# COMBATING SPERM DNA FRAGMENTATION IN MALE INFERTILITY: EFFICACY OF COMBINATION ANTIOXIDANT THERAPY AND A PREDICTIVE HIGH-DFI RISK CLASSIFIER

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Male factors contribute to nearly 50% of infertility cases. Oxidative stress–induced sperm DNA fragmentation (DFI) is a key determinant of poor reproductive outcomes and pregnancy loss. Antioxidant supplementation may improve sperm DNA integrity and enhance fertility outcomes.

In this prospective, placebo-controlled trial, 31 men with abnormal semen parameters and elevated DFI were randomized to receive either combination antioxidant therapy (n = 21) or placebo (n = 10) for three months, along with an antioxidant-rich diet and lifestyle modifications. Semen parameters, DFI, and oxidative stress markers were assessed pre- and post-treatment. Separately, 125 semen analyzer–derived datasets were analyzed to identify predictors of high DFI. Significant variables were integrated into machine learning algorithms to construct an ensemble predictive model.

Baseline characteristics were comparable between groups ($p > 0.05$). Post-treatment, the antioxidant group showed significantly lower DFI ($p = 0.039$) and abnormal head morphology ($p = 0.035$), and higher total antioxidant capacity (TAC; $p = 0.002$). ANCOVA confirmed treatment effects on DFI ($p = 0.018$), TAC ($p = 0.007$), head morphology ($p = 0.014$), concentration ($p = 0.05$), and normal morphology ($p = 0.04$). Paired analyses (n = 20) revealed significant pre-to-post improvements in DFI ($p = 0.0005$), TAC ($p = 0.017$), and concentration ($p = 0.011$) only in the antioxidant group. PCA demonstrated a distinct post-treatment shift, and pregnancy rates were higher with antioxidants (28.8% vs. 10%). Twenty-four semen parameters predictive of high DFI were identified and integrated into an ensemble model achieving excellent performance (AUC = 0.945).

Combination antioxidant therapy improved sperm DNA integrity, antioxidant capacity, and semen quality, with higher pregnancy incidences. The predictive model supports early risk detection for elevated DFI, optimizing patient selection for DFI testing and antioxidant therapy, though validation in larger multicenter trials is warranted.