TNF-alpha Induced Embryotoxicity and Role of TNF-alpha Blocker-Infliximab on In Vitro Blastocyst Development Rate

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Objective: TNF-α is required both for the establishment and maintenance of endometriosis. Evidence shows that peritoneal fluid from patients with endometriosis has elevated levels of TNF-α levels that may be responsible for endometriosis-associated infertility. TNF-blockers such as Remicade (Infliximab) may help neutralize the toxic effects of TNF-α. In our earlier studies we demonstrated that infliximab is not embryotoxic at concentration of up to 400µg/mL. Our study was designed to evaluate: 1) the embryotoxic effect of TNF-α that may be present in the peritoneal fluid of women with endometriosis, and 2) examine if infliximab could reverse the TNF-α induced embryotoxicity.

Design: Prospective in vitro study.

Materials and Methods: 150 two-cell mouse embryos were cultured in 6 different concentrations of diluted in human tubal fluid for 72 h. Blastocyst development rate (%BDR) was examined after 72 hours of incubation in the following concentrations of TNF-α: 100, 200, 400, 500, 1000, and 2000ng/mL. Similarly, a second set containing infliximab (200µg/mL) + TNF-α(500ng/mL) was cultured under identical conditions to study if infliximab at this concentration was effective in reducing TNF-α induced embryotoxicity.

Results: A dose dependent decrease in %BDR was seen using different concentrations of TNF-α compared with controls (see Figure). A significant decrease in %BDR was seen at 400ng/mL compared with control (%BDR: 59% vs. 98%; P<0.0008), which further decreased to 21% at a concentration of 500ng/mL of TNF-α (P<0.05). Higher concentrations of TNF-α resulted in complete embryotoxicity (%BDR = 0). Infliximab alone had 100% BDR and was comparable with controls. Infliximab, in the presence of TNF-α, completely neutralized the embryotoxic effect of TNF-α and %BDR increased significantly from 55% to 100% (P<0.05).
Figure: Effect of various concentrations of TNF-α on the percent blastocyst development rate (%BDR) after 72 h of culture. Each point represents the mean of 3 sets of readings with 6-8 embryos in each group.

Conclusion: TNF-α concentrations of 400ng/mL or higher are embryotoxic. Endometriosis patients with TNF-α concentrations of 400ng/mL or higher in their peritoneal fluid may have significantly impaired fertilization rates. The use of infliximab in such cases may be beneficial in combating TNF-α induced toxicity. Targeting TNF-α with specific blockers may be a novel approach in understanding the pathophysiology of endometriosis associated infertility and in the treatment of this disease.

Support: None

Author Disclosure Block: X. Zhang, None; R.K. Sharma, None; A. Agarwal, None; T. Falcone, None.

Category (Complete): Endometriosis (GPC)
Keyword (Complete): endometriosis ; tumor necrosis factor-alpha (TNF-α) ; blastocyst ; infertility

Additional (Complete):
Presenting Author Fellow : Yes
In-Training Award: : True
ACCME Disclosure: : I will not be discussing non-FDA approved products
I Agree : True

Status: Complete