ORIGINAL ARTICLE

Effect of Cigarettes Smoking on Embryo Development through its Effect on Sperm DNA Fragmentation - A Systematic Review

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Abstract

Background: The negative deleterious effects of cigarette smoking are widely known, especially the relationship its influence on semen quality and sperm DNA fragmentation. Male cigarette smoking was highlighted and hypothesized to not only affect cause DNA fragmentation but also affect the early embryo development. To summarize various literature studies, a systematic review of relevant observational studies was conducted to determine the relationship between cigarette smoking among men and DNA fragmentation and the ultimate influence on embryo development. **Methods:** A methodical explore of the observational literature on the subject was carried out on Google Scholar. All papers relevant observational papers reporting on the tie of cigarette smoking with sperm DNA fragmentation and embryo growth were included. The retrieval of pertinent reports was done and subsequently the systematic search of reference lists to help in the identification of studies qualifying for inclusion. **Results:** Of the 14 studies, 4 papers were retrieved reporting observational findings that cigarette smoking causes adverse DNA damage which is evidentially correlated with poor embryo growth. However, the remaining studies had no information implying any existent relationship between cigarette smoking, DNA damage, and development of the embryo. **Conclusions:** The literature asserts that cigarette smoking through sperm DNA fragmentation affects early embryonic development. Well-designed research literature with evidence-based, pre-defined criteria for subject selection, the definition of cigarette smoking, and its contents are essential in achieving consistent affirmation on the result of smoking on DNA fragmentation and ultimately, embryo development.

Key words: Blastocyst development, cigarette smoking, DNA fragmentation

INTRODUCTION

This systematic review seeks to determine the correspondence linking cigarette smoking amongst men and DNA fragmentation and the ultimate influence on embryo development. Substantial evidence-based assertions from human research reveal that the smoke from cigarette comprises deleterious carcinogens and mutagens, which may gradually ensue in the induction of nuclear damage od spermatozoa DNA, defective semen quality, and compromising chances of healthy embryo development.

The harmful substances include nicotine, alkaloids, hydoxycotinine, nitrosamines, and cotinine. Research suggests that the substances produce overly reactive oxygen (O_2) species (ROS). Observational evidence asserts the effect of the ROS on the reproductive cycle as they affect the probity of the sperm nucleus DNA through multiple base adjustments, abnormal packing of the chromatins, and abnormal DNA strand breaks. The structure of the sperm DNA keeps nuclear chromatins compact and highly stable; conversely, pro-mutagenic change is caused by DNA damage which in severe degrees affect the germline quality, preventing embryo development.[1] Studies reveal high levels of negative association between multiple reproductive indices such as the rate of fertilization, embryo cleavage, implantation, and the degree of DNA fragmentation or damage. Furthermore, researchers established recently that severe damage to spermatozoa DNA may be consequential to recurrent spontaneous abortion.

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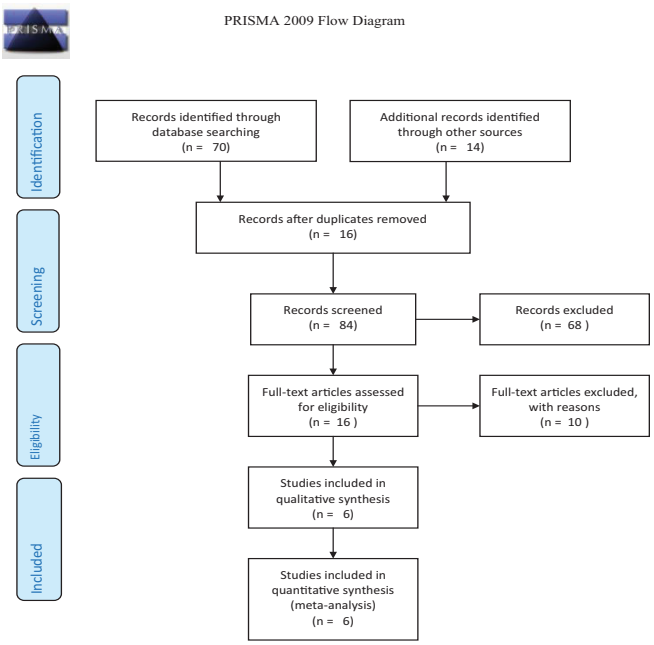
METHODS

Research strategy and selection criteria

The systematic review was conducted on studies detailing the effects of cigarettes smoking on embryo development through its effect on sperm DNA fragmentation. The analysis complied with the PRISMA criteria in reporting results. We conducted research using Google Scholar database from the beginning of January using the following keywords: "DNA fragmentation," cigarettes, and blastocyst development. Only full studies published in the English language were included in the search. 14 additional observational studies were included in our personal journal collection. Two investigators were actively engaged in conducting an independent review of the literature to establish any discrepancies and eligibility. Notably, discrepancies were resolved accordingly in a group discussion.

Eligibility and data extraction

Studies that evaluated the link between cigarette smoking by the male partner, the impairment to Spermatozoa DNA through nuclear DNA fragmentation and the negative effects on embryo development were selected. Patient choice, male involvement and omission criteria, sperm DNA assay types, the connection between sperm DNA damage results as a result of cigarette smoking, and embryo development test results were recorded. Embryo development was referred to as "cleavage rate" in some instances.[2] Information on DNA fragmentation as a result of cigarette smoking was collected[3] from the sources. Detailed information related to cigarette smoking, spermatozoa DNA fragmentation and embryo development were recorded from a number of studies[4] while one source[5] detailed test results revealing that cigarette smoking indeed causes oxidation, but does not necessarily result in poor quality of sperms through DNA fragmentation.



RESULTS

Studies selected

Overall, a total of 84 studies were retrieved, 14 from personal journal collections and 70 from the Google Scholar database. However, a review of the abstracts, respective titles and introductory content indicated that the 68 were not directly relevant to the subject. From the remaining 16 citations, full articles were obtained following an explorative review of the 16 research papers, five as they did not mention DNA fragmentation or cigarette smoking. Of the remaining 11, one study was excluded for reporting on sperm DNA quality in relation to Intrauterine Insemination without any mention of the other keywords of the study while four were omitted for relating paternal influence (*in vitro* fertilization) with poor embryo development following intracytoplasmic sperm injection.[6] The remaining six research studies reported findings of observational studies revealing relational factors between cigarette smoking, sperm DNA devastate, and the development of the embryo.

Study characteristics

The six eligible researches, one reported on the repercussion of cigarette smoking on DNA fragmentation and sperm quality, a questionnaire was employed in the assessment of smoking intoxication and measured using CO-Tester.

Study design

Two were prospective studies, one cohort, two cross-sectional, and two retrospective studies.

Test results

Findings suggest deleterious effects on the nuclear quality of the spermatozoa for cigarette smokers. DNA fragmentation, therefore, can be examined as a self-determining framework that has strategic, diagnostic, and prognostic efficacy in the treatment of infertility. In addition, cigarette smoking, high DNA stainability (HDS) and DNA fragmentation index (DFI) were also tested.

DNA fragmentation

Findings from results investigating the link joining cigarette smoking and sperm DNA fragmentation were not uniform. Spaniard *et al*. analyzed sperm samples and revealed that the rate of DNA fragmentation was between 5.1% and 69.2% and the mean was 28.8%.[5] There was a remarkable variance between non-smokers and smokers in the fragmentation of their DNA spermatozoa ($P < 0.001$). In general, it is evident that the consumption of tobacco results in increased rates of aneuploidy for specific chromosomes, their susceptibility

Table 1: Summary of findings

People: Fertile non-smokers, infertile non-smokers, infertile smokers
Methodology: Prospective cohort, retrospective and cross-sectional studies
Comparison: Fertility status and smoking of cigarettes

Outcomes	Impacts	Number of subjects	Certainty of the evidence (GRADE)*
DNA fragmentation (Calogero *et al*., Soares and Melo, Zini *et al*., Elshal *et al*. Spaniak *et al*.)	DFI is a result of abnormal sperm morphology, sperm motility evidenced in HDS in close consideration of the vital roles the parameters play in embryo development, cigarette smoke affects DNA chromatin integrity.	5	⊕⊕⊖⊖ low
Cigarette smoking (Calogero *et al*., Spaniak *et al*., Soares and Melo)	Cigarettes smoking has negative impacts on sperm DNA chromatin integrity	3	⊕⊕⊕⊖ moderate
HDS (Viloria *et al*.)	The %HDS was negatively correlated with sperm motility and higher amongst infertile non-smokers, an indication of a close relationship between cigarette smoking, high %HDS and DNA fragmentation	3	⊕⊕⊕⊖ moderate
Semen analysis (Spaniak *et al*.)	Cigarette smoking affects sperm morphology negatively hence influencing the degree of damage to the sperm DNA and ultimately embryo development. Semen parameters (motility and morphology) revealed negative correlation with %DFI	2	⊕⊖⊖⊖ very low
Embryo development (Zini *et al*.)	Embryo quality influenced by sperm DNA damage negatively causing poor embryo development	1	⊕⊕⊕⊖ moderate

* GRADE Working Group grades of evidence. High=This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low. Moderate=This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate. Low=This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high. Very low=This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high. Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med, 2009; 6 (7): e1000097. doi: 10.1371/journal.pmed1000097)

to nondisjunction caused by smoking at some point in male meiosis varies among various chromosome pairs.[3]

HDS

Percentage of cells exhibiting immature chromatin, hence, high levels of HDS was found to be significantly higher among non-fertile cigarette smokers.[7]

Cigarette smoking

Drawing from the results, evidence revealing the positive association between the percentage of HDS, DFI, and significant sperm DNA fragmentation was found. Cigarette smoking showed positive, reliable and significant correlation with the percentage of DFI.[7] In essence, it was clearly outlined that cigarette smoking shows a negative association with sperms with normal morphology ($P < 0.001$).

Embryo development

Of the six eligible research, one gave account on the correlation between damaged DNA through sperm DNA fragmentation and embryo growth.[8] There was a noteworthy positive association connecting embryo quality, sperm DNA damage and poor embryo development, and damage to DNA fragmentation.

Sperm morphology

Over time, sperm morphology, and motility have been employed in the evaluation of male fertility potential. One study conducted heterogeneity causes in two subgroup analyses.[5] Sperm morphology was examined and mean as per the criteria of the WHO in both controls and patients ranged from 21.2% to 72.0% and 8.4% and 30.8%, respectively. The study concluded that varicocele affects sperm morphology

negatively hence influencing the degree of damage to the sperm DNA and ultimately embryo development.

Outcome measures

The study's primary outcome measures were specified as sperm DNA fragmentation (percentage DFI), sperm morphology (percentage normal forms), and sperms with high rates of HDS (percentage high DNA sustainability).[7] The parameters are frequently employed in clinical settings as laboratory measures for the investigations on varicocele. The description of results is presented as mean ± S.D. While some works of literature provided required data on all outcomes, others covered one or two outcome measures. For each study, we assessed the following characteristics: Semen analysis methods, control type, and study design [Table 1].

Risk of bias assessment

Cochrane Collaboration guidelines were employed in the analysis of the risk of bias in the literature. We conducted an evaluation of allocation concealment, blinding, sequence generation, and incomplete outcome measures data and bias from confounding. The studies were heterogenous hence a moderate bias risk to non-random studies was assumed. We assumed a moderate risk grade because other studies utilized a comparable exclusion criterion. A number of vital confounders such as toxic exposure and infections were excluded. We assumed any degree of detection bias among observers who were tasked with conducting semen analyses. The bias for incomplete outcomes data was unclear as missing data for smoking history parameter were not articulately reported in corresponding studies.

DISCUSSION AND CONCLUSION

This manuscript carried out a systemized appraisal of various research on cigarette smoking, DNA fragmentation, and embryo growth, and development. The examination divulged that smoking is relatively related with multivariate sperm parameter percentages in respect to modifications - 10% sperm motility, 13% normal spermatozoa, and 13% sperm density. It is, therefore, clear that significantly lower amounts of viable and motile sperms are found in cigarette smokers compared to cigarette non-smokers.[1] In furthering, the evidence of the degree of damage that smoking causes on sperms, the studies highlighted surmountable evidence that a higher number of cigarette smokers are asthenozoospermic.

Conversely, though, limited evidence was provided suggesting that there is no relationship between cigarettes smoking and oxidative DNA damage amongst infertile men. The study was conducted in fertile and infertile men (non-smokers and smokers) proposing further future studies in establishing a correlation between the mechanism through which smoking cigarette affects fertility. The findings provided evidence showing that through a molecular pathway, the sperm physiology was subjected to a degree of impairment by tobacco compounds. While the studies acknowledge the adverse effects of tobacco toxic factors on sperm quality, which result in sperm DNA fragmentation and embryo quality, the pathways involved in the respective molecular pathway are not clearly articulated. Consequently, the study was unable to detect a direct correlation between cigarette smoking and increased oxidative damage to sperm DNA fragmentation. Notably, though, cigarette smoking among men is highly associated with higher percentages of HDS and DFI.[5] Consequently, cigarette smoking results in increased sperm DNA fragmentation, which affects sperm integrity and ultimately embryo development, due to the fact that a higher percentage of the abnormal organization of chromatins was associated with evidenced oxidative stress caused by ROS.[5] The heterogeneity of the studies analyzed in this systematic review weaken the conclusions of this paper and embryo scoring in regard to data collection, embryo development, and sperm DNA test types.[4] Consequently, probable studies are required to help analyze further the interconnection existent between DNA fragmentation and embryo growth.

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