Toxicity of Tumor Necrosis Factor (TNF)-α on Human Spermatozoa - Possible Role in Endometriosis Associated Infertility

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Objective: TNF-α is a pleiotropic cytokine with numerous biological functions that include modulation of spermatogenesis and apoptosis in addition to acting as a pro-inflammatory cytokine. Spermatozoa may be exposed to abnormal levels of TNF-α in the male reproductive tract or along the passage in the female reproductive tract in cases of endometriosis. The objective of our study was to examine the toxic effects of TNF-α on human spermatozoa and to establish the minimum concentration that can affect both the sperm function and genomic integrity.

Design: Prospective-controlled study.

Materials and Methods: Semen samples were collected from 25 normozoospermic males with semen parameters exceeding WHO (1999) reference ranges for the normal fertile population. Following liquefaction, mature spermatozoa were separated on a double density gradient centrifugation and resuspended in Biggers, Whitten and Whittingham media. Spermatozoa were incubated with 100, 300, 400, and 500 pg/mL human recombinant TNF-α (rTNF-α, R & D Systems, Minneapolis, MN) for 0, 2, 6, 12 and 24 hours. Each aliquot had its corresponding control without TNF-α. All aliquots were tested for sperm motility, plasma membrane integrity by hypoosmotic swelling (HOS) test and DNA damage by TUNEL assay at each time point.

Results: Significant reduction in sperm motility was observed following incubation for 24 hours with both 400 pg/mL and 500 pg/mL TNF-α compared to controls (400 pg/mL: 26.4 ± 9.28 vs. 42.8 ± 6.26, P = 0.005; 500 pg/mL: 20.4 ± 7.4 vs. 35 ± 6.67, P = 0.009). The lowest concentration of TNF-α that affected sperm motility after 24h was 300 pg/mL (P = 0.003). Sperm exposed to 500 pg/mL had significantly lower HOS values compared to controls after 12 h (P = 0.03). A significant increase in percentage of sperm with DNA fragmentation was seen following incubation for 24 hours with 400 pg/mL and 500 pg/mL of TNF-α compared to controls (400 pg/mL: 31.71% ± 9.12% vs. 14.8% ± 7.0%, P = 0.01; 500 pg/mL: 30.08% ± 15.07% vs. 18.12% ± 9.21%, P = 0.02).

Conclusion: Exposure of spermatozoa to pathological concentrations of TNF-α, similar to what may be present in endometriosis patients, can significantly result in loss of sperm.
motility, plasma membrane functional integrity as well as DNA damage. This may be one of the causes of infertility in cases of endometriosis. Future research should be directed towards evaluating the benefits of TNF-α inhibitors for treatment of infertile patients with endometriosis.

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