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P-074 Sperm deoxyribonucleic acid integrity decreases with age and exhibits a rapid decline beyond the age of 35: a retrospective evaluation of 3446 semen samples

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Study question: Does advancing paternal age correlate with sperm DNA fragmentation index (DFI) and is there a cut-off age beyond which sperm DFI increases significantly?

Summary answer: In infertile men, DFI correlate with advancing paternal age and should be routinely screened starting 35 years of age.

What is known already: In recent decades, birth rates have substantially increased for men older than 30 years because of advanced age of marriage, rising life expectancy at birth, modern societal norms, and accessibility to assisted reproductive technology (ART). Advanced paternal age has been associated with a decline in conventional semen parameters (volume, concentration, motility, DFI), as well as, reduced fertility, increased risk of miscarriage, structural chromosomal aberrations and complex epigenetic disorders. Several studies have recommended testing sperm DFI in infertile men with advanced age ($\geq$40 years) as it may provide prognostic information for couple attempting natural and assisted reproduction.

Study design, size, duration: This is a retrospective study of 3446 semen samples from patients under investigation for infertility between April 2016 and January 2022. Semen samples were obtained after 2-3 days of sexual abstinence. Patients were stratified into seven groups based on their age: patients $\leq$ 29 years (n = 127; 3.7%), 30-35 years (n = 868; 25.2%), 36-39 years (n = 863; 25.0%), 40-45 years (n = 1017, 29.5%), 46-49 years (n = 321; 9.3%), 50-55 years (n = 179, 5.2%) and $\geq$ 56 years (n = 71, 2.1%).

Participants/materials, setting, methods: Conventional semen parameters were assessed according to the WHO criteria and DFI was evaluated by TUNEL assay using the APODirect Kit run on BDAccuriC6 flow cytometer. Pearson's r was used for correlation analysis between sperm concentration, DFI and paternal age. DFI results for each stratified patient group were evaluated by one-way ANOVA, followed by Tukey pos-hoc multiple comparison test. Results are presented as the mean$\pm$standard error and a P-value of $<$ 0.05 was considered statistically significant.

Main results and the role of chance: In this cohort of men with a mean age of 39.5 years $\pm$ 0.1 (range 23-76 years), sperm deoxyribonucleic acid (DNA) fragmentation (21.1% $\pm$ 0.2) was positively correlated with age (r = 0.23, p<0.001). In contrast, the correlation between sperm concentration and age was non-significant (r = 0.03, p = 0.07). Mean DFI in patients segregated into seven age groups were: $\leq$29 years (15.7% $\pm$ 0.8), 30-35 years (17.7% $\pm$ 0.4), 36-39 years (19.7% $\pm$ 0.4), 40-45 years (22.6% $\pm$ 0.4), 46-49 years (26.2% $\pm$ 0.9), 50-55 years (26.7% $\pm$ 1.2) and $\geq$ 56 years (31.1% $\pm$ 2.0). Mean %DFI level in the 26-29 and 30-35 age groups were non-significantly different (p = 0.65). However, mean %DFI level in the 36-39 age group was significantly higher than in the 26-29 and 30-35 age groups (p = 0.02 and

$p = 0.03$, respectively). Mean %DFI level in the older age groups (40-45, 46-49, 50-55 and $\geq$ 56 years) were all significantly higher than in the 26-29 or 30-35 age groups ($p<0.001$). Using a %DFI threshold level of 16.9%, 46.0% of patients <36, 52.2% of men aged 36-39, 60.2% of men aged 40-45, 67.3% of men aged 46-49, 72.6% of men aged 50-55 and 74.7% of men aged $\geq$56 years had an elevated DFI.

Limitations, reasons for caution: This is a retrospective analysis that did not account for confounding variables (e.g., clinical diagnosis, gonadotoxin exposure, febrile illness) that may affect conventional sperm parameters and DFI.

Wider implications of the findings: Our results underline the relationship between paternal age and sperm DFI and demonstrate a significant decline in sperm DNA fragmentation in men over the age of 35 years. The data suggest that we may want to reconsider the age cut-off we traditionally use to define advanced paternal age.

Trial registration number: No trial registration