

Impact of emotional disorders on semen quality in men treated for infertility

Artur Wdowiak¹, Agnieszka Bień², Grażyna Iwanowicz-Palus²,
 Marta Makara-Studzińska³, Iwona Bojar⁴

- 1 Diagnostic Techniques Unit, Faculty of Health Sciences, Medical University of Lublin, Poland
 2 Faculty of Health Sciences, Medical University of Lublin, Poland
 3 Department of Health Psychology, Jagiellonian University Medical College, Cracow, Poland
 4 Department for Woman Health, Institute of Rural Health, Lublin, Poland

Correspondence to: Dr. Agnieszka Bień, PhD.
 Faculty of Health Sciences, Medical University of Lublin
 4-6 Staszica St., 20-081 Lublin, Poland.
 TEL: +48 81-448-68-40; FAX: +48-81-448-6841; E-MAIL: agnesmbien@gmail.com

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Abstract

OBJECTIVE: Semen quality depends on factors such as lifestyle, environment, and hormone secretion. Objective: The purpose of the study was to assess the correlation between emotional disorders and the secretion of selected hormones, and to assess the impact of these disorders on semen quality.

METHODS: The study covered 60 fertile and 112 subfertile males. The sperm was obtained by masturbation, and examined directly after liquidation according to the 2010 criteria of the World Health Organization. The research instruments used were: the Beck Depression Inventory (BDI), and the State-Trait Anxiety Inventory (STAI). A morning blood sample (5 mL volume) was obtained and sent to an authorized laboratory to assess serum levels of testosterone, LH, FSH, prolactin, SHBG, DHEA-S and cortisol.

RESULTS: In the group of infertility patients, higher BDI scores were correlated with significantly decreased testosterone levels ($p=0.001$), and increased prolactin and cortisol ($p<0.001$); statistically significant negative correlations were also found between BDI score and SHBG and DHEA-S ($p<0.001$) levels. Higher STAI-1 and STAI-2 in the low-fertility group were associated with higher mean prolactin and cortisol levels ($p<0.001$). Sperm count was shown to be correlated with BDI, STAI-1 and STAI-2 scores ($p<0.001$). Semen volume also correlated with BDI, STAI-1 and STAI-2 scores ($p<0.001$).

CONCLUSION: Depression and anxiety in subfertile males are associated with lower secretion of SHBG and DHEA-S, and higher secretion of cortisol and prolactin. Depression and anxiety in male patients cause decreased semen volume and sperm density.

INTRODUCTION

Infertility affects nearly one in five couples of reproductive age. In many cases, the main cause of infertility is decreased semen quality in the male

partner (Szkodziak *et al.* 2016). Semen quality depend on factors such as lifestyle, environment, and sex hormone secretion (Wdowiak *et al.* 2015; Wdowiak *et al.* 2014). The latter is affected by the hypothalamic–pituitary–gonadal axis and by cere-

bral cortex activity, which can be altered by disorders such as depression and anxiety (Bhongade *et al.* 2015).

Hormone secretion in the testes is controlled by pituitary gonadotropins: the luteinizing hormone (LH), stimulating sex hormone production by Leydig cells, and follicle-stimulating hormone (FSH), which, together with testosterone, acts upon seminiferous tubules via Sertoli cells to induce and maintain spermatogenesis. The release of these two gonadotropins from the pituitary gland is controlled by hypothalamic decapeptide, gonadotropin releasing hormone (GnRH). FSH plays a primary role in hormonal regulation of spermatogenesis, but androgen activity independent of FSH is also recognized. FSH stimulates division and differentiation, inhibits apoptosis of spermatogonia, and stimulates meiosis processes, while testosterone controls the course of meiosis, spermatid transformation and elongation, and spermatid adhesion to Sertoli cells (WHO 2010). Normal release of gonadotropins (FSH and LH) occurs with the pulsatile secretion of GnRH. A number of factors, including psychogenic ones such as stress disrupt the pulse activity of the hypothalamus, decreasing gonadotropin levels to a varying extent (Tellam *et al.* 2000).

Some steroid hormones acting as androgens are also synthesized in the adrenal cortex. One adrenal androgen is dehydroepiandrosterone sulfate (DHEA-S), transformed into dehydroepiandrosterone (DHEA) in a range of tissues. The chemical structure of DHEA is similar to that of testosterone and other androgens, to which DHEA is an easily transformed precursor (de Menezes *et al.* 2016). The adrenal cortex also produces cortisol, and its release is increased by stress. Prolactin (PRL) secretion by the pituitary gland is also stimulated by stress, and can inhibit the production of FSH and LH (Wdowiak *et al.* 2014). Androgen transport in the body is dependent on sex hormone binding globulin (SHBG), which is synthesized in the liver and shows high affinity for 17-hydroxysteroid hormones. Hormones bound to SHBG are biologically inactive (Handelsman *et al.* 2016). The purpose of the study was to assess the correlation between emotional disorders and the secretion of selected hormones, and to assess the impact of these disorders on semen quality.

MATERIALS AND METHODS

The study was carried out in 2015 and 2016, at the privately-owned "Ovum" Fertility Clinic in Lublin, Poland. The study was approved by the Bioethics Committee of the Institute of Rural Health in Lublin (approval no. 24/2013).

The experimental group included 112 men admitted to the clinic for the first time due to the failure to conceive after 12 months of regular unprotected sexual intercourse with a regularly ovulating female partner; 60 confirmed fertile sperm donors were included as controls. Men in both groups were aged between 27 and 33

years, had a BMI between 18.5 and 24.9, were non-smokers with no history of hazardous alcohol consumption, and used no medications. Patients with azoospermia, varicocele, and hypogonadotropic hypogonadism were excluded from the study. Prior to enrollment, all patients signed a written consent form, allowing the use of the medical data gathered for research purposes.

Semen was obtained by masturbation, and examined directly after liquidation according to the 2010 World Health Organization criteria (WHO, 2010). Prior to the examination, the patients maintained a 4-day abstinence from sex and alcohol. A morning blood sample (5 mL volume) was obtained and sent to an authorized laboratory to assess serum levels of testosterone, LH, FSH, prolactin, SHBG, DHEA-S and cortisol on the day of semen collection. The study used two questionnaires: the Beck Depression Inventory (BDI), and the State-Trait Anxiety Inventory (STAI). The Beck Depression Inventory (BDI) is a 21-item scale that enables the distinction between healthy individuals and those with symptoms of depression, as well as the evaluation of depression severity. Responses are rated on a 4-point Likert scale and range from 0 (not at all) to 3 (severely). The total score for all symptoms, ranging between 0 and 63 points, is considered an indicator of depression severity. For interpretation of study findings, the following cut-off values for depression severity degrees were used: 0–11 – no depression, 12–26 – mild depression, 27–49 – moderate depression, 50–63 – severe depression. The resulting Beck Anxiety Inventory (BAI) is a 21-item scale that showed high internal consistency ($\alpha=0.92$) and test–retest reliability over 1 week, $r(81)=0.75$ (Beck *et al.* 1961; Beck *et al.* 1988).

The State-Trait Anxiety Inventory (STAI) by C.D. Spielberger, R.L. Gorsuch and R.E. Lushene allows the evaluation of anxiety as a relatively enduring personality trait and as a situation-induced state. The questionnaire comprises two scales: STAI-1 is used for investigating state anxiety, and STAI-2 – for investigating trait anxiety. Each scale comprises 20 statements. The respondents describe their subjective feelings about each statement using a 1–4 scale. Sten results of 1–4 indicate low anxiety severity, 5–6 – moderate severity, and 7–10 – high severity (Sosnowski *et al.* 2011). Internal consistency coefficients for the scale ranged from 0.86 to 0.95; test-retest reliability coefficients ranged from 0.65 to 0.75 over a 2-month interval (Spielberger *et al.* 1983).

Quantitative parameters were presented using means and standard deviations as well as median, minimum and maximum values. Variable distribution in the groups studied was tested using the Shapiro-Wilk test for normality. Differences between the groups were tested using the nonparametric Mann-Whitney U-test. Correlations between variables were analyzed using Pearson's r correlation coefficients. Differences or correlations at $p<0.05$ were considered statistically significant. The software used for data bases and statistical analysis was Statistica 9.1 (StatSoft, Poland).

RESULTS

The comparison of mean serum levels of selected hormones showed lower mean FSH levels in the experimental group (5.25 IU/L), compared with controls (5.63 IU/L, $p>0.05$). Mean LH levels in the confirmed-fertile group (5.99 IU/L) were higher than in patients treated for fertility disorders (5.53 IU/L), but the differences were not significant ($p>0.05$). Testosterone levels were higher in fertile controls (21.03 nmol/L) than in patients treated for infertility (13.15 nmol/L; $Z=-6.813$; $p<0.001$). The sperm donors had significantly lower mean PRL levels (16.93 ng/mL) compared to the low-fertility patients (25.76 ng/mL; $Z=5.10$; $p<0.001$). Similar dependence were found for SHBG and DHEA-S. In controls, mean SHBG levels were higher (142.60 nmol/L) than in the experimental group (77.29 nmol/L), and the difference was statistically significant ($Z=-6.608$; $p<0.001$). The mean DHEA-S

concentration in fertile men was 161.28 mg/mL, and in the low-fertility patients – 94.24 mg/mL ($Z=-6.14$; $p<0.001$). In the experimental group, the mean cortisol level was 165.35 µg/dL, and in controls it was 130.78 µg/dL ($Z=5.965$; $p<0.001$) (Table 1).

In the confirmed-fertile group, the mean sperm count was 57.84 M/mL and was significantly higher than in the group treated for infertility, where the mean value was 35.46 M/mL ($Z=-5.529$; $p<0.001$). The mean ejaculate volume was also higher in the sperm donors (5.56 ml) than in the infertility patients (3.38 ml) ($Z=-6.077$; $p<0.001$). Differences between the two groups in terms of other semen parameters were not statistically significant ($p>0.05$) (Table 2).

The infertile patients had higher mean BDI scores than the sperm donors: 18.69 vs. 5.27 ($p<0.001$). The mean state anxiety (STAI-1) score in the experimental group was 6.05, while in the controls it was 2.15, and the difference was statistically significant ($p<0.001$).

Tab. 1. Hormone levels in the two groups.

Hormones	Experimental group			Control group			Z	p-value
	Mean ± SD	Median	Range	Mean ± SD	Median	Range		
FSH [IU/l]	5.25±3.83	4.51	0.55–15.78	5.63±1.75	5.51	1.78–9.97	-2.187	0.029
LH [IU/l]	5.53±3.91	4.67	0.77–16.56	5.99±2.47	5.90	1.59–18.55	-1.703	0.089
Testosterone [nmol/l]	13.15±6.51	12.00	5–31	21.03±5.78	22.00	9–31	-6.814	<0.001
Prolactin [ng/ml]	25.76±10.61	25.00	8.5–42.8	16.93±6.58	16.40	8.2–33.5	5.105	<0.001
SHBG [nmol/l]	77.29±55.26	52.00	18–170	142.6±16.97	145.00	100–171	-6.608	<0.001
DHEA-S [mg/ml]	94.24±74.83	84.00	25–351	161.28±79.29	130.00	78–390	-6.145	<0.001
Cortisol [µg/dL]	165.35±38.69	160.00	105–237	130.78±24.67	121.00	105–210	5.965	<0.001

Tab. 2. Comparison of semen quality between confirmed-fertile and infertile men.

Semen characteristics	Experimental group			Control group			Z	p-value
	Mean ± SD	Median	Range	Mean ± SD	Median	Range		
Sperm count [mln/ml]	35.46±23.66	24.00	8–118	57.84±21.59	51.00	32–132	-5.530	<0.001
Progressive motility [%]	51.79±7.67	53.86	25.18–62.91	49.64±8.63	51.36	25.18–62.73	1.603	0.109
Viability [%]	75.7±12.9	79.00	29–91	74.77±14.84	78.00	29–91	0.153	0.878
Normal morphology [%]	8.84±4.43	9.00	1–19	9.77±5.18	11.00	1–19	-1.330	0.184
Semen volume [ml]	3.38±1.97	3.00	0.5–9.5	5.57±2	5.50	1.5–9.5	-6.077	<0.001
MAR test IgG [%]	7.46±14.42	0.00	0–95	5.62±7.01	5.00	0–35	-0.081	0.935
MAR test IgA [%]	10.87±15.81	5.00	0–98	9.1±9.59	7.00	0–40	-0.023	0.982

Tab. 3. The mean BDI, STAI-1, and STAI-2 scores in the two groups.

Scale	Experimental group			Control group			Z	p-value
	Mean ± SD	Median	Range	Mean ± SD	Median	Range		
BDI	18.69±15.62	11.00	0.5–9.5	5.27±1.92	5.00	1.5–9.5	7.882	<0.001
STAI-1	6.05±2.68	7.00	29–91	2.15±0.95	2.00	29–91	8.263	<0.001
STAI-2	5.79±2.92	6.50	25.18–62.91	1.50±0.68	1.00	25.18–62.73	8.578	<0.001

A similar distribution of scores was obtained for trait anxiety (STAI-2): the mean score for infertility patients was 5.79, while for sperm donors it was 1.50 ($p < 0.001$) (Table 3).

In the experimental group, higher BDI scores were associated with significantly decreased testosterone ($r = -0.322$; $p < 0.001$), increased prolactin ($r = 0.562$; $p < 0.001$), and increased cortisol levels ($r = 0.657$; $p < 0.001$). Statistical analysis also showed significant negative correlations between BDI score and SHBG ($r = -0.712$; $p < 0.001$) and DHEA-S levels ($r = -0.588$; $p < 0.001$) in the group. No significant correlations were found for FSH and LH ($p > 0.05$). In the confirmed-fertile group there were no statistically significant correlations between BDI scores and the mean levels of the hormones studied ($p > 0.05$). Our analyses showed that higher STAI-1 scores in the infertility patient group were associated with higher mean prolactin ($r = 0.598$; $p < 0.001$) and cortisol levels ($r = 0.697$; $p < 0.001$), and with lower SHBG ($r = -0.843$; $p < 0.001$) and DHEA-S levels ($r = -0.766$; $p < 0.001$). No significant correlations were found between STAI-1 and FSH, LH, or testosterone ($p > 0.05$). In the confirmed-fertile group there were no statistically significant correlations between STAI-1 scores and the hormones studied ($p > 0.05$). In the low-fertility group, higher STAI-2 scores were correlated with lower SHBG ($r = -0.858$; $p < 0.001$) and DHEA-S levels ($r = -0.732$; $p < 0.001$). The study also showed a positive correlation between STAI-2 scores and prolactin ($r = 0.639$; $p < 0.001$) and cortisol ($r = 0.665$; $p < 0.001$). No statistically significant correlations were found between STAI-2 and FSH, LH, or testosterone in the experimental group ($p > 0.05$). In the control group, the

only positive significant correlation was found between STAI-2 and LH ($r = 0.354$; $p < 0.01$) (Table 4).

In the low-fertility group, statistically significant negative correlations were found between sperm count and scores in the BDI ($r = -0.496$; $p < 0.001$) (Figure 1), STAI-1 ($r = -0.665$; $p < 0.001$) (Figure 2), and STAI-2 ($r = -0.645$; $p < 0.001$) (Figure 3).

Ejaculate volume was negative correlated with BDI ($r = -0.484$; $p < 0.001$) (Figure 4), STAI-1 ($r = -0.568$; $p < 0.001$) (Figure 5), and STAI-2 ($r = -0.656$; $p < 0.001$) (Figure 6) in the infertility patient group.

In the low-fertility group higher percentages of sperm with progressive motility were associated with lower STAI-1 ($r = -0.239$; $p < 0.05$) and STAI-2 scores

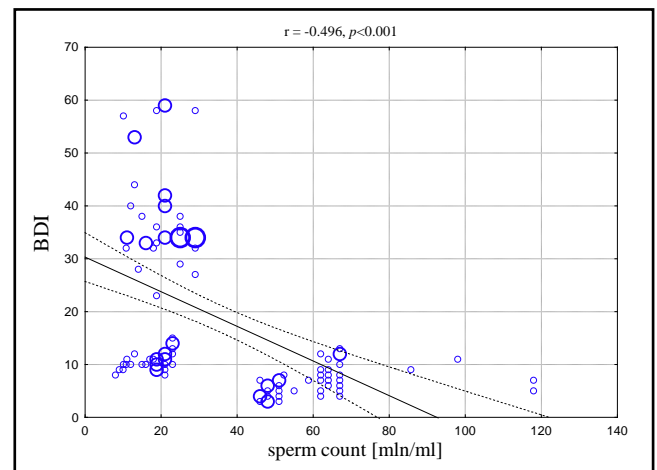


Fig. 1. Correlation between BDI scores and sperm count in the experimental group.

Tab. 4. Correlations between BDI, STAI-1, and STAI-2 scores and mean hormone levels in the experimental group and in the controls.

Hormones	BDI		STAI-1		STAI-2	
	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
FSH [IU/l]	-0.046 $p = 0.631$	-0.141 $p = 0.286$	-0.044 $p = 0.645$	-0.224 $p = 0.085$	-0.061 $p = 0.523$	0.151 $p = 0.252$
LH [IU/l]	0.031 $p = 0.752$	-0.079 $p = 0.548$	0.007 $p = 0.941$	-0.081 $p = 0.537$	0.033 $p = 0.729$	0.354 $p < 0.01$
Testosterone [nmol/l]	-0.322 $p < 0.001$	-0.007 $p = 0.958$	-0.048 $p = 0.612$	-0.019 $p = 0.882$	-0.074 $p = 0.443$	0.013 $p = 0.924$
Prolactin [ng/ml]	0.562 $p < 0.001$	-0.045 $p = 0.734$	0.598 $p < 0.001$	0.167 $p = 0.201$	0.639 $p < 0.001$	-0.173 $p = 0.187$
SHBG [nmol/l]	-0.712 $p < 0.001$	0.115 $p = 0.381$	-0.843 $p < 0.001$	-0.013 $p = 0.917$	-0.858 $p < 0.001$	0.021 $p = 0.873$
DHEA-S [mg/ml]	-0.588 $p = 0.000$	0.268 $p = 0.039$	-0.766 $p < 0.001$	-0.074 $p = 0.573$	-0.732 $p < 0.001$	0.142 $p = 0.279$
Cortisol [μ g/dL]	0.657 $p < 0.001$	-0.036 $p = 0.787$	0.697 $p < 0.001$	0.162 $p = 0.215$	0.665 $p < 0.001$	-0.031 $p = 0.818$

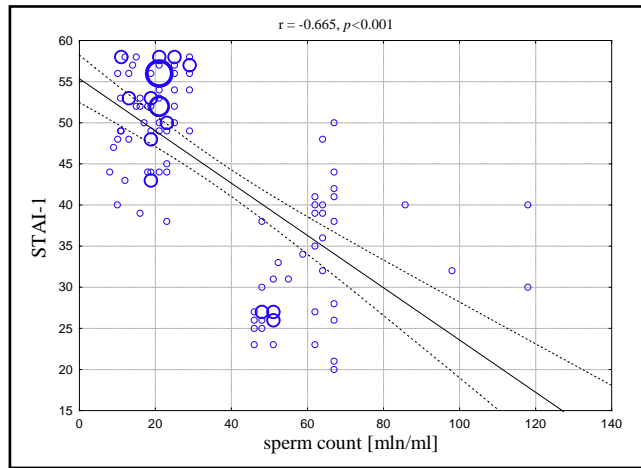


Fig. 2. Correlation between STAI-1 scores and sperm count in the experimental group.

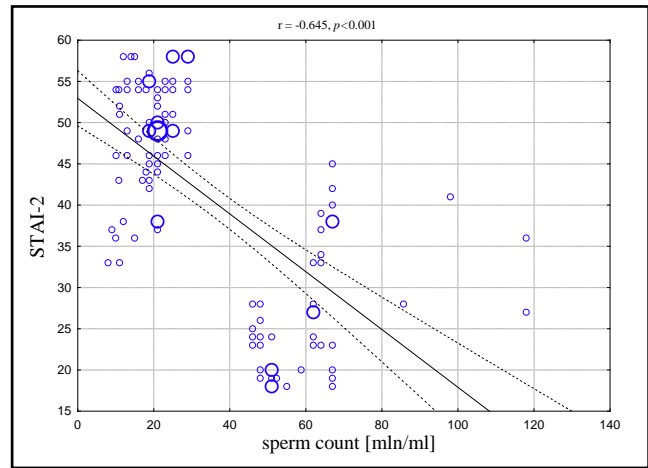


Fig. 3. Correlation between STAI-2 scores and sperm count in the experimental group.

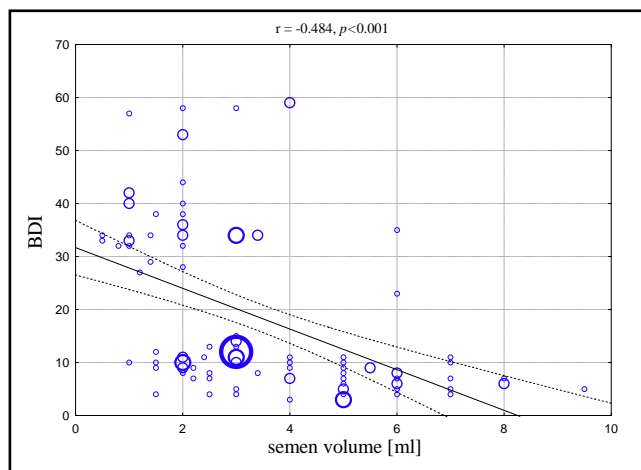


Fig. 4. Correlation between BDI scores and ejaculate volume in the experimental group.

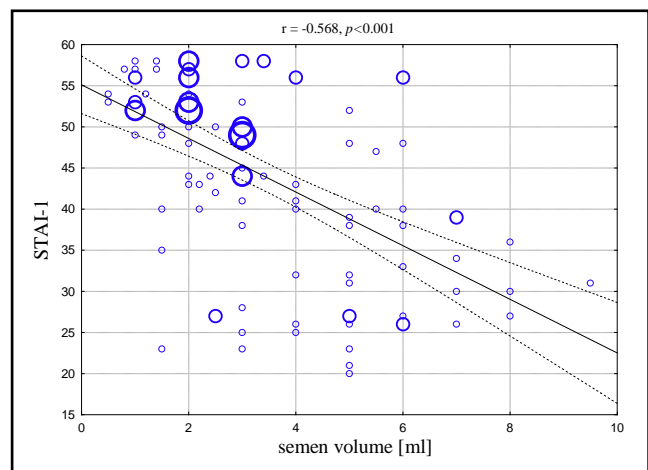


Fig. 5. Correlation between STAI-1 scores and ejaculate volume in the experimental group.

($r=-0.255$; $p<0.01$). In this group, there were also weak correlations between sperm morphology and scores in the BDI ($r=-0.256$; $p<0.01$), STAI-1 ($r=-0.224$; $p<0.01$), and STAI-2 ($r=-0.253$; $p<0.01$) scales. No statistically significant correlations were found in the experimental group between BDI scores, and sperm motility, vitality, IgG-MAR, or IgA-MAR ($p>0.05$). Similarly, neither STAI-1 nor STAI-2 were significant correlated with sperm vitality, IgG-MAR, or IgA-MAR ($p>0.05$) in this group. In the confirmed-fertile group, no correlation was found between the depression and anxiety scales and any semen characteristics analyzed ($p>0.05$) (Table 5).

DISCUSSION

Literature on the subject of male infertility becomes more extensive every year. It provides a wealth of information on infertility, including its causes, treatment, and social and psychological aspects (Newson *et al.* 2007; Drosdzol & Skrzypulec 2009; Gollenberg *et al.* 2010; Wichman *et al.* 2011; Fisher & Hammarberg

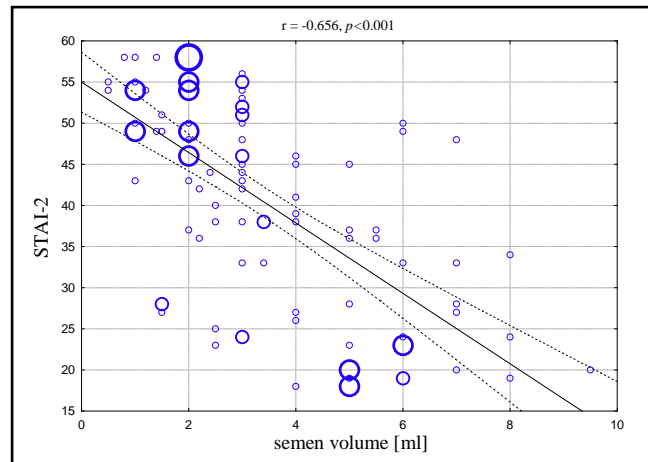


Fig. 6. Correlation between STAI-2 scores and ejaculate volume in the experimental group.

2012; Wdowiak *et al.* 2017). The purpose of the study was to assess the correlation between emotional disorders and the secretion of selected hormones, and to assess the impact of these disorders on semen quality

Tab. 5. Correlations between BDI, STAI-1, and STAI-2 scores and semen characteristics in the experimental group and in the controls.

Hormones	BDI		STAI-1		STAI-2	
	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
Progressive motility [%]	-0.162 <i>p</i> =0.088	0.125 <i>p</i> =0.340	-0.239 <i>p</i> <0.05	-0.112 <i>p</i> =0.397	-0.255 <i>p</i> <0.01	0.084 <i>p</i> =0.523
Viability [%]	-0.161 <i>p</i> =0.090	0.078 <i>p</i> =0.555	-0.152 <i>p</i> =0.109	-0.149 <i>p</i> =0.256	-0.124 <i>p</i> =0.194	0.063 <i>p</i> =0.632
Normal morphology [%]	-0.256 <i>p</i> <0.01	-0.067 <i>p</i> =0.611	-0.224 <i>p</i> <0.01	-0.029 <i>p</i> =0.822	-0.253 <i>p</i> <0.01	-0.201 <i>p</i> =0.125
MAR test IgG [%]	0.169 <i>p</i> =0.075	-0.009 <i>p</i> =0.940	0.173 <i>p</i> =0.069	0.072 <i>p</i> =0.584	0.119 <i>p</i> =0.213	0.119 <i>p</i> =0.364
MAR test IgA [%]	0.142 <i>p</i> =0.134	-0.034 <i>p</i> =0.798	0.171 <i>p</i> =0.071	0.016 <i>p</i> =0.902	0.108 <i>p</i> =0.259	0.209 <i>p</i> =0.109

in men treated for infertility. Study findings showed that men with fertility problems are more likely to have emotional disorders than fertile sperm donors. In the patients, more severe depressive symptoms (BDI: 18.69 vs. 5.277), state anxiety (STAI-1: 6.05 vs. 2.15), and trait anxiety (STAI-2: 5.79 vs. 1.50) were found. Analyses of the results showed that the mean BDI in the experimental group indicated mild depression, while mean STAI scores indicated moderate anxiety. These findings are in line with those reported by Drozdol and Skrzypulec, and Wichman *et al.* (Drozdol & Skrzypulec 2009; Wichman *et al.* 2011). A study by Volgsten *et al.* including 545 couples treated for infertility showed that approximately 30% of infertile women and 10% of infertile men fulfilled the diagnostic criteria for depression and/or anxiety disorders, including subthreshold diagnoses (Volgsten *et al.* 2008). Furthermore, a study by Tüzer *et al.* indicated that depressive symptoms in men predicted increased anxiety during infertility treatment (Tüzer *et al.* 2010). One should consider that stress levels in infertile patients tend to increase as treatment continues, in proportion to time in treatment, meaning that the mean severity of depression and anxiety can increase (Gollenberg *et al.* 2010; Fisher & Hammarberg 2012). This may be due e.g. to repeated treatment procedures (such as semen collection), fertility treatment costs, or the male patients' awareness of being the one with the fertility problem (Tüzer *et al.* 2010). On the other hand, Wichman *et al.*'s analysis of the clinical indicators of mental health in infertile and healthy men showed no significant differences between the two groups. However, the impact of a range of factors on infertile men's psychological state should be emphasized. Men with a tendency towards social isolation, with an avoidance coping style, and perceiving stressful events as overwhelming, are more likely to experience severe anxiety than those without these traits (Wichman *et al.* 2011).

Increased emotional tension or emotional disturbance associated with infertility diagnostics and treatment can interfere with normal functioning of the body. The present study of interaction between depression and anxiety disorders on the one hand, and hormone secretion on the other, showed higher depression severity to be correlated with lower testosterone, SHBG, and DHEA-S levels, and with increased prolactin and cortisol levels. No similar association with FSH or LH was found. Meanwhile, Bak *et al.* in their study of men with nonobstructive azoospermia (NOA), reported a positive correlation between FSH and LH and anxiety, in contrast to testosterone, which was inversely associated with anxiety (Bak *et al.* 2012). Similar results were obtained by Bhongade *et al.* who investigated the impact of psychological stress on male sex hormones. Men with a higher severity of anxiety and depression had higher serum levels of FSH and LH than those without similar disorders (Bhongade *et al.* 2015).

Abnormal testosterone levels can impair the mechanisms of spermatogenesis and spermiogenesis. Furthermore, low testosterone concentration is a marker of HPA activation. One factor that can dysregulate testosterone secretion is chronic anxiety and depression (Lieberman *et al.* 2016). In the present study, higher depression severity was associated with lower testosterone. This is not, however, corroborated by Ponholzer *et al.*'s study, where testosterone levels were not correlated with depression or its severity (Ponholzer *et al.* 2009). By testing for total testosterone and SHBG levels it is possible to determine the bioavailability of testosterone. Increased SHBG levels indicate that the concentration of unbound testosterone available to tissues is lower than can be expected based on the total testosterone level. In turn, decreased SHBG suggests a higher bioavailability of testosterone (Handelsman *et al.* 2016; Li *et al.* 2016). In the present study, the mean SHBG level was inversely associated with mean depression sever-

ity (BDI) and anxiety (STAI-1 and STAI-2) scores in the infertility patient group only. The available literature includes no reports on correlations between SHBG levels and emotional disorders.

The present study showed an association between increased prolactin levels and higher severity of depression and anxiety. Available literature reports regarding the role of PRL secretion in emotional disorders are equivocal, both for humans and for animal models. Animal studies by Torner *et al.* demonstrated that exogenous PRL administration has an anxiolytic effect in rats of both sexes (Torner *et al.* 2001). Long-term prolactin administration in ovariectomized female rats used to simulate the endocrine status of pregnancy was shown to decrease anxiety (Donner *et al.* 2007). Meanwhile, another study involving rodents showed an association between high prolactin levels and increased anxiety. Increased basal and stress-induced levels of PRL were reported in male rats bred for high-anxiety behavior as compared to low-anxiety behavior rats (Landgraf *et al.* 1999). Similarly conflicting results are reported in human models. On the one hand, patients with hyperprolactinemia report more anxiety and hostility than controls (Reavley *et al.* 1997). On the other hand, experiments by Reavley *et al.* and by Oliveira *et al.* found no differences in terms of depression between patients with hyperprolactinemia and controls (Reavley *et al.* 1997; Oliveira *et al.* 2000). Literature on the subject does not include studies directly investigating the association between emotional disorders and prolactin secretion in male patients treated for infertility. Existing reports regarding animal and human models without reference to fertility disorders point to a need for further investigation of this area in the light of the present findings. DHEA-S is a marker of stress that persists longer after secretion than cortisol and plays a role in modulating the body's susceptibility to the negative effects of stress (Morgan *et al.* 2004). In the experimental group, negative correlations were found between DHEA-S levels and mean depression, state anxiety, and trait anxiety scores. This is corroborated by Maninger *et al.* and Mocking *et al.* reporting an association between depression and low DHEA-S levels, especially when related to high cortisol, though the authors emphasize that the findings are not conclusive (Maninger *et al.* 2009; Mocking *et al.* 2015).

Cortisol is a biological marker of hypothalamic-pituitary-adrenal (HPA) axis activation in humans. It also shows complex associations with depressive disorders (Morgan *et al.* 2004; Mocking *et al.* 2015). Bhongade *et al.*, Ogawa *et al.* and Slade *et al.* analyzing stress levels in men treated for infertility, showed it to be higher than in healthy men (Bhongade *et al.* 2015; Ogawa *et al.* 2011; Slade *et al.* (2007). In men, stress adversely affects semen quality and can inhibit GnRH secretion through hypothalamic-pituitary axis activation (Tellam *et al.* 2000; Pantalone & Faiman 2012). Stress-induced spermatogenesis impairment is typically

manifested in decreased sperm count and motility, and an increased percentage of morphologically abnormal sperm. Importantly, hormonal imbalances depend on the strength and type of stressor, the time the stressor is active, and the initial state of the patient.

The present analysis showed high BDI, STAI-1, and STAI-2 scores to be correlated with high cortisol levels. Disorders affecting the hypothalamic-pituitary-adrenal (HPA) axis, glucocorticoids such as cortisol, and pituitary proopiomelanocortin derivatives induced by the corticotropin-releasing hormone (CRH) inhibit hypothalamic-pituitary-gonadal axis control. The adverse impact of stress on the reproductive function might also be due to an increased level of tumor necrosis factor (TNF) and an increased number of natural killer (NK) cells (Cwikel *et al.* 2004). An increase in stress hormone levels, i.e. cortisol and adrenocorticotrophic hormone (ACTH), can impair androstenedione to testosterone conversion in Leydig cells. This disrupts the hormonal transformation cycle required for testosterone secretion, leading to lower average values of semen volume and sperm density (Gollenberg *et al.* 2010; Klimek *et al.* 2005). Moreover, acute or chronic stress in men can activate the HPA, as demonstrated by increased levels of the catabolic hormone cortisol and suppressed release of the anabolic hormone testosterone (Lieberman *et al.* 2016).

The present study demonstrated that correlations between scores in the STAI and BDI scales and the hormone levels and semen characteristics analyzed are only statistically significant in the group of men treated for infertility, and not in the confirmed-fertile group. It is likely that this is due to the fact that the fertile controls were less affected by emotional disorders. The negative correlation between BDI scores and testosterone levels in the infertility patient group can be related to the lower sperm density and semen volume resulting from spermatogenesis dysfunction induced by depression (which affects the hypothalamic-pituitary-gonadal axis). The impact of sex hormone secretion on reproductive dysfunction has been confirmed in a number of studies, including Wdowiak *et al.*, Tellam *et al.* and Pantalone and Faiman (Wdowiak *et al.* 2014; Tellam *et al.* 2000; Pantalone & Faiman 2012).

The present results corroborate the report by Bhongade *et al.* who administered the Hospital Anxiety and Depression Score (HADS) questionnaire to 70 men treated for infertility, and compared the results to sex hormone levels and semen parameters. The patients were divided into two groups: those with normal HADS (<8) and those with increased HADS (diagnosed with emotional disturbance). Patients with emotional disturbance were found by Bhongade *et al.* to have lower testosterone levels and sperm density. Based on the correlation between HADS and sperm density, the authors found that higher HADS is associated with lower sperm density and motility and higher percentage of morphologically abnormal sperm, which is cor-

roborated by the present study (Bhongade *et al.* 2015). Somewhat different findings were reported by Gürhan *et al.* who investigated associations between depression (BDI) and anxiety (STAI), and sperm count and motility, among other factors. The authors found no correlation between men's emotional disorders and the semen characteristics studied (Gürhan *et al.* 2009).

Zorn *et al.*'s regression analyses indicated a significant positive correlation between the sperm concentration and the WHO Well-Being Index score; successive correlations were found between psychological factors and sperm's rapid progressive motility and normal morphology (Zorn *et al.* 2008). With regard to sperm density, these results are in line with those of the present study and those reported by Bhongade *et al.* but they differ with regard to sperm motility and morphology (Zorn *et al.* 2008; Bhongade *et al.* 2015). Eskiocak *et al.* explained the sperm quality decrease from stressors by referring to the decrease in glutathione and free sulphhydryl in seminal plasma (Eskiocak *et al.* 2005). These authors investigated the impact of psychological stress (assessed using the STAI questionnaire) on seminal glutathione and free sulphhydryl content and sperm quality. Two semen samples were collected from each of 34 healthy volunteers: one under stress, and one in the absence of stressors. The analysis demonstrated that under stress, the motility index of spermatozoa was significantly lower, whereas the percentage of morphologically abnormal spermatozoa was higher than during the non-stress period. An association between seminal plasma glutathione and motility index was observed at both periods. These results confirm the impact of stress on sperm density, in line with the present findings and those reported by other authors (Eskiocak *et al.* 2005; Zorn *et al.* 2008; Bhongade *et al.* 2015). Gollenberg *et al.* note that the experience of two or more stressful life events is associated with decreased sperm density and the percentage of motile sperm, as well as an increased likelihood of testing below normal ranges for concentration, motility, and morphology. However, as emphasized by the authors, further studies should investigate whether the elimination of stressful life events could effect an increase in semen quality, and whether the adverse impact of stress is lasting or temporary (Gollenberg *et al.* 2010).

Postmeiotic germ cells grow in an immune-privileged site, thanks to the barrier formed by Sertoli cell tight junctions. If the "blood-testis barrier" is breached, antibodies are formed against spermatozoa. Conditions resulting in damage to the blood-testis barrier and antisperm antibody formation include testis trauma, toxicity, inflammation and infection (Niederberger, 2011). Antibody levels determined in both groups in the present study were not correlated with the participants' emotional state. The available literature also lacks reports associating antibody levels in the semen with emotional disorders. However, the report on IgG, IgM, and IgA antibodies in blood serum of women by Kian-

bakth *et al.* indicates that IgG secretion is decreased in depressive patients (Kianbakth *et al.* 2013). A similar finding was reported by Goldm *et al.* regarding IgA antibodies, whose secretion was decreased in depressive patients, while IgG and IgM levels were not associated with emotional disorders (Gold *et al.* 2012). The issue of immune response and emotional disorders will undoubtedly require further investigation.

The present study demonstrated that depression and anxiety disorders can disrupt hormonal balance and adversely affect semen quality. They can also have a negative impact on infertility treatment outcomes, thus warranting the development of management guidelines for cases of emotional disorders in the course of such treatment. The psychological background of infertility is difficult to diagnose by a physician, requiring collaboration with other specialists: psychiatrists, psychologists, psychotherapists. On the other hand, Fisher and Hammarberg report that men with fertility problems prefer to receive emotional support from infertility clinicians rather than from mental health professionals, self-help support groups or friends (Fisher & Hammarberg 2012).

CONCLUSIONS

- Men treated for infertility are found to have more severe depression and anxiety than those confirmed to be fertile.
- Depressive disorders in men treated for infertility contribute to decreased testosterone levels.
- Depression and anxiety in low-fertility male patients are associated with lower secretion of SHBG and DHEA-S, and higher secretion of cortisol and prolactin.
- Depression and anxiety in male patients cause decreased semen volume and sperm density.

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