**IMPORTANCE OF IMMUNOLOGICAL MEDIATORS FOR PROGNOSTIC DIAGNOSIS OF MALE INFERTILITY**

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**ABSTRACT**

 The concentration of interleukin (IL) -2 , IL-6 and IL-8 were determined in human sera from fertile and infertile males with various types of infertility ;Azoospermia, Oligozoospermia ,Asthenozoospermia and Teratozoospermia in AL-Najaf AL-Asharaf governorate during March 2013 to August 2013. Oligozoospermia was predominant in age group 19-29yrs (48) men, while azospermia recorded lowest number (6) men in group >40 yrs. Oligozoospermia was found the biggest numbers of patients 117 men (36%) followed by asthenozoospermia 97 men (30%), teratozoospermia 73 men(22%) and azospermia 41 men (12%) with statistical differences between various types of infertility P<0.05. Mean level of concentration of interleukin -2 was elevated in serum of infertile men reached159.63 pg/ml in comparison with fertile men ( control) which reached 24.35 pg/ml. Mean level of concentration of interleukin -6 was elevated in serum of infertile men reached 328.75 pg/ml in comparison with fertile men which reached 116.24 pg/ml. Mean level of concentration of interleukin -8 was elevated in serum of infertile men reached 575.68 pg/ml in comparison with fertile men which reached 141.51 pg/ml .The means of interleukins concentration among various types of infertility of infertile men and control (fertile men)were evaluated in the present study .There are very highly differences between interleukin concentration and between various types of infertility P<0.001.and between concentration of interleukin in control group P<0.01.

**key words:** interleukins, infertile men

**introduction**

 Cytokines play an important role in intercellular communication. They are involved in numerous physiological and pathological processes, particularly in the mediation of inflammatory responses,1 and have important functions in the reproductive physiology of women and men. Apart from their role in immune modulation, there is evidence that some of these polypeptides are directly involved in the regulation of testicular function, and also may be potent modulators of steroid release from the testes.2 There are complex mechanisms for control of their action. Human semen contains a repertoire of cytokines whose effects on semen quality and sperm function, however, are subject to debate. Inflammatory cytokines are produced by white blood cells (WBC), mainly by macrophages, in response to foreign antigens, pathogens (infection challenge) and also in chronic inflammation (immunological activation). 3,4,5 Acute and chronic infections may play a contributory role in male infertility. The clinical relevance of silent infection in asymptomatic patients is, however, not clear.6 Moreover, the interpretation of the markers commonly used for its diagnosis is controversial; for example the role of seminal leukocytes and clinically significant thresholds. 7 Positive semen cultures, a frequent finding during extended infertility investigation in asymptomatic men, and with bacterial prevalence depending on the extent of the microbial screening, are insufficient to diagnose male genital tract infection .The reproductive tracts of both men and women contain a myriad of immune response cells. 8Activation of these cells, for example by microorganisms, stimulates them to secrete lymphokines and monokines.2,9 4,6,10 IL-8 may be involved, within a network of other cytokines, in intratesticular signal transduction, and may also adversely affect sperm membrane properties. 11 Few investigations have been made concerning this cytokine with regard to reproduction. Interleukins are part of the local defence mechanism against infectious diseases, but they are also implicated as mediators of the pathology of these diseases. 12,13,14,15

 The purpose of this study was to document the prevalence and concentration

of interleukins 2, 6 and 8 in fertile and infertile men, to provide further insight into mediators of immune defense and reproductive function in the normal male genital

tract, and to establish reference values to support future studies on the role of these factors in pathologic conditions.

**PATIENTS AND METHODS**

**Patients( Infertile men)**

 A total of 328 Seminal fluid and 65 sera samples were collected from patients (males) aged between 19-60 yrs who were attending to the fertility center / AL-Sadder medical City in AL-Najaf AL-Asharaf governorate from March 2013 to August 2013. None of the patients had clinical signs ofgenital tract infection apart from their infertility problem, and were therefore considered asymptomatic of sexually transmitted disease they were healthy individuals. During the time of the study, none of the patients was treated with antibiotics, corticosteroids or antiphlogistics.

\*all above samples collected through MSc study of Kais Khudhair A. ALhadrawi Submitted to the Council of Faculty of Education for girls- University of Kufa ,2013 50 with approvement of ethical committee under supervision of specialists.

**Fertile controls**

Semen and sera samples were analysed from 20 fertile men attending at the same above center. The control group are similar in age and demographic characters of the patients.

 Seminal fluid analysis and classification of infertitity types in to Azoospermia, Oligozoospermia ,Asthenozoospermia and Teratozoospermiain comparison with normal fertility status (control)Normospermia were done according to (WHO , 1999)51

Detection and quantitation of the various cytokines( interleukins 2,6and 8) were done for both fertile and infertile men and accomplished using commercially available enzyme-linked immunosorbent assay (ELISA) kits or the Boster Immunoleader , BOSTER BIOLOGICAL TECHNOLOGY Co.,Ltd**.** Fremont, CA 94538, USA ( [www.bosterbio.com](http://www.bosterbio.com)) following the manufacturers’ protocols

**RESULT**

Table(1) illustrated the numbers and percentages of studied infertile male and infertility types according to age stages. oligozoospermia was predominant in age group 19-29yrs (48)men , while azospermia recorded lowest number (6) men in group >40 yrs. there are significantly differences between the various types of infertility p<0.05

**Table-1: Numbers and percentages of studied infertile male and infertility**

 **types according to age stages.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Age****(Yrs)** | **Oligozoospermia** | **Asthenozoo spermia** | **Teratozoospemia** | **Azoo spermia** | **Total** |
| **29 – 19** | **48\*** | **45** | **29** | **21** | **143(%44)** |
| **39 – 30** | **40** | **33** | **22** | **14** | **109(33%)** |
| **>40** | **29** | **19** | **22** | **6** | **76(23%)** |
| **total** | **117** | **97** | **73** | **41** | **328(100%)** |

**\* 0.05˂ p**

Figure (1). Showed the various types of infertility . oligozoospermia find in the biggest numbers of patients 117 men (36%) followed by asthenozoospermia 97 men(30%), teratozoospermia 73 men(22%) and azospermia 41 men (12%) with statistical differences between various types of infertility P<0.05

**Figure-1: Numbers and percentages of studied infertile male according to infertility types .**

**P<0.05**

Mean level of concentration of interleukin -2 was elevated in serum of infertile men reached159.63 pg/ml in comparison with fertile men ( control) which reached 24.35 pg/ml , with very highly statistical differences between two groups P<0001.table 2.

**Table-2 : concentration of interleukine-2 among fertile and infertile men.**

|  |  |  |  |
| --- | --- | --- | --- |
| **P-value** | **ANOVA Test** | **Conc. Of****IL-2****(Pg/ml)****±SD** | **Studied groups** |
| **0.000** | **68.364** | **24.35****± 6.38** | **Fertile control men** |
| **159.63****±17.41** | **Infertile men** |

Mean level of concentration of interleukin -6 was elevated in serum of infertile men reached 328.75 pg/ml in comparison with fertile men ( control) which reached 116.24 pg/ml , with very highly statistical differences between two groups P<0001.table 3.

**Table-3 : concentration of interleukine-6 among fertile and infertile men.**

|  |  |  |  |
| --- | --- | --- | --- |
| **P-value** | **ANOVA Test** | **Conc. Of****IL-6****(Pg/ml)****±SD** | **Studied groups** |
| **0.000** | **80.861** | **116.24****± 14.22** | **Fertile control men** |
| **328.75****±36.41** | **Infertile men** |

Mean level of concentration of interleukin -8 was elevated in serum of infertile men reached 575.68 pg/ml in comparison with fertile men ( control) which reached 141.51 pg/ml , with very highly statistical differences between two groups P<0001.table 4.

**Table-4 : concentration of interleukine-8 among fertile and infertile men.**

|  |  |  |  |
| --- | --- | --- | --- |
| **P-value** | **ANOVA Test** | **Conc. Of****IL-8****(Pg/ml)****±SD** | **Studied groups** |
| **0.000** | **48.398** | **142.51****± 22.34** | **Fertile control men** |
| **575.68****±48.937** | **Infertile men** |

Table 5 illustrated the determination means of interleukins concentrationamong various types of infertility of infertile men and control (fertile men) .there are very highly differences between interleukin concentration and between various types of infertility P<0.001.and between concentration of interleukin in control group P<0.01.

**Table-5 : Means of interleukins concentration among various types of infertility of infertile men and control (fertile men) .**

|  |  |  |  |
| --- | --- | --- | --- |
| **Studied groups** | **Infertility types** | **Means of interleukin concentration****Pg/ml** | **P-value** |
| **IL2** | **IL6** | **IL8** |
| **Infertile****Men** | **Oligozoospermia** | **160.33** | **356.22** | **612.45** | **0.000** |
| **Asthenozoo spermia** | **165.38** | **358.45** | **598.34** | **0.000** |
| **Teratozoospemia** | **142.82** | **339.87** | **588.57** | **0.000** |
| **Azoo spermia** | **153.52** | **345.21** | **547.61** | **0.000** |
| **Fertile men****normospermia** | **24.35** | **116.24** | **142.51** | **0.00** |

**Discussion**

 Proinflammatory cytokines of humoral and cellular immune defense were detectable at normal (low) levels in fertile men in comparison with high level in infertility men. These data can serve as reference values for future studies on the role of these factors in male genital tract infection and infertility . increased concentration of cytokines , as an increased production of some pro-inflammatory cytokines has also been reported during immune responses in major depression. Genetic factors also substantially influence the production of cytokines.52 Also cytokine concentrations may more accurately indicate an early phase of infection/inflammation.53 Cytokines are potent polypeptides that are released from inflammatory cells as part of the host response. Many cell types, including monocytes/macrophages, T cells and neutrophils, can produce IL-8 in response to a wide variety of signals frequently initiated by infection or injury.54 Cytokines play a pivotal role as a mediator of numerous physiological and pathological processes, particularly in the initiation of the immuno-inflammatory cascade .55,56,57,58 Cytokines are also involved in allograft rejection. An increased production of some pro-inflammatory cytokines has also been reported during immune responses in major depression .59 Genetic factors also substantially influence the production of cytokines .60 . 5,8 The results of the present study were approved the results of other studies which reported that certain kinds of cytokine in the sera and seminal plasma might play an important role in improving semen quality .16,18,19 Although , the seminal plasma concentration of IL-8, an important mediator of inflammatory processes and is significantly associated with seminal leukocyte , Interleukin-6 is a multifunctional cytokine found in human sera that is produced by various types of cells in the genital tract. Levels of IL-6 correlate with the secretory activity of Sertoli cells 56,57. Currently, little is known about IL-6 levels in seminal plasma of men characterized according to the etiological diagnosis of infertility. Significantly elevated IL-6 levels were seen in vasectomy reversal patients, compared with normal healthy men. However, high IL-6 levels have been associated with male infertility. 49 The relationship of pro-inflammatory cytokines (e.g. IL-6) with semen quality in other studies is controversial. In landmark studies, others showed a significant effect of soluble products of activated immune cells and of some lymphokines and tumour necrosis factor (in high concentrations) on sperm motility and on the outcome of the zona-free hamster egg test.55,57,59,60 This contrasts with other reports which did not show a relationship of, for example, IL-6 with standard parameters of semen analysis , possibly due to differing population characteristics and assay methods.65,69,71

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