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Cigarette Smoking and Semen Quality: A New Meta-analysis Examining the Effect of the 2010 World Health Organization Laboratory Methods for the Examination of Human Semen

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Abstract

Objective: Approximately 37% of men of reproductive age smoke cigarettes, with Europe having the highest tobacco use among all the World Health Organization (WHO) regions. Toxins from tobacco smoking can potentially affect sperm development and function, with a negative effect on semen parameters. Given the high prevalence of smoking and recent changes in the WHO laboratory methods for the examination of human semen, the role of this exposure in face of new WHO methods needs to be clarified.
Evidence acquisition: We conducted a systematic review, followed by a meta-analysis, to determine whether cigarette smoking affects human semen parameters. PubMed, Saint Joseph's University Discover, and Google Scholar were used to identify relevant studies published after release of the latest WHO methods for laboratory evaluation of human semen. Participants were from fertility/urologic clinics and andrology laboratories. The outcome measures were semen volume, sperm concentration, motility, and morphology, the parameters usually used in clinical settings to assess fertility.
Evidence synthesis: Twenty studies with 5865 participants were included in the meta-analysis. Exposure to cigarette smoking was associated with reduced sperm count (mean difference [MD]: -9.72×10^6/ml; 95% confidence interval [CI], −13.32 to −6.12), motility (MD: −3.48%; 95% CI, −5.53 to −1.44), and morphology (MD: −1.37%; 95% CI, −2.63 to −0.11). Subgroup analyses indicated that effect size was higher in infertile men than in the general population and in moderate/heavy smokers than in mild smokers. The overall effect size on semen volume, sperm count, and motility remained similar when 2010 and earlier WHO manuals were used for semen analysis but was lower with regard to sperm morphology.
Conclusions: Our results suggest that cigarette smoking has an overall negative effect on semen parameters. The latest WHO laboratory methods for the examination of human semen had a minimal impact on the magnitude of effect size, thus confirming the observed negative effect of smoking on conventional semen parameters.
Patient summary: A new systematic review and meta-analysis comprising 5865 men shows that cigarette smoking is associated with reduced sperm count and motility. Deterioration of semen quality is more pronounced in moderate and heavy smokers.

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1. Introduction

Approximately 37% of male adults worldwide use tobacco, mainly cigarettes [1]. Smoking rates have gradually declined in the United States, but Europe still has the highest tobacco use among all the World Health Organization (WHO) regions [1,2]. Tobacco combustion produces approximately 4000 chemical compounds, and smokers inhale a host of toxins including nicotine, carbon monoxide, cadmium, and other mutagenic compounds, all with potential deleterious effects on male germ cells [3]. The toxins originating from cigarette smoke can decrease sperm mitochondrial activity and damage the chromatin structure in human sperm, therefore impairing fertilization capacity both in vivo and in vitro [4,5].

Smoking cigarettes has been associated with a deterioration of sperm quality including motility, concentration, and morphology, which are the parameters most frequently used in clinical settings to assess fertility [6–8]. However, the evidence is not unequivocal, and some studies have found no effect on semen quality [9–11].

In 2010, the WHO established new criteria for the laboratory examination of human semen [12]. The changes specifically included assessments of (1) volume by weight rather than graduated pipette; (2) motility by two categories, namely progressive and nonprogressive, in contrast with four categories in previous versions; and (3) morphology by strict criteria (Tygerberg) as opposed to the WHO criteria in previous manuals. New reference values for semen characteristics were also proposed that were markedly lower than those reported in previous manuals. In a recent study evaluating the impact of these changes, semen characteristics of approximately 15% of patients considered abnormal according to the 1999 WHO reference values were reclassified as normal based on the 2010 WHO reference values [13]. Therefore, varying results may be expected with regard to semen analysis when one manual is followed versus another, with obvious implications for counseling, diagnosis, and management of men seeking fertility evaluation. These data reinforce the need for a careful examination of the 2010 WHO criteria for the laboratory examination of human semen to help health care providers understand the clinical impact of such changes.

We conducted a systematic review and aggregated the available published data on the effect of cigarette smoking on semen parameters using a meta-analysis. The aim was to summarize the evidence of the effect of cigarette smoking on human semen characteristics in view of the new 2010 WHO criteria for the laboratory examination of human semen.

2. Evidence acquisition

2.1. Search strategy

We conducted a systematic search using PubMed, Saint Joseph's University Discover (SJUD), and Google Scholar to identify all relevant studies published from 2010 to August 2015. For SJUD, which includes 189 databases (http://www.sju.edu/int/resources/libraries/drexel/), and PubMed, the Medical Subject Headings search terms used were **smoking* OR cigarette AND semen or sperm* OR *fertil** in any language. The following selections were made for the advanced search: "Only studies in humans" and "date range from 2010 onwards." Article types selected were clinical study, comparative study, journal article, observational study, randomized controlled trial, review, and systematic review. Trial registers searched were Current Controlled Trials (http://www.controlled-trials.com), ClinicalTrials.gov (http://clinicaltrials.gov), and the World Health Organization International Trials Registry Platform search portal (http://www.who.int/trialsearch). The gray literature was searched using Google Scholar.

The titles and abstracts retrieved were initially screened. Full texts of selected abstracts matching inclusion criteria were obtained. Review articles and reference lists were hand-searched. Studies were analyzed for inclusion independently by two of the authors, and any discrepancies were resolved by discussion.

2.2. Selection of studies and validity assessment

Articles were included only if full texts were available, enrolled human participants, did not use workplace passive cigarette smoking, and were not review articles. Smokers were defined as those smoking only cigarettes, whereas nonsmokers were those men who did not smoke at all at the time of each particular study. Studies focusing on the effect of smoking on semen parameters in men with existing specific conditions were excluded (Supplementary Table 1). Authors of unpublished or incomplete data sets were not contacted to request their data for this meta-analysis.

Participants were males aged $\geq$13 yr regardless of population size and origin. We specified the primary outcome measures a priori as semen volume, sperm count, motility, and morphology because these parameters are the most commonly used measures in the investigation of male fertility. Some studies provided data on all of these measures and others on just some of them. One exposure (smoking) was compared at once (no multivariate analysis). The following characteristics were assessed for each study: study population (infertile vs general population), cigarette consumption per day, and data collection methods (eg, semen analysis according to the edition of the WHO manual).

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement to report the results [14]. The initial search yielded 15 119 articles. Of those, 145 abstracts were selected, and 124 full-text articles were obtained. From these, 104 studies were excluded with reasons (Supplement 1, item 5). Twenty studies fulfilled all criteria and were included in the meta-analysis. To determine validity, each included study was assessed according to the criteria for nonrandomized studies to assess the risk of bias [15] (Supplement 1 and Supplementary Table 2).

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