Do sperm DNA integrity tests predict pregnancy with in vitro fertilization?

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CRD summary
This review assessed whether sperm DNA integrity tests could predict pregnancy from in vitro fertilisation treatment. The authors concluded that the evidence was not strong enough to imply routine use of these tests. This is an appropriately cautious conclusion, given the variable accuracy results, but a limited search and lack of study validity assessment are limitations of the review.

Authors' objectives
To assess whether sperm DNA integrity testing can predict pregnancy for couples undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).

Searching
MEDLINE was searched from 1999 to December 2006. Reference lists of included studies were also searched. Search terms were reported. There were no language restrictions.

Study selection
Studies that evaluated assayed sperm DNA integrity in fresh ejaculated sperm and reported pregnancy or live birth as an outcome were eligible for inclusion. Included studies had to report results to allow the creation of a 2x2 table. Meeting abstracts were excluded.

Most included studies were of in vitro fertilisation and intracytoplasmic sperm injection; only a few assessed one technique alone. Assays used were sperm chromatin structure assay (SCSA) or terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick end labelling (TUNEL) assay. The cut-off points used to identify a positive test were: sperm DNA fragmentation index less than 30% for SCSA; and less than 4% for TUNEL assay. If results were reported for more than one cut-off, the one closest to the most frequently reported in other studies was used. The number of treatment cycles ranged from 47 to 388.

The authors did not state how studies were selected for the review.

Assessment of study quality
The authors did not state that they assessed study validity.

Data extraction
Data were extracted on: dates of recruitment; whether or not recruitment was consecutive; treatment; assay cut-points; and outcomes (clinical pregnancy, ongoing pregnancy, delivery and live birth). If a 2x2 table was not reported, it was estimated from reported sensitivity, specificity and sample size. For each study, sensitivity, specificity, overall diagnostic accuracy, positive and negative likelihood ratios, diagnostic odds ratios (DOR) with 95% confidence intervals (CI) and the proportion of abnormal tests were calculated.

The authors did not state how data were extracted for the review, or how many reviewers performed the extraction.

Methods of synthesis
Logarithms of the diagnostic odds ratios were calculated for each study and pooled using a random-effects model with inverse variance weights. Statistical heterogeneity was assessed using Cochran's Q test (with a 10% significance level) and the I² statistic. Receiver operating characteristics curves were also used to visually assess differences between studies. Subgroup analyses were used to explore the effects of assay type and treatment. Publication bias was assessed using a funnel plot and the Begg and Mazumdar rank correlation test.
Results of the review
Thirteen studies were included in the review, providing data for 18 sets of IVF or ICSI treatment (2,161 cycles). All studies were cohort studies and only two were retrospective. Pregnancy was the reference standard in all studies, although the definitions varied.

Sensitivity ranged from 0.06 to 0.64, and specificity ranged from 0.38 to 0.97; both were highly heterogeneous (p<0.0001). The pooled diagnostic odds ratios was 1.44 (95% CI: 1.03, 2.03). The pooled positive likelihood ratio was 1.23 (95% CI: 0.98, 1.54) and the pooled negative likelihood ratio was 0.81 (95% CI: 0.67, 0.98). The funnel plot (not shown) and correlation test (p=0.13) did not show any evidence of publication bias.

Subgroup analyses showed no evidence of a difference between IVF treatment (DOR 1.53, 95% CI 0.77 to 3.02), ICSI treatment (DOR 1.12, 95% CI 0.59 to 2.15) or both treatments together (DOR 1.91, 95% CI 0.79 to 4.57). There was also no difference between sperm chromatin structure assay (DOR 1.31, 95% CI 0.81 to 2.11) and TUNEL assay (DOR 1.67, 95% CI 0.89 to 3.11).

Authors' conclusions
The observed small statistically significant association between sperm DNA integrity tests and pregnancy from IVF and ICSI treatment was not strong enough to give a clinical indication for the routine use of these tests. Some subgroups may benefit from these tests but further research is needed to identify them.

CRD commentary
This review had a clearly stated question, which addressed the relevant test, outcome and treatment. The inclusion criteria were stated and covered the index test, reference standard, and relevant outcomes. The search was not limited by language, but it only covered MEDLINE, so relevant studies may have been missed. The authors did assess publication bias and found no evidence to suggest it, but searching only one database is a limitation of this review. It was reported that the effect of methodological characteristics on diagnostic accuracy were assessed in regression analyses, but no details of the validity of each study were provided. Only those measures not showing significant heterogeneity were pooled using meta-analysis (which appeared appropriate), but pooling diagnostic odds ratio is no longer recommended, and newer more appropriate methods of meta-analysis are available. The authors' conclusions are suitably cautious, given that the diagnostic accuracy of these tests appears variable and generally poor, but the limited search and lack of full validity assessment are drawbacks of this review.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research using robust study designs with consecutive recruitment, typical infertile couples, blinded assay results and an adequate sample size calculation, that report pregnancy as an outcome, are needed. They also stated that studies identifying subgroups where these tests would be most valuable, and studies identifying novel markers of DNA damage, are needed.

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