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TITLE: REAL-WORLD ASSESSMENT OF EPIGENETIC SPERM QUALITY TESTING FOR PREDICTING FERTILITY TREATMENT SUCCESS: A MULTI-SITE ANALYSIS OF 537 PATIENTS

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Background: Infertility affects 1 in 6 couples, with male factor infertility contributing to 40-50% of cases. Diagnostic methods, such as semen analysis, are limited in predicting fertility outcomes, often resulting in unnecessary procedures, high costs, and extended time to pregnancy. The Sperm Quality Test (SpermQT), an epigenetic semen analysis introduced in 2022, assesses DNA methylation patterns on 1,233 genes related to sperm function, potentially offering more accurate predictions of male fertility potential. Early clinical studies demonstrated that abnormal SpermQT results correlate with lower pregnancy and live birth rates in intrauterine insemination (IUI) cycles, but not with in vitro fertilization-intracytoplasmic sperm injection (IVF-ICSI) outcomes.

Objective: To evaluate the real-world clinical utility of SpermQT as a predictor of pregnancy outcomes in men undergoing IUI and IVF-ICSI treatments.

Materials and Methods: This multi-site study analyzed 537 SpermQT results from patients treated at 11 U.S. fertility clinics between May 2022 and December 2023. Sperm samples were collected from non-azoospermic men and analyzed for DNA methylation at a CLIA-certified laboratory. De-identified data were aggregated, including male and female partner ages, pre-wash total motile sperm count (TMC), number of IUI and IVF-ICSI embryo transfer (ET) cycles completed, and pregnancy outcomes (biochemical and ultrasound-confirmed pregnancies). Statistical analyses, including two-sided t-tests and multivariate regressions, were performed to assess the relationship between SpermQT results and pregnancy outcomes. Dysregulated genes were analyzed using Chi-squared tests and the Panther Classification System to identify enriched molecular and biological pathways.

Results: Of the 537 patients, 83.6% had normal SpermQT results, while 16.4% had abnormal results. No significant differences in male and female ages or TMC were observed between groups. In IUI cycles, patients with abnormal SpermQT results had significantly lower pregnancy rates compared to those with normal results (0% vs. 22%, p=0.009), regardless of age or TMC. In IVF-ICSI cycles, no significant differences in pregnancy outcomes were observed between normal and abnormal SpermQT groups, with abnormal SpermQT patients achieving comparable pregnancy rates to those with normal results (68.2% vs. 52.9%, p>0.05). Multivariate analysis indicated that SpermQT was a significant predictor of pregnancy in IUI cycles (p=0.019), but not in IVF-ICSI cycles.

Gene promoter analysis identified 329 dysregulated genes in men with abnormal SpermQT results, with significant enrichment in binding (GO:0005488) and catalytic activity (GO:0003824) functions. Key genes associated with abnormal sperm quality included C18orf63, LCN9, and SERPINB13, which are involved in spermatogenesis and sperm function.

Conclusion: SpermQT demonstrates significant potential as a diagnostic tool for male factor infertility, with abnormal results strongly correlating with reduced pregnancy rates in IUI cycles. These findings support the use of SpermQT to guide fertility treatment decisions and optimize time to pregnancy. However, SpermQT results do not predict pregnancy outcomes in IVF-ICSI cycles, suggesting that this procedure can overcome epigenetic sperm quality issues. Further studies with larger sample sizes are needed to confirm these findings and explore the biological pathways underlying abnormal SpermQT results.