Summary & Conclusion

SUMMARY AND CONCLUSIONS

Varicocele is a major cause of primary infertility. Varicocele is an abnormal dilatation of the pampiniform plexus of veins resulting from absence or incompetence of the valves of the internal spermatic vein with subsequent retrograde venous flow.

The mechanism by which varicocele affects fertility remains unclear and various possibilities continue to be discussed. Reduced testicular perfusion of the affected testis because of increased venous pressure leading to atrophy with typical reduction in testicular volume was suggested by some investigators. Renal/adrenal reflux is another possible mechanism that could explain the effect of varicocele on fertility.

Various studies have been performed examining the potential differences between serum concentration of various substances in the internal spermatic vein and the peripheral venous blood (e.g. catecholamines, cortisol, prostaglandins and serotonin) but the results were controvesial.

IL-6 is a multifunctional cytokine produced by various cell types. Elevated level of IL-6 have been observed in a number of pathological conditions.

The inclusion of IL-6 in this study is based on the fact that IL-6 is produced by both Leydig and Sertoli cells, and varicocele is a pathological condition having a pantesticular affection. So, it appears benificial to examine the effect of varicocele on such cytokine.

Our study was designed to measure testosterone, dihydrotestosterone (DHT), serotonin and IL-6 in the internal spermatic vein, peripheral venous blood and seminal plasma of varicocele patients in comparison with the control subjects without varicocele.

This study included 41 varicocele patients with their age ranging from 23 to 43 years, attending the Andrology Out-patient Clinic and Surgery Out-patient Clinic, Benha and Mansoura University Hospitals. In addition 5 normal fertile non-varicocele men were studied as healthy controls. Among the varicocele patients, they were classified into two groups:

a) Infertile varicocele group in whom the indication of varicocelectomy was infertility (36).
b) Fertile varicocele group in whom the indication of varicocelectomy was either for pain or for prophylaxis against subsequent development of infertility.

All patients and controls were subjected to:

- Thorough history taking.
- Thorough general examination.

- Thorough local examination of inguino-scrotal region.
- Investigations including:
  a- Colour-coded Doplex Doppler Ultrasound, to exclude any other testicular or epididymal pathology and to prove the presence and the degree of reflux of blood into the pampiniform plexus.
  b- Semen analysis by Computer assisted method (Autosperm system) with determination of velocity, linear velocity, morphology, fructose and α-glucosidase level.

- Inguinal varicocelectomy or herniorrhaphy according to the indication.
- Operative blood samples from peripheral venous blood and internal spermatic vein were taken.
- Peripheral venous blood, internal spermatic vein and seminal plasma samples were compared with each other for the concentrations of testosterone, DHT, serotonin and IL-6 in the infertile varicocele group, fertile varicocele group and the controls.

Our results showed that:

- The levels of testosterone in the peripheral venous blood, I.S.V. and seminal plasma were significantly lower in the infertile varicocele group as compared with the control group, while its concentration in the I.S.V was significantly lower in the infertile varicocele group as compared with the fertile varicocele group. Testosterone concentration in I.S.V was found to be 4 times higher than its concentration in the peripheral venous blood in the infertile varicocele group. Testosterone concentrations in the peripheral venous blood, I.S.V and seminal

plasma were significantly correlated with sperm concentration, grade (a) motility, grade (a+b) motility, morphology, velocity, linear velocity and α-glucosidase concentration. However, testosterone concentrations in the peripheral venous blood, I.S.V and seminal plasma were inversely correlated with CDU score.

- The levels of DHT in the peripheral venous blood, I.S.V. and seminal plasma were significantly lower in the infertile varicocele group as compared with the control group, while its concentration in the I.S.V and seminal plasma were significantly lower in the infertile varicocele group as compared with the fertile varicocele group. DHT concentration in I.S.V. was found to be 9 times higher than its concentration in the peripheral venous blood in the infertile varicocele group. DHT concentrations in the I.S.V and seminal plasma were significantly correlated with sperm concentration, grade (a) motility, grade (a+b) motility, morphology, velocity, linear velocity, WBCs and α-glucosidase concentration. DHT concentration in the peripheral venous blood was significantly correlated with sperm concentration, morphology, velocity, linear velocity and α-glucosidase concentration. However, DHT concentrations in the peripheral venous blood, I.S.V. and seminal plasma were inversely correlated with total CDU score.
- The levels of serotonin in the peripheral venous blood, I.S.V and seminal plasma were elevated in the infertile varicocele patients as compared with the fertile and control groups, and its concentration in the I.S.V was significantly higher than its concentration is the peripheral venous blood. Serotonin concentrations in the peripheral

venous blood and I.S.V were inversely correlated with sperm concentration, grade (a) motility, grade (a+b) motility, morphology, velocity, linear velocity and α-glucosidase. However, its concentrations in the peripheral venous blood and I.S.V were directly correlated with CDU score. Serotonin concentration in the seminal plasma was directly correlated with sperm concentration, grade (a) motility, grade (a+b) motility, morphology, velocity, linear velocity and α-glucosidase. However, serotonin concentration in the seminal plasma was inversely correlated with CDU score.

- The levels of IL-6 in the peripheral venous blood, I.S.V and seminal plasma wee elevated in the infertile varicocele patients without accessory gland inflammation, as compared with fertile and control groups. In addition, IL-6 was significantly higher in infertile varicocele patients with accessory gland inflammation. IL-6 concentration in the peripheral venous blood was inversely correlated with sperm concentration, morphology, velocity, linear velocity and α-glucosidase, while its concentration in the I.S.V was inversely correlated with sperm concentration, morphology, and α-glucosidase. However, IL-6 concentrations in the seminal plasma, peripheral blood and I.S.V. were directly correlated with WBCs concentration.
- ROC curve analysis indicates that internal spermatic vein testosterone, DHT and serotonin are the most specific for discrimination between fertile and infertile patients. Also, motile sperm concentration show sensitivity 90% and specificity of 96.2% for a criterion value >42 mill./ml to discriminate between fertile and infertile groups.

CONCLUSIONS

1- Determination of androgens, particularly DHT, yield information about impaired steroidogenesis in Leydig cells in varicocele which occurs in parallel with spermatogenic deterioration. In addition, epididymal function has been influenced in varicocele patients which explain the unfavorable effect on the maturation of spermatozoa.

2- Evidence for involvement of IL-6 in the pathogenesis of testicular dysfunction of patients with varicocele was demonstrated in our study. The present data confirm that IL-6 is an accurate marker of accessory sex gland inflammation.

3- Interestingly, the higher concentrations of serotonin in testicular vein of patients with varicocele cause vasconstriction and testicular ischemia, that may explain its detrimental effect on semen quality. Serotonin in seminal plasma may have a role as infertility determinant.

4- Our study has revealed the role of varicocele in the etiology of male testicular dysfunction and may be relevant for the development of antagonist therapies to block the detrimental effect of serotonin and cytokines.

Recommendations:

1- Further studies are recommended to assess the role of IL-6 and other cytokines in the pathogenesis of varicocele, and to evaluate their clinical usefullness.

2- Further studies should focus on the clinical impliations of antiserotonergic treatment in patients with varicocele.