another dimension was added to the results of this study when it examined the ratio of IFN-γ/IL-10 in women with RSA which was 1.97 and about three times that of women with first abortion which lends further support to the findings of our study as it was in consistence with the previous studies [1,14,16,18].

Although this study showed that the expression of the Type 1 cytokine (IFN-γ) in women with recurrent miscarriage was significantly higher than that of normal pregnancy or first abortion groups, the current study, like many of the studies on human pregnancy failure, has not addressed a direct cause-and-effect relationship between Th1-type reactivity and pregnancy loss. However, there are many evidences support this suggestion such as, the administration of one of the Th1 cytokines like IFN-γ, TNF-α or IL-2 to normal pregnant mice causes abortion [38]. IFN-γ and TNF-α inhibit the proliferation of human trophoblast cells *in vitro* (39) and are toxic to human trophoblast cells [40]. Uterine resorption sites in a murine model of recurrent abortion were infiltrated by NK cells [41]; given the fact that the activation of NK cells has been shown to be detrimental to murine pregnancy and that NK cells are activated by the Th1 cytokine; IFN-γ [42]. Furthermore, strong Th1-dominant responses against pathogens compromise pregnancy; for example infection by *Leishmania major* results in resorptions, with a concurrent increase in the concentrations of IFN-γ in the placenta [43].

References

1. Saito S, Miyazaki S, Sasaki Y. Th1/Th2 Balance of the implantation site in humans: Immunology of Pregnancy. 2nd eds. Edited by Mor G. Eurekah. com. 2004; pp. (1-12).

2. Dungy LJ, Siddiqi TA, Khan S. Transforming growth factor-beta 1 expression during placental development. Am J Obstet Gynecol. 199l; 165: 1853-1856.

3. Roth I, Corry DB, Locksley RM, Abrams JS, Litton MJ, Fisher SJ. Human placental cytotrophoblasts produce the immunosuppressive cytokine interleukin 10. J Exp Med. 1996; 184: 539-548.

4. Sargent IL. Maternal and fetal immune responses during pregnancy. Exp Clin Immunogenet. 1993; 10: 85-97.

5. Wegmann TG, Lin H, Guilbert L. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a Th2 phenomenon? Immunol Today. 1993; 14: 353-356.

6. Lin H, Mosmann TR, Guilbert L, Tuntipopipat S, Wegmann TG. Synthesis of T helper 2-type cytokines at the maternal-fetal interface. The Journal of Immunology. 1993; 151: 4562-4573.

7. Cadet P, Rady PL and Tyring SK. IL-10 mRNA in human placenta: implications of a role for IL-10 in fetal allograft protection. *Am J Obstet Gynecol.* 1995; 173: 25029-25033.

8. Moore KW, O'Garra A, de Waal-Malefyt R, Vieira P and Mosmann TR. Interleukin-10. *Annu Rev Immunol.* 1993; 11: 165-170.

9. Moore KW, de Waal MR and Coffman RL. Interleukin-10 and the interleukin-10 receptor. *Annu Rev Immunol.* 2001; 19: 683-765.

10. Wang P, Wu P and Siegel MI. IL-10 inhibits transcription of cytokine genes in human peripheral blood mononuclear cells. *J Immunol.* 1994; 153: 811-816.

11. Takeshita S, Gage JR and Kishimoto TV. Differential regulation of IL-6 gene transcription and expression by IL-4 and IL-10 in human monocytic cell lines. *J Immunol.* 1996; 156: 2591-2598.

12. Michel G, Mirmohammadsadegh A and Olsaz E. Demonstration and functional analysis of IL-10 receptors in human epidermal cells: decreased expression in psoriatic skin, down-modulation by IL-8, and up-regulation by an anti-psoriatic glucocortico-steroid in normal cultured keratinocytes. *J Immunol.* 1997; 159: 6291-6297.

13. Raghupathy R. Th-I type immunity is incompatible with successful pregnancy. *Immunol Today.* 1997; 18: 478-482.

14. Hill JA, Polgar K and Andreson DJ. T-helper type-1 immunity to trophoblast in women with recurrent spontaneous abortion. *J Am Med Assoc.* 1995; 273: 1933-1936.

15. Raghupathy R, Makhseed M and Azizieh F. Maternal Th1- and Th2-type reactivity to placental antigens in normal and unexplained recurrent Spontaneous abortions. *Cell Immunol.* 1999; 196: 122-130.

16. Raghupathy R, Makhseed M, Azizieh F, Omu A, Gupta M and Farhat B. Cytokine production by maternal lymphocytes during