**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

**REFERENCES**

1. Inhorn MC( 2003) : Global infertility and the globalization of new reproductive

technologies: illustrations from *Egypt Soc Sci Med* May;56(9):1837-51.

2. Araoye MO ( 2003): Epidemiology of infertility: social problems of the infertile

couples. *West Afr J Med* Jun;22(2):190-6

3. Dohle GR (2003): Inflammatoryassociated obstructions of the male reproductive tract *. Andrologia* Oct;35(5):321-4.

4. Yanushpolsky EH, Politch JA, Hill JA and Anderson DJ(1996) : Is

leukocytospermia clinically relevant? *Fertil Steril*, 66, 822–25.

5. Huleihel M, Lunenfeld E, Levy A. (1996) :Distinct expression levels of

cytokines and soluble cytokine receptors in seminal plasma of fertile and infertile

men. *Ferti. Steril;*66:135–39.

6. Celinska A, Fracki S, Sangidorj D, Barcz E (2006) : Role of inflammatory

cytokines in male infertility *Ginekol Pol* May;77(5):404-11

7. Buch J, Kolon F, Maulik N. (1994) : Cytokines stimulate lipid membrane peroxidation of human sperm. *Fertil. Steril;* 62:186–88.

8. Eggert-Kruse W, Boit R, Rohr G. (2001) : Relationship of seminal plasma

interleukin (IL)-8 and IL-6 with semen quality. *Hum Reprod.*, 16, 517–528

10. Wolff H, Politch J, Martinez A, Hartinez A, Haimovici S, *et al*. (1990)

:Leukocytospermia is associated with poor semen quality. *Fert Steri;* 53:528–36

11. Pannekoek Y, Trum JW, Bleker OP, van der Veen F.(2000) Cytokine

concentrations in seminal plasma from subfertile men are not indicative of the

presence of Ureaplasma urealyticum or Mycoplasma hominis in the lower genital

tract*. J Med Microbiol* Aug;49(8):697- 700.

12. Vicari E and Mongioi A.(1995):Effectiveness of long-acting gonadotrophin-releasing hormone agonist treatment in combination with conventional therapy on testicular outcome in human orchitis/epididymo-orchitis. *Hum Reprod*. Aug; 10(8) :2072-2078.

13. Levy R, Layani-Milon MP, Giscard D'Estaing S*.*(1999): Screening for

*Chlamydia trachomatis* and *Ureaplasma urealyticum* infection in semen from

asymptomatic male partners of infertile couples prior to in vitro fertilization. *Int J*

*Androl.* Apr;22(2):113-8.

14. Santos C, Teixeira F, Vicente A, Astolfi-Filho S (2003): Detection of

Chlamydia trachomatis in endocervical smears of sexually active women in

Manaus-AM, Brazil, by PCR. *Braz J Infect Dis*;Apr;7(2):91-5.

15. Mena L, Wang X, Mroczkowski TF, Martin DH ( 2002): *Mycoplasma*

*genitalium* infections in asymptomatic men and men with urethritis attending a

sexually transmitted diseases clinic in New Orleans. *Clin Infect Dis*. Nov

15;35(10):1167-73.

16. Shimoya K, Matsuzaki N, Tsutsui T . (1993): Detection of interleukin-8 (IL-

8) in seminal plasma and elevated IL-8 in seminal plasma of infertile patients with

leukospermia. *Fertil Steril.*, 59, 885–888.

17. Wu H(2002):Nitric oxide and cytokine levels in the seminal plasma of infertile

men. *Zhonghua Wai Ke Za Zhi.* Nov;40(11):858-9.

18. Micic S, Macura M, Lalic N and Dotlic R. (1989): Elastase as an indicator of

silent genital tract infection in infertile men. *Int. J. Androl.*, 12, 423–42

19. Murayama, T., Ohara, Y., Obuchi, M. (1998): Human cytomegalovirus

Egyptian Journal of Medical Microbiology, October 2006 Vol. 15, No 4:707

20. Koumantakis, E., Matalliotakis, I., Kyriakou, D. (1998) :Increased levels of interleukin 8 in human seminal plasma. *Andrologia*, 30:339–43.

21. Zhang Q, K. Shimoya, K. Temma, T. Kimura. (2004);,Expression of fractalkine in the Fallopian tube and of CX3CR1 in sperm . *Hum. Reprod.,*

February 1, 19(2): 409 - 414.

22. Furuya Y, Akashi T, Fuse H (2003) : Soluble Fas and interleukin-6 and

interleukin-8 levels in seminal plasma of infertile men. *Arch Androl*;Nov-

Dec;49(6):449-52.

23. Leutscher PD, Pedersen M, Raharisolo C. (2005): Increased prevalence of

leukocytes and elevated cytokine levels in semen from Schistosoma haematobium infected individuals. *J Infect Dis;*May 15;191(10):1639-47.

24. Maes M, Bosmans E, De Jongh R .(1997) :Increased serum IL 6 and IL 1

receptor antagonist concentrations in major depression and treatment resistant

depression. *Cytokine*;9:853–858.

25. Westendorp RG, Langermans JA, Huizinga TW*.*(1997): Genetic influence on cytokine production in meningococcal disease. *Lancet*. Jun 28;349:1912-1913

26. Eggert-Kruse W, Pohl S, Näher H . (1992) : Microbial colonization and

sperm-mucus interaction: results in 1000 infertile couples. *Hum. Reprod;*7:612–

620.

27. Paavonen J and Eggert-Kruse W (1999) : *Chlamydia trachomatis*: impact

on human reproduction. *Hum. Reprod. Update*, 5, 433–447.

28. Mazzoli S., Cai T, Rupealta V., Gavazzi A.(2006) :Intereukin 8 and Anti-

Chlamydia trachomatis Mucosal IgA as Urogenital Immunologic Markers in

Patients with C. trachomatis Prostatic Infection. *Eur Urol*. 2006 Nov 3

29. Razin S,Yogev D,Naot Y.(1998) : Molecular biology and pathogenicity of

mycoplasmas .*Microbiol Mol Biol Rev*:62:1094-1156.

30. Samra Z, Soffer Y, Pansky M (1994): Prevalence of genital chlamydia and

mycoplasma infection in couples attending a male infertility clinic.*Eur J Epidemiol*; Feb;10(1):69-73.

31. Witkin SS. (2002): Immunological aspects of genital chlamydia infections.*Best Pract Res Clin Obstet Gynaecol*. Dec;16(6):865-74

32. Khadra A, Fletcher P, Luzzi G, Shattock R, Hay P (2006) : Interleukin-

8 levels in seminal plasma in chronic prostatitis/chronic pelvic pain syndrome

and nonspecific urethritis. *BJU Int*. May;97(5):1043-6.

33.Si Y and Okuno M. (1999) Role of tyrosine phosphorylation of flagellar proteins in hamster sperm hyperactivation. Biol Reprod 61, 240–246.

34.Stahl N, Boulton TG, Farruggella T, Ip NY, Davis S, Witthuhn BA, Quelle

FW, Silvennoinen O, Barbieri G, Pellegrini S. (1994) Association and

activation of Jak-Tyk kinases by CNTF-LIF-OSM-IL-6 beta receptor components.

Science 263,92–95.

35.Tabibzadeh S and Sun XZ. (1992) Cytokine expression in human endometrium throughout the menstrual cycle. Hum Reprod 7,1214–1221.

36.Tabibzadeh S, Santhanam U, Sehgal PB and May L .(1989) Cytokine-induced production of interferon b2/interleukin-6 by freshly explanted human

endometrial stromal cells. Modulation by estradio-17b. J Immunol 142, 3134–3139.

37.Tabibzadeh S, Kong QF, Babaknia A and May LT .(1995) Progressive rise in the expression of interleukin-6 in human endometrium during menstrual

cycle is initiated during the implantation window. Hum Reprod 10, 2793–2799.

38.Taga T. (1996) Gp130, a shared signal transducing receptor component for

hematopoietic and neuropoietic cytokines. J Neurochem 67,1–10.

39.Taga T, Narazaki M, Yasukawa K, Saito T, Miki D, Hamaguchi M, Davis S,Shoyab M, Yancopoulos GD and Kishimoto T. (1992) Functional inhibition

of hematopoietic and neurotrophic cytokines by blocking the interleukin

6 signal transducer gp130. Proc Natl Acad Sci USA 89,

10998–11001.

40.Towbin H, Staehlin T and Gordon J. (1979) Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and

some applications. Proc Natl Acad Sci USA 76,4350–4354.

41.Vandermolen DT and Gu Y .(1996) Human endometrial interleukin-6 (IL-6):

in vivo messenger ribonucleic acid expression, in vitro protein production,

and stimulation thereof by IL-1 beta. Fertil Steril 66,741–747.

42.Vermes C, Jacobs JJ, Zhang J, Firneisz G, Roebuck KA and Glant TT.

(2002) Shedding of the interleukin-6 (IL-6) receptor (gp80) determines the

ability of IL-6 to induce gp130 phosphorylation in human osteoblasts.

J Biol Chem 277,16879–16887.

43.Visconti PE, Westbrook VA, Chertihin O, Demarco I, Sleight S and

Diekman AB .(2002) Novel signaling pathways involved in sperm acquisition

of fertilizing capacity. J Reprod Immunol 53,133–150.

44.Von Wolff M, Thaler CJ, Zepf C, Becker V, Beier HM and Strowitzki T.

(2002) Endometrial expression and secretion of interleukin-6 throughout

the menstrual cycle. Gynecol Endocrinol 16,121–129.

45.Yanagimachi R .(1994) Mammalian fertilization. In Knobil E and Neill JD

(eds), The Physiology of Reproduction. Raven Press Ltd, New-York, pp.

189–317.

46.Yoshida S, Harada T, Iwabe T, Taniguchi F, Mitsunari M, Yamauchi N,

Deura I, Horie S and Terakawa N. (2004) A combination of interleukin-6

and its soluble receptor impairs sperm motility: implications in infertility associated with endometriosis. Hum Reprod 19,1821–1825.

47.Aggarwal S, Gurney AL.( 2002) IL-17: prototype member of an emerging cytokine family. J Leukoc Biol;71:1–8.

48. Alfano M, Poli G.(2005). Role of cytokines and chemokines in the regulation of innate immunity and HIV infection. Mol Immunol;42:161–182.

49.Anderson DJ.(2007) Genitourinary immune defense. In: Holmes KK (ed). Sexually Transmitted Diseases. New York: McGraw-Hill,.

50. Kais Khudhair Abdulabbas ALhadrawi.(2014) .Immunological Study of Infertility Cases in Male which Associated with Bacterial Infection in AL-Najaf AL-Ashraf Governorate. MSc. Thesis of Faculty of Education for girls . University of Kufa.

51. WHO (1999) World Health Organization Laboratory Manual for the Examination of Human Semen and Semen-Cervical Mucus Interaction. Cambridge University Press, Cambridge.

52.Anderson DJ, Politch JA, Tucker LD, Fichorova R, Haimovici F, Tuomala RE,Mayer KH.(1998) Quantitation of mediators of inflammation and immunity in

genital tract secretions and their relevance to HIV type 1 transmission.

AIDS Res Hum Retroviruses .14(Suppl. 1):S43–S49.

53.Ara T, Nakamura Y, Egawa T, Sugiyama T, Abe K, Kishimoto T, Matsui Y, Nagasawa T.(2003) Impaired colonization of the gonads by primordial germ

cells in mice lacking a chemokine, stromal cell-derived factor-1 (SDF-1).

Proc Natl Acad Sci USA;100:5319–5323.

54. Bezold G, Politch JA, Kiviat NB, Kuypers JM, Wolff H, Anderson DJ.(2007) Prevalence of sexually transmissable pathogens in semen from

asymptomatic male infertility patients with and without leukocytospermia.

Fertil Steril ;87:1087–1097.

55.Camejo MI, Segnini A, Proverbio F.(2001) Interleukin-6 (IL-6) in seminal plasma of infertile men, and lipid peroxidation of their sperm. Arch Androl.

47:97–101.

56.Comhaire F, Bosmans E, Ombelet W, Punjabi U, Schoonjans F. (1994)Cytokines in semen of normal men and of patients with andrological diseases. Am J Reprod Immunol 1994;31:99–103.

57.Depuydt CE, Bosmans E, Zalata A, Schoonjans F, Comhaire FH.(1996). The relation between reactive oxygen species and cytokines in andrological patients with or without male accessory gland infection. J Androl .17:699–707.

58.Dousset B, Hussenet F, Daudin M, Bujan L, Foliguet B, Nabet P.(1997) Seminal cytokine concentrations (IL-1beta, IL-2, IL-6, sR IL-2, sR IL-6), semen

parameters and blood hormonal status in male infertility. Hum Reprod .12:1476–1479.

59.Eggert-Kruse W, Boit R, Rohr G, Aufenanger J, Hund M, Strowitzki T.(2001). Relationship of seminal plasma interleukin (IL) -8 and IL-6 with semen

quality. Hum Reprod 2001;16:517–528.

60.Gruschwitz MS, Brezinschek R, Brezinschek HP. (1996).Cytokine levels in the seminal plasma of infertile males. J Androl .17:158–163.

61.Hedger MP, Meinhardt A. (2003).Cytokines and the immune-testicular axis. J Reprod Immunol 2003;58:1–26.

62.Kastner C, Jakse G.(2003). Measurement of immunoglobulins in seminal fluid with modified nephelometry–an alternative diagnostic tool for chronic prostatitis. Prostate Cancer Prostatic Dis .6:86–89.

63.Lackner JE, Herwig R, Schmidbauer J, Schatzl G, Kratzik C, Marberger M. (2006). Correlation of leukocytospermia with clinical infection and the positive

effect of antiinflammatory treatment on semen quality. Fertil Steril .86:601–605.

Letterio JJ, Roberts AB. (1998).Regulation of immune responses by TGF-beta. Annu Rev Immunol 1998;16:137–161.

64.Leutscher PD, Pedersen M, Raharisolo C, Jensen JS, Hoffmann S, Lisse I,

Ostrowski SR, Reimert CM, Mauclere P, Ullum H. (2005).Increased prevalence

of leukocytes and elevated cytokine levels in semen from Schistosoma

haematobium-infected individuals. J Infect Dis .191:1639–1647.

65.Lokeshwar BL, Block NL.(1992). Isolation of a prostate carcinoma cell

proliferation-inhibiting factor from human seminal plasma and its similarity

to transforming growth factor beta. Cancer Res .52:5821–5825.

66.Loras B, Vetele F, El Malki A, Rollet J, Soufir JC, Benahmed M. (1999).Seminal transforming growth factor-beta in normal and infertile men. Hum Reprod .14:1534–1539.

67.Luckas MJ, Buckett WM, Aird IA, Johnson PM, Lewis-Jones DI.(1998). Seminal plasma immunoglobulin concentrations in autoimmune male subfertility.

J Reprod Immunol .37:171–180.

68.Maegawa M, Kamada M, Irahara M, Yamamoto S, Yoshikawa S, Kasai Y,

Ohmoto Y, Gima H, Thaler CJ, Aono T. (2002).A repertoire of cytokines in

human seminal plasma. J Reprod Immunol .54:33–42.

69.Matalliotakis I, Arici A, Goumenou A, Koumantakis G, Selam B, Matalliotakis G, Koumantakis E.(2002). Distinct expression pattern of cytokines in semen of men with genital infection and oligo-terato-asthenozoospermia. Am J Reprod Immunol .48:170–175.

70.Matalliotakis IM, Cakmak H, Fragouli Y, Kourtis A, Arici A, Huszar G.(2006). Increased IL-18 levels in seminal plasma of infertile men with genital tract infections. Am J Reprod Immunol .55:428–433.

71.Moldoveanu Z, Huang WQ, Kulhavy R, Pate MS, Mestecky J.(2005). Human male genital tract secretions: both mucosal and systemic immune compartments

contribute to the humoral immunity. J Immunol .175:4127–4136.

72.Watanabe M, Ueno Y, Yajima T, Iwao Y, Tsuchiya M, Ishikawa H, Aiso S,

Hibi T, Ishii H.(1995). Interleukin 7 is produced by human intestinal epithelial

cells and regulates the proliferation of intestinal mucosal lymphocytes. J

Clin Invest .95:2945–2953.

73.Anderson Di, HillJA. (1988)Cell-mediated immunity in infertility*A*.*m J ReprodImmunol* . 17:22-30.