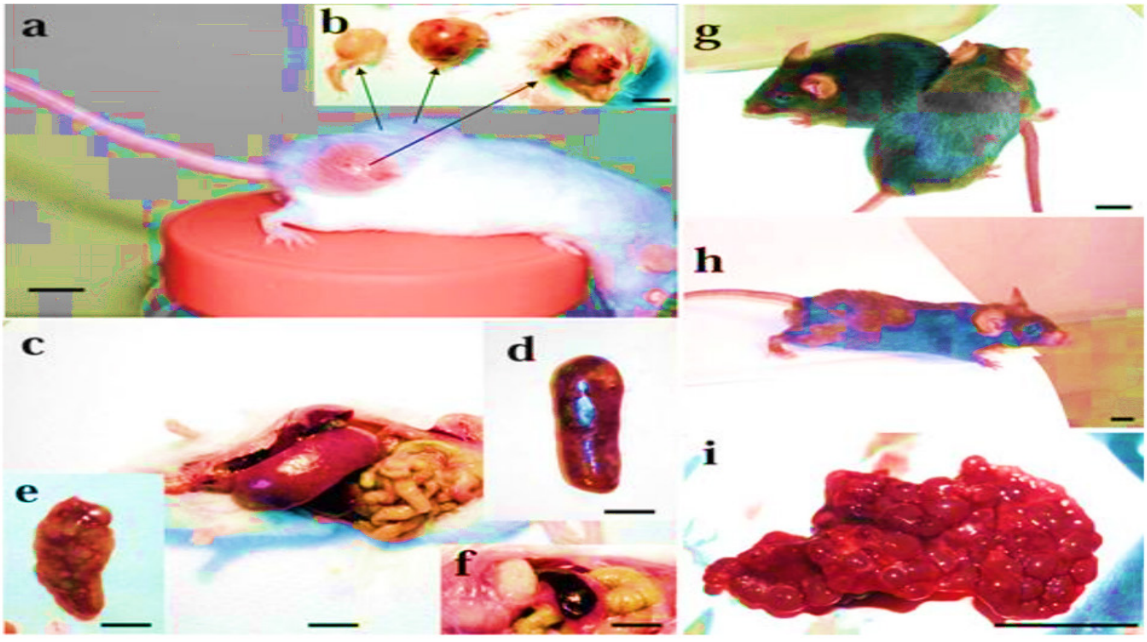


Figure 3: Impact of ICSI generated mice with SDF. a,b,f and mice showed tumour development, while some showed premature cutaneous symptom of aging phenotype(g and h) [9].

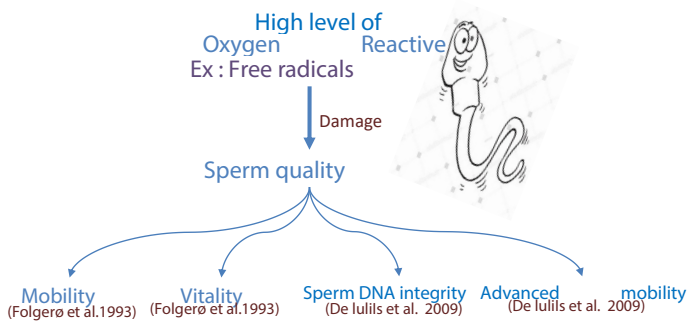
DNA quality. In addition, varicocele treatment showed increased pregnancy success in both natural conceptions and ART by improved SDF rate. Therefore, varicocelectomy can be a potential solution to enhance fertility [3]. Surgical varicocele treatment is applied to treat infertile men with varicocele. Certainly, such treatment will impact male fertility, and it's associated with significant improvements to various biomarkers of male infertility, such as pregnancy rates. Moreover, varicocelectomy has been adopted to alleviate oxidatively induced SDF and defend upon the progressive nature of varicocele and its consistent upregulation [16].

Thirdly, oxidative stress is the primary factor that produces male infertility by impairing sperm DNA. Researchers have found that seminal antioxidant capacity is suppressed in infertile men with high ROS levels compared to males with normal ROS levels; thus, its treatment will improve SDF and positively influence pregnancy rate and embryo development. Dietary antioxidants can help decrease sperm DNA damage, incredibly in male with high levels of DNA fragmentation; several studies confirm the usage of various antioxidants had significant impact on DNA fragmentation and chromatin integrity [17]. The most effective antioxidants recognised are vitamin E, vitamin C, selenium, coenzyme Q10, N-acetylcysteine, zinc, and L-carnitine [5]. Furthermore, the mixture of different antioxidants has also shown notable influence on the rate of SDF; for instance, the Chinese medicine compound Xuanju Capsule with vitamin E used for three months reduced the degree of DNA fragmentation index better than to just vitamin E [18]. Additionally, a combination of 2-month oral treatment with vitamin C and vitamin E, both at a daily dose of 1 g, was given to SDF patients, where a significant decrease in the rate of DNA fragmentation in ejaculated spermatozoa after two months was recorded. The DNA fragmentation rate was 22.1 ± 7.7 before treatment, and it decreased to 9.1 ± 7.2 [19].

Finally, laboratory techniques such as conventional swim up method can be used to select low level DNA fragmented sperms. Also, Intracytoplasmic morphologically selected sperm injection (IMSI) applies high magnification to choose the most morphologically normal sperm, as the appearance of vacuoles in the nuclear region can be linked to high SDF. Additionally, methods like physiological intracytoplasmic sperm injection (PICSI), based on sperm binding to hyaluronic acid, and microfluidic devices, allowing sperm migration along microchannels can also be helpful.

Oxidative stress

Although low levels of ROS are required for critical steps (e.g., capacitation, acrosome reaction and oocyte-sperm fusion) in fertilization. However, oxidative stress can be deleterious to spermatozoa if the antioxidant capacity of the body is exceeded and levels of oxygenated free radicals (OFRs) are elevated in seminal plasma and/or sperm cytoplasm. It turns out that cellular stress in all its forms can lead to DNA fragmentation and affect male fertility. According to Twigg, seminal ROS levels can lead to sperm damage and therefore male infertility through the degradation of characteristic sperm quality parameters (motility, vitality, DNA fragmentation, chromatin decondensation and advanced motility parameters). Thus, it is very important for the clinician managing male infertility to know how to explain to his patient the need to reduce the sources of oxidative stress linked to his lifestyle, i.e., smoking, hot baths, exposure to endocrine disruptors and the treatment of ROS-generating pathologies such as varicocele, infections of the male accessory glands. The lack of consensus on the pathophysiological limits of ROS remains the crucial issue.



Conclusion

Several factors can cause sperm DNA fragmentation; each element can act differently to cause sperm DNA damage, eventually decreasing pregnancy rate and embryo development rate, as sperm with oxidative DNA damage can still hold the potential to fertilize the oocyte and achieve fertilization. Several studies have conducted experiments to monitor the influence of SDF, where it has been found that SDF can potentially lead to conception failure, abortions, malformations, and genetic diseases. The SDF management is crucial and it can be easily control be treating any existing infections, or changing lifestyle habits.

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References

1. García-Ferreyra J. Sperm DNA Fragmentation and Its Relation with Fertility. New Discoveries in Embryology. 2015.
2. Comar V, Ricci J, Dieamant F, et al. The effects of male age on sperm DNA damage: an evaluation of 2,178 semen samples. JBRA Assisted Reproduction. 2018; 323-330.
3. Agarwal A, Majzoub A, Baskaran S, et al. Sperm DNA Fragmentation: A New Guideline for Clinicians. The World Journal of Men's Health. 2020; 38: 412.

4. Ribas-Maynou J, Benet J. Single and Double Strand Sperm DNA Damage: Different Reproductive Effects on Male Fertility. Genes. 2019; 10: 105.
5. Kim G. What should be done for men with sperm DNA fragmentation? Clinical and Experimental Reproductive Medicine. 2018; 45: 101-109.
6. Ribas-Maynou J, Garcia-Peiro A, Abad C, et al. Alkaline and neutral Comet assay profiles of sperm DNA damage in clinical groups. Human Reproduction. 2012; 27: 652-658.
7. Agarwal A, Majzoub A, Esteves S, et al. Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios. Translational Andrology and Urology. 2016; 5: 935-950.
8. Benchaib M. Sperm DNA fragmentation decreases the pregnancy rate in an assisted reproductive technique. Human Reproduction. 2003; 18: 1023-1028.
9. Fernández-Gonzalez R, Moreira P, Pérez-Crespo M, et al. Long-Term Effects of Mouse Intracytoplasmic Sperm Injection with DNA-Fragmented Sperm on Health and Behavior of Adult Offspring1. Biology of Reproduction. 2008; 78: 761-772.
10. Chen Q, Zhao J, Xue X, et al. The association between sperm DNA fragmentation and reproductive outcomes following intrauterine insemination, a meta-analysis. Reproductive Toxicology. 2019; 86: 50-55.
11. Simon L, Brunborg G, Stevenson M, et al. Clinical significance of sperm DNA damage in assisted reproduction outcome. Human Reproduction. 2010; 25: 1594-1608.
12. Larson-Cook K, Brannian J, Hansen K, et al. Relationship between the outcomes of assisted reproductive techniques and sperm DNA fragmentation as measured by the sperm chromatin structure assay. Fertility and Sterility. 2003; 80: 895-902.
13. Deng C, Li T, Xie Y, et al. Sperm DNA fragmentation index influences assisted reproductive technology outcome: A systematic review and meta-analysis combined with a retrospective cohort study. Andrologia. 2019; 51: e13263.
14. Gallegos G, Ramos B, Santiso R, et al. Sperm DNA fragmentation in infertile men with genitourinary infection by Chlamydia trachomatis and Mycoplasma. Fertility and Sterility. 2008; 90: 328-334.
15. Hamada A, Agarwal A, Sharma R, et al. Empirical Treatment of Low-level Leukocytospermia with Doxycycline in Male Infertility Patients. Urology. 2011; 78: 1320-1325.
16. Roque M, Esteves S. Effect of varicocele repair on sperm DNA fragmentation: a review. International Urology and Nephrology. 2008; 50: 583-603.
17. Imamovic Kumalic S, Pinter B. Review of Clinical Trials on Effects of Oral Antioxidants on Basic Semen and Other Parameters in Idiopathic Oligoasthenoteratozoospermia. BioMed Research International. 2014; 1-11.
18. Rybak R, Faldikova L, Faldyna M, et al. Bull and boar sperm DNA integrity evaluated by sperm chromatin structure assay in the Czech Republic. Veterinární Medicína. 2012; 49: 1-8.
19. Greco E. Reduction of the Incidence of Sperm DNA Fragmentation by Oral Antioxidant Treatment. Journal of Andrology. 2005; 26: 349-353.