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# Treatment of Infertility in Men with Post-traumatic Stress Disorder (PTSD) with the Method of Intrauterine Insemination

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## ABSTRACT

**Objective:** Our objective was to determine the effect of PTSD on changing the quality of sperm in veterans with PTSD, and the percentage of successful procedures intrauterine insemination (IUI) as a first-line treatment of male infertility patients with post-traumatic stress disorder (PTSD). **Patients and methods:** The study is designed as a prospective observational study. The study was started from February 2013 until May of 2014. Our study included a total of 51 patients who were treatment for infertility in private Hospital for gynecology, endocrinology and infertility, IVF Center in Peja, and those who were outpatients treated for chronic PTSD in the Polyclinic, Biolab-Zafi, in Klinia the Republic of Kosovo. All subjects divide into two groups; The first, consisting of 21 respondents to the participants of the war in Kosovo, which was established diagnosis of PTSD. The second group of 30 who have not lived in Kosovo for the time War, and without signs of PTSD. **Results:** Subjects with PTSD were somewhat older than the control group ( $p = 0.235$ ) but it was not a significant difference ( $44.5 \pm 5.6$  vs  $43.8 \pm 2.3$ ). When the question of type of infertility, secondary infertility is significantly higher in patients with PTSD (62% vs 20%) (Table 2). The total number of sperm and semen volume no significant differences between the two groups ( $p > 0.05$ ). Sperm motility showed a significant reduction in cases of PTSD ( $p < 0.0001$ ), from observation semen parameters were found more abnormal forms of spermatozoa in the ejaculate cases with PTSD ( $p < 0.0001$ ) (Table 2). The percentage of pregnancies IUI procedure was slightly higher in patients with PTSD than the control group without PTSD (19% vs. 16.6%). **Conclusion:** A combination of analytical oriented psychotherapy techniques and assisted reproductive techniques (ART) such as IUI procedures, increases the chances for healing infertility in patients with PTSD.

**Key words:** PTSD, IUI, Semen samples, Infertility.

## 1. INTRODUCTION

Kosovo currently has the youngest population in Europe, with fertility estimated by the Census from 2.4 children per woman. In recent years, however, the growth rate of the population of Kosovo started to slow, and the birth rate is reduced as a consequence of increasing the rate of infertility. Infertility is the inability to conceive after one year of unprotected intercourse (1-5). It can be divided into primary, in which there was no previous pregnancy, a condition secondary to the inability to conceive after at least one previous pregnancy (6-10). War is the result of stress complex effects of various physical, physiological, chemical and biological stress a direct impact on health, and the profound negative social and economic consequences of the war, which is an additional burden for society. PTSD is characterized by re extremely traumatic

experience (certainly falls into this war experience and the experience of fighting) in the form of intrusive memories, nightmares and very vivid images, sounds and scents that reflect the traumatic experience (11-17).

Our goal was to determine the effect of PTSD on changing the quality of sperm in veterans with PTSD, intrauterine insemination applications (IUI) procedure as a first-line treatment of male infertility patients with post-traumatic stress disorder (PTSD).

## 2. MATERIALS AND METHODS

Our study included a total of 51 patients for fertility treatment in a private hospital for gynecology, endocrinology and infertility, in Pec, and those who were outpatients in chronic PTSD clinic „ Biolab-Zafi „, in Klinia the Republic of Kosovo. The research was started from

February 2013 to May 2014. All subjects divided into two groups. The first, consisting of 21 persons, participants of the Kosovo war, which was established diagnosis of PTSD. Another group of 30 who did not live in Kosovo at the time of the war, and no signs of PTSD. The diagnosis of PTSD is based on the criteria of ICD-10 (International Classification of Diseases and Related Health Problems, Tenth Revision) (18-20), and for the purposes of this study diagnostic on the day of collection of samples confirmed based on the diagnostic and statistical manual of mental disorders (Diagnostic and Statistical Manual of Mental Disorders, DSM) IV-3 with clinical scale to assess post-traumatic stress disorder (Eng. Clinician administered PTSD Scale, CAPS) (3). Each participant signed an agreement to participate in the study, after oral explanations.

### 2.1. Laboratory tests

The concentration of the hormone cortisol and prolactin levels were measured using techniques ELFA (Enzyme Linked Fluorescent testing) in the mini Vidas device (Biomérieux SA France). The levels of these two hormones determined twice; T1 at the beginning of treatment, and T2 on the day when he finished IUI procedure, in order to compare, possible differences in not burdening the day and the day of the procedure when the respondents know that the day should give ejaculate for intrauterine insemination

### 2.2. Sperm assessment and IUI procedure

Masturbation ejaculate collected in a separate room in the hospital after three days abstention. Most patients with PTSD have failed in the first attempt to provide ejaculate, and after a break of up to 2 hours could bring ejaculate from home, while patients in the control group only three cases brought ejaculate out of the house. Analysis ejaculate carried out in accordance with the new criteria of the World Health Organization since 2010 (19). Undiluted semen (25 ul) numbered in the Makler chamber. The concentration of sperm per milliliter is determined by increasing  $\times 400$ . Mobility assesses progressive, low progressive and non-progressive. For sperm morphology, using smears prepared and the percentage of morphologically normal sperm and sperm of various disorders is estimated at 100 sperm in the final increase  $\times 1000$ . For IUI procedure selected patients with unexplained infertility and control group, and patients with PTSD. For ovarian stimulation, each female subject received 50-75 IU recombinant FSH (r-FSH, Gonal-F, Serono, Switzerland) every day of the third day to 12 day cycle. Follicular development was monitored by vaginal ultrasound, dose r-FSH is discontinued or reduced based on the responses of the ovaries and estradiol levels. When noted a follicle size of 17-18 mm, a recombinant hCG (r-hCG; Pregnyl®, NV Organon, The Netherlands) for better oocyte maturation. Each patient underwent IUI procedures or after 36-40 hours after the r-hCG). Ejaculate for IUI prepared method Swim-up. Each patient received medication for luteal phase support vaginal natural progesterone. Pregnancy is diagnosed based on the increase in serum  $\beta$ -hCG concentration 14 days after IUI. Clinical pregnancy was defined as the presence of a gestational sac, which is ac-

companied by a picture of the embryo / fetus cardiac activity on transvaginal ultrasound 4 weeks after IUI.

### 2.3. Statistical analysis

Data were reported as means  $\pm$  standard errors of means (SEM) comparisons of the data between the PTSD and non-PTSD groups were made by the independent t-test. Analysis of the data was performed by using SPSS (Version 10) in the home computer. A p-value of less than 0.05 was considered to be statistically significant.

## 3. RESULTS

| Parameters            | PTSD cases<br>(mean $\pm$ SD)<br>(n=30) | Controls<br>(mean $\pm$ SD)<br>(n=50) | p-value |
|-----------------------|---|---------------------------------------|---------|
| Age (years)           | 44.5 $\pm$ 5.6                          | 43.8 $\pm$ 5.0                        | 0.235   |
| Economic status (n,%) |   |                                       |         |
| Bad/unemployed        | 8 (38.0%)                               | 6 (20%)                               | 0.210   |
| Satisfying            | 9 (42.8%)                               | 16 (53.3%)                            | 0.155   |
| Good                  | 4 (19.0%)                               | 8 (26.7)                              | 0.081   |

**Table 1. Demographic and social characteristics of war veterans with post-traumatic stress disorders (PTSD) and control infertility mean. The result is not significant at  $p > 0.05^*$**

The subjects with PTSD were older than the control group, but this was not significant (44.5  $\pm$  5.6 vs 43.8  $\pm$  5.0). Based on the economic status of patients divided three groups; poor, unemployment or significantly worse than most other people. Satisfying their economic status, neither better nor worse than most other people. Good economic status, significantly or slightly better than most other people, there was no significant statistical difference between the control group and PTSD. Mean body mass index and infertility period did not differ between groups. No significant differences between the two groups in some semen parameters such as; semen volume, total sperm count ( $p > 0.05$ ). Sperm motility showed a significant reduction in cases of PTSD ( $p < 0.0001$ ), with parameters observation seeds found more abnormal forms of sperm in the ejaculate cases with PTSD ( $p < 0.0001$ ) (Table 2). When the question is infertility, secondary infertility

| Parameters  | PTSD cases<br>(mean $\pm$ SD)<br>(n=30) | Controls<br>(mean $\pm$ SD)<br>(n=50) | p-value  |
|---|---|---------------------------------------|----------|
| BMI (kg/m <sup>2</sup> )                            | 27.22 $\pm$ 1.65                        | 26.88 $\pm$ 8.8                       | 0.196    |
| Duration of infertility (years)                     | 2.8 $\pm$ 1.3                           | 3.2 $\pm$ 1.8                         | 0.075    |
| Type of infertility (n,%)                           |   |                                       |          |
| primary   | 9 (30.0%)                               | 40 (80%)                              | 0.0001   |
| secondary   | 21 (70.0%)                              | 10 (20%)                              | 0.0066   |
| Abstinence  | 3.63 $\pm$ 1.11                         | 3.08 $\pm$ 0.74                       | 0.025    |
| Sperm count 1.0 ml ( $\times 10^6$ / Ejaculate)     | 39.08 $\pm$ 10.53                       | 12.99 $\pm$ 3.86                      | <0.00001 |
| Motility (% spermatozoa) (rapid + slow progressive) | 43.2 $\pm$ 11.3                         | 54.7 $\pm$ 9.5                        | <0.00001 |
| Rapid progressive                                   | 24.96 $\pm$ 2.65                        | 14.42 $\pm$ 2.63                      | <0.00001 |
| Normal morphology(% spermatozoa)                    | 32.4 $\pm$ 2.05                         | 13.5 $\pm$ 2.12                       | <0.00001 |

**Table 2. Quantitative analysis of various parameters of semen profile. The result is significant at  $p < 0.05^*$**

was significantly higher in patients with PTSD ( $p = 0.026$ ) (Table 2).

| Parameters             | PTSD cases<br>(mean ± SD)<br>(n=30) | Controls<br>(mean ± SD)<br>(n=50) | p value    |
|------------------------|-------------------------------------|-----------------------------------|------------|
| Cortisol (ng/ml), T1   | 175.36 ± 20.41                      | 154.75 ± 32.17                    | < 0.00001* |
| Cortisol (ng/ml), T2   | 181.10 ± 23.89                      | 171.75 ± 23.66                    | 0.126      |
| Prolactine (ng/ml), T1 | 15.18 ± 3.51                        | 10.50 ± 0.98                      | < 0.00001* |
| Prolactine (ng/ml), T2 | 14.26 ± 3.04                        | 12.15 ± 0.21                      | 0.0002*    |

**Table 3. Measured levels of stress hormones in the treatment start (T1) and on the day of IUI procedures (T2).. The result is significant at  $p < 0.05^*$**

The concentration of cortisol in the first measurement (T1) was elevated in patients with PTSD (Table 4) as compared to the control group ( $p < 0.00001$ ). In the second measurement (P2), there were significant decrease cortisol levels in PTSD group, so that this group is not different from controls ( $p = 0.126$ ), or an increase in cortisol levels in the control group in the second period of blood collection. Prolactin in a person with PTSD was higher in the first ( $p < 0.00001$ , and the second measurement ( $p = 0.0002$ ) (Table 3).

| Parameters            | PTSD cases<br>(n=30) | Controls<br>(n=50) | p value |
|-----------------------|----------------------|--------------------|---------|
| Pregnancy rates (n,%) | 4 (19%)              | 5 (16.6%)          | 0.313   |

**Table 4. The percentage of pregnancies IUI procedure between patients with PTSD and without PTSD**

Tabular results are shown in Table 4 show the percentage of positive pregnancy between the two groups ( $p = 0.509$ ), a group of PTSD is slightly higher (19.0% vs. 16.6%).

#### 4. DISCUSSION

In recent years, more and more often occur opinion that before fertility treatments should take care of the removal, chronic and acute stress. Removing stress will contribute to greater “natural fertility” and to reduce the number of required method of assisted reproduction cycles, and the use of invasive techniques such as in vitro fertilization method. Dealing with stress role in the treatment of infertility certainly brings fewer ethical and religious dilemmas in relation to methods of assisted reproduction (4). Stress is certainly one of the important psychological impact of infertility. The difficulties in achieving parenthood often cause problems with regard to the range of the deterioration of human relationships and letting the person who is ‘guilty of infertility’. US scientists have discovered that a series of traumatic experiences can lead to PTSD (war deployment) and the feeling that other people do not understand the traumatized person from the environment, creates a sense of alienation, distrust, loss of connection with the world, changing views of family life (16). By measuring the quality of male sperm you can classify the degree of fertility. In fact, it can be defined male infertility with certain limitations in the results of the analysis of seeds, and those people who have scores below those limits are defined as “infertile” or “sub-fertile” (11). There are numerous reasons why PTSD symptoms may increase with age (5). In our study, age of patients with PTSD is

a little older than the control group ( $44.5 \pm 5.6$  vs.  $43, 8 \pm 2.3$ ), but not significantly ( $p = 0.235$ ). Socio-economic status is often measured as a combination of education, income and occupation. Low socio-economic status and its correlates, such as lower education, poverty and poor health, and ultimately affect the society as a whole (17). In our research division of the patient on the basis of socioeconomic status into three groups as bad (unemployment), satisfactory and good status, no differences were patient with the control group (Table 1) and PTSD. The relationship between male infertility and obesity can be attributed to more than sexual dysfunction and other physical manifestations of altered obesity. Although spermatogenesis and fertility decreased in most obese men, a disproportionate number of people seeking treatment for infertility obese. There have been several studies on the relationship between obesity and quality of seeds, with the inverse of the correlation between these parameters are often expressed (15). BMI in both groups of patients in our study was  $27.5 \pm 3.1$ , which is within normal limits ( $p = 0.290$ ). The link between stress and sperm parameters obtained from several studies (14). Previous studies have observed different results on the impact of stress on semen quality. Much research has focused on changing the quality of sperm in men exposed to stress. One study estimates the impact of the Lebanese civil war on the parameters of seeds and reported that the concentration of sperm was significantly lower in the war in relation to the post-war period. However, the percentage of abnormal sperm morphology increased in the postwar period. A significant decline in sperm concentration can be attributed to increased levels of stress during the war (1). In one study (7), in people under stress found that psychological stress significantly ( $p < 0.001$ ) lowered sperm concentration and rapidly progressive sperm motility and percentage of sperm with abnormal morphology tend to increase with stress, but it the change was not significant. These results were not complete agreement with our results. From our results (Table 2) it can be concluded that patients with PTSD had lower (%) for mobility and sperm morphology ( $p < 0.0001$ ), while no significant difference ( $p = 0.132$ ) in total sperm concentration ( $p = 0.132$ ) and the volume of ejaculate ( $p = 0.268$ ). Hypothalamic-pituitary-adrenal axis is an important factor in the pathogenesis of infertility. Changes in life changes the secretion of cortisol, which are accompanied by mental stress has a negative feedback on the HPG owl (6). Level cortisol in our patients with PTSD are higher than in the control group ( $p < 0.0001$ ) in the first assessment (T1). Cortisol results reconciled in the second period (T2) on the day of IUI procedures, the results are not significant. This fact can be explained by the increased levels of stress in the control group, given the expectations of the results of the procedure, and repeat several times due to lower level of performance. Other authors (14) has suggested that deterioration of sperm variables associated with elevated prolactin levels was also detected in stressed men. Our results (Table 4) show higher levels of prolactin in patients with PTSD than in the control group, and two (T1 and T2) measurements ( $p < 0.00001$  and  $p = 0.002$ ). This could mean that long-term stress, which manifests itself in war veterans (PTSD) can



have a negative impact on sperm production and male sex hormones in the testes and circulation. We assume that changes in cortisol and prolactin secretion caused by stress leads to hormonal imbalance in the critical period from conception. Pregnancy rates after IUI cycles are very variable in the literature. General pregnancy for COH with IUI vary in accordance with the instructions, and are in the range 15 to 20% (11). Low rates of pregnancy are associated with poor semen parameters. The total pregnancy rate per cycle with COH/IUI in our study was 13.7%, while the rate for the group was 14.2% for patients with PTSD and 13.3% of control patients (Table 5). Our results are consistent with other studies in the literature (9). The main advantage of IUI procedures in patients with PTSD suffer from infertility is a shortening of primary or secondary infertility, as opposed to requiring a longer treatment of PTSD. The importance of this process adds the age of women, which is negatively correlated with age. Perhaps, the greater the sample size can help in formulating better predictive models IUI success in these patients.

## 5. CONCLUSION

Based on existing literature and our clinical experience in the area of marital infertility can conclude the following: that PTSD in patients who are cures for infertility accompanied with psychological problems such as PTSD interact with previous traumatic experiences are more secure important factor along with many other factors that accompany infertility pairs. Preference should be given a combination of analytical oriented psychotherapeutic techniques and assisted reproductive techniques (ART) such as IUI procedures. Finally, our results confirm that the intrauterine insemination (IUI) procedures can be the first line treatment of male infertility patients with post-traumatic stress disorder (PTSD).

**CONFLICT OF INTEREST: NONE DECLARED.**

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