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Impact of depression and the potential effect of its treatment on semen parameters

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Abstract

Background Up to 30% of male infertility may be idiopathic. Researchers are looking into psychological problems, particularly depression, as possible risk factors for such idiopathic etiology. We aimed to assess how depression affects Egyptian patients' semen parameters and its indicators for male fertility and to evaluate the potential positive influence of improving the score of depression on these parameters. A prospective observational pilot clinical study included twenty-one male patients with moderate, severe, or very severe depression. They were subjected to baseline semen analysis. All patients were treated by serotonin and norepinephrine reuptake inhibitors (SNRIs). Those who showed improvement in their depression, within the following 6 months, were eligible for a second evaluation of their semen. We compared baseline semen parameters of all patients to 2021-WHO lower normal limit as well as post-improvement values.

Results Only 16 patients showed improvement in their depression after treatment with SNRIs and were candidates for the 2nd assessment of semen analysis. No significant improvements could be detected except for volume. Yet, on repeating the comparisons including only patients with abnormal baseline semen parameters, significant improvements were observed in most semen parameters, including semen volume, sperm count per ejaculate, and percentage of sperm motility either progressive or total.

Conclusion The results addressed the potential impact of depression on male fertility in a sample of Egyptian patients through a negative effect on semen parameters. This effect is neither sole nor direct and may require either predisposed individuals or the existence of other co-factors to be manifested. However, the appropriate treatment of depression may reverse such effects and help in the management of male infertility.

Keywords Infertility, Depression, Male, Psychotherapy

Background

Infertility is a widespread issue affecting around 15% of people globally. About 50% of cases worldwide involve a male element. Numerous causes, including hereditary, immunological, obstructive, biological illnesses, or infections, are implicated in male infertility. Many psychiatric illnesses, particularly depression, are also implicated, pointing to the importance of mental health for male fertility [1, 2].

It has been reported that the hypothalamic-pituitary–gonadal axis (HPG) and cerebral cortex activity play a role in how depression affects fertility [3]. Besides, Beeder et al. [4] illustrated that men with moderate to intense depression have a reduced amount of testosterone, decreased concentrations of dehydroepiandrosterone sulfate (DHEA-S), and sex hormone-binding globulin, and a higher amount of cortisol and prolactin production.

In the same context, male infertility can be treated by lifestyle changes, such as quitting smoking and

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drinking, losing weight, and enhancing sleep habits [5]. Numerous research is currently attempting to determine if psychotherapy should be a part of managing male infertility [6, 7]. Contradictory reports on the potential enhancement of fertility by antidepressants have been published [8, 9]. There are reports that most antidepressants can affect semen parameters negatively [10]. Nevertheless, there are no reports about significant adverse effects of serotonin and norepinephrine reuptake inhibitors (SNRIs), e.g., venlafaxine, levomilnacipran, duloxetine, and desvenlafaxine on neither sperm DNA structure nor semen characteristics [4, 11].

In this study, we examined a sample of Egyptian male patients suffering from depression to explore its effect on semen parameters, as well as tracing these parameters' values after the improvement of the depression score.

Methods

Cases

Twenty-one male Egyptian patients with 18–45 years who have moderate, severe, or very severe depression, according to the diagnostic and statistical manual of mental disorders fifth edition (DSM5) criteria [12, 13] and Hamilton depression rating scale (HAM-D) [14, 15], were recruited from the psychiatry outpatient clinic and then examined at the andrology clinic of Ain-Shams University Hospitals. Only 16 patients out of the 21 completed the study till the end. The study was approved by the research ethics committee of the Faculty of Medicine, Ain Shams University (FWA 000017585), and informed consent was obtained from each patient after the explanation of the purpose of the study.

We have excluded patients who have a history of drug intake that can affect semen parameters, e.g., cytotoxic drugs, anti-androgens, sulfasalazine, gonadal hormones or nitrofurans, or smoking within the last 3 months; a chronic disorder such as diabetes mellitus, hypertension, obesity, chronic liver, or renal disease; and organic diseases that can affect fertility, i.e., varicocele, testicular tumor, or undescended testis, genitourinary diseases, or surgeries as well as psychiatric disorders other than depression by using structured clinical interview for DSM-IV questionnaire (SCID-1) [16].

Patients' personal history was taken as regards age and special habits of medical importance and reproductive history as regards previous investigations or treatment for infertility, presence of chronic illness or anosmia, exposure to gonadotoxic substances within the last 3 months, sexual history including the sexual desire, erection, ejaculation, and frequency and timing of intercourse as well as surgical history were gathered.

Examination

Secondary sexual characteristics were evaluated, and any gynecoid characteristics, such as gynecomastia or gynecoid hair distribution, were checked. Besides, the penis was examined for any plaques, curvature, epi, or hypospadias; the testicles were examined to determine the size and rule out the presence of masses; the epididymis was examined for any tenderness; the spermatic cord was examined for varicocele; and the vas deferens was examined to ensure existence.

Procedures

Patients with other psychiatric disorders using the SCID-1 scale were excluded by the psychiatrist. Hamilton depression rating scale (HAM-D), a 17-item questionnaire used to diagnose depression and assess its severity, was filled out by the patient at the andrology outpatient clinic using a reliable Arabic version [14, 15, 17]. The calculation of the score and determination of severity were done by the investigator under the supervision of the psychiatrist.

A semen specimen was provided through masturbation by the patient in a sterile container after 4 days of abstinence from sexual activity, and the specimen was examined in a single lab by a single-blinded investigator. All values were evaluated according to the 2021 WHO criteria. The volume of the semen was determined. The sample was placed in an incubator set at 37℃ and monitored every 15 min for an hour to determine the liquefaction time and viscosity. Using the microscope, at least two slides were examined at magnification powers of 100 and 400. Motility was then evaluated as either rapid progressive, sluggish progressive, non-progressive motility, or the percentage of immotile sperms. In order to calculate the concentration and total sperm count in the ejaculate, a diluted sample of semen was placed in a hemocytometer chamber (Rs' Science, Germany) and the number of sperms per milliliter was calculated. Using a microscope, the proportion of normal morphology, aggregation, and agglutination were also assessed [18].

Patients were treated by SNRIs (venlafaxine 75–150 mg/day, desvenlafaxine 50 mg/day, or duloxetine 60–120 mg/day) according to the American Psychiatric Association practice guidelines 2010 [19]. The drug, dose, and duration of treatment were decided by psychiatry specialists according to each patient's condition.

HAM-D scale was administered once more after a 3-month period, and those who demonstrated improvement in depression score were eligible for the second evaluation of semen (post-improvement); the depressed patients' group who had normal semen first assessment were candidates for the second assessment of semen to

verify the results. Those who did not improve, on the other hand, underwent re-evaluation each month, until a total of 6 months had passed since their participation in the study. In case of improvement, a post-improvement semen analysis would have been performed; otherwise, exclusion from the study would be the decision.

Data were gathered, edited, coded, and entered into IBM SPSS version 23 of the Statistical Package for Social Science. When the quantitative data were parametric, they were displayed as means, standard deviations, and ranges, while non-parametric were displayed as medians and interquartile ranges (IQR). Qualitative variables were also shown as percentages and numbers. When the predicted count in any cell was less than 5, the Fisher's exact test or the chi-square test was used to compare groups with qualitative data. The independent *t* test was used to compare two independent groups with quantitative data and a parametric distribution, while the Mann–Whitney test was used with a non-parametric distribution. Paired *t* test was used to compare quantitative data between two paired groups with parametric distribution, whereas the Wilcoxon rank test was used for non-parametric distribution. In order to evaluate the association between two quantitative parameters belonging to the same group, Spearman correlation coefficients were utilized. The allowable margin of error was set at 5%, while the confidence interval was set at 95%. So, the *p* value was interpreted as the following: $P > 0.05$, non-significant (NS); $P < 0.05$, significant (S); and $P < 0.01$, highly significant (HS).

Results

Demographic data

This study included twenty-one male patients with moderate, severe, or very severe depression, attending the psychiatry OPC of Ain-Shams University Hospitals, from March 2022 till November 2022. Non-compliant patients were excluded, and only sixteen patients completed the study. Their age ranged from 21 to 50 years, with a mean of 32.19 years ± 8.19. Six patients (37.5%) were single, 9 (56.2%) were married with a history of previous pregnancy of wives, and 1 patient (6.2%) was married with no history of previous pregnancy of his wife.

Clinical data

Assessment of depression improvement by HAM-D scale

There was a significant decrease in the HAM-D scale score and severity of depression after treatment by SNRIs in all the sixteen patients. HAM-D score declined from 16.5 (15–22) at baseline down to 9 (6–11) [median (IQR)] post-improvement (P value = 0.000, Wilcoxon-signed rank test). As regards the severity of depression, at baseline, 11 (68.8%) patients had moderate depression, 1 (6.2%) had severe depression, and 4 (25%) had very severe depression. On the final assessment, 7 (43.8%) were cured, 7 (43.8%) had mild depression, and 2 (12.5%) had moderate depression, while no patients had severe or very severe depression (P value = 0.000, chi-square test).

Baseline semen parameters compared to 2021-WHO lower normal limit

The median of baseline semen parameters of patients was within normal levels for semen volume, sperm count, motility, and percentage of sperm normal morphology, according to 2021 WHO criteria, when taken collectively. However, on individual bases, there was a number of patients with abnormal baseline in selective semen parameters (Table 1).

Comparison of semen parameters between baseline and post-improvement in all patients

Semen volume was significantly increased after improvement of depression (1 to 9.5 ml) compared to baseline (0.5 to 5 ml) with a P value of 0.033 (Table 2). There was no significant change in other parameters: sperm aggregation, agglutination, count, motility, spermatogenic cells, and normal morphology percentage after improvement of depression compared to baseline ($P = 0.288$, 0.154, 0.079, 0.145, 0.362, and 0.362, respectively) (Table 2). Although changes were statistically insignificant, some findings, that followed improvement of depression, deserved some attention. The number of patients with

Table 1 Comparison between baseline semen parameters of all patients and 2021-WHO lower limit

Semen analysis	Patients' number		Patients (baseline) Median (IQR)	2021 WHO lower limit
Volume (ml)	7 hypospermia	9 normal	2.25 (1–3.5)	1.4 (1.3–1.5)
Count/ejaculate (million)	5 oligozoospermia	11 normal	88.5 (23.2–159)	39 (35–40)
Progressive motility	5 asthenozoospermia	11 normal	40 (17.5–55)	30 (29–31)
Total motility	7 asthenozoospermia	9 normal	50 (37.5–70)	42 (40–43)
Normal morphology (percent)	0 teratozoospermia	16 normal	65.00 ± 10.95	4 (3.9–4)

Table 2 Comparison of semen parameters between baseline and post-improvement in all patients

Semen analysis		Baseline	Post-improvement	Test value	*P* value	Sig.
Volume (ml)	Median (IQR) Range	2.25 (1–3.5) 0.5–5	2 (2–4.5) 1–9.5	−2.138[b]	0.033	S
Sperm aggregation	Negative Positive	7 (43.8%) 9 (56.2%)	10 (62.5%) 6 (37.5%)	1.129[a]	0.288	NS
Sperm agglutination	Negative Positive	7 (43.8%) 9 (56.2%)	11 (68.8%) 5 (31.2%)	2.032[a]	0.154	NS
Concentration/ml (million)	Median (IQR) Range	29.25 (15.6–89.6) 0.5–166	48.4 (20.75–94.78) 3.2–169	−1.603[b]	0.109	NS
Count /ejaculate (million)	Median (IQR) Range	88.5 (23.2–159) 0.25–451.2	129 (62.35–205.25) 3.2–931	−1.758[b]	0.079	NS
Progressive motility (percent)	Median (IQR) Range	40 (17.5–55) 0–66	45 (37.5–50) 30–60	−1.393[b]	0.163	NS
Total motility (percent)	Median (IQR) Range	50 (37.5–70) 0–80	57.5 (55–62.5) 40–70	1.458[b]	0.145	NS
Spermatogenic cells	Median (IQR) Range	5(3.5–8) 3–15	6 (5–8) 2–20	−0.912[b]	0.362	NS
Normal morphology (percent)	Median ± Range Range	65.00 ± 10.95 45–80	62.19 ± 12.11 35–80	0.940	0.362	NS

P-value > 0.05: Non—significant; *P*-value < 0.05: Significant; *P*-value < 0.01: Highly significant

[a] Chi-square test

[b] Wilcoxon Signed Ranks test

positive sperm aggregation and agglutination decreased from 9 and 9 to 6 and 5, respectively. The median concentration of sperms (million)/milliliters and their count/ejaculate insignificantly increased from 29.25 and 88.5 to 48.4 and 129, respectively. The median of progressive and total sperm motility (%) insignificantly increased from 40 and 50 to 45 and 57.5, respectively.

Comparison of semen parameters between baseline and post-improvement (in patients with abnormal baseline parameters)

Semen volume of the 7 patients with hypospermia was significantly increased from 1 0.5–1 at baseline to 2 (1–2) [median (IQR)] ($P=0.026$, Wilcoxon-signed rank test) (Table 3). Semen count/ejaculate of the 5 patients with

Table 3 Comparison of semen parameters between baseline and post improvement (in patients with abnormal baseline semen parameters)

		Baseline	Post-improvement	Test value	*P* value	Sig.
Volume (ml)						
Median (IQR)		1 (0.5–1)	2 (1–2)	−2.232[a]	0.026	S
Range		0.5–1	1–2			
Count/ejaculate (million)						
Median (IQR)		14.1 (0.95–20.4)	70.5 (41–109.4)	−2.023[a]	0.043	S
Range		0.5–26	3.2–339			
Concentration/ml (million)						
Median (IQR)		0.95 (0.5–6.5)	20.5 (3.2–56.5)	−1.604	0.109	NS
Range		0.5–6.5	3.2–56.5			
Motility (percent)						
Total motility	Median (IQR) Range	35 (5–40) 0–40	55 (50–55) 40–70	−2.375[a]	0.018	S
Progressive motility	Median (IQR) Range	15 (4–15) 0–20	40 (35–40) 30–45	−2.023[a]	0.043	S

P value > 0.05, non-significant; *P value < 0.05*, significant; *P value < 0.01*, highly significant

[*] Chi-square test

[a] Wilcoxon signed-rank test

baseline oligozoospermia was significantly increased from 14.1 (0.95–20.4) at baseline to 70.5 (41–109.4) [median (IQR)] ($P=0.043$, Wilcoxon-signed rank test) (Table 3). There was also an increase in sperm concentration/milliliter among the three patients with baseline oligozoospermia; 0.95 (0.5–6.5) to 20.5 (3.2–56.5) [median (IQR)], but it was not enough to show significance ($P=0.109$, Wilcoxon-signed rank test) (Table 3). Lastly, there was significant increase in total sperm motility among the 7 patients with baseline asthenozoospermia from 35 (5–40) to 55 (50–55) [median (IQR)], and a significant increase in progressive sperm motility among the 5 patients with baseline asthenozoospermia, from 15 (4–15) to 40 (35–40) [median (IQR)] ($P=0.018$, 0.043, respectively, Wilcoxon-signed rank test) (Table 3).

Correlations between semen parameters and HAM-D score

There were insignificant correlations between the HAM-D score and each of the semen parameters (semen volume, sperm concentration/ml, count/ejaculate, progressive and total motility, spermatogenic cells, normal morphology percentage, sperm aggregation, and agglutination) at baseline and after depression improvement among all patients as well as those with abnormal baseline semen parameters ($P>0.05$, Spearman correlation coefficient). On the correlation of change (%) in each of semen parameters against change (%) in the HAM-D scale, between baseline and post-improvement (among all patients as well as those with abnormal baseline semen parameters); similarly, no statistically significant relation was found ($P>0.05$, Spearman correlation coefficient).

Discussion

About 50% of cases of infertility worldwide are caused by the male factor [20]. Pretesticular, testicular, or post-testicular conditions may be the causes. In roughly 30% of cases, it may also be idiopathic [21]. Psychological disorders, especially depression, are reported as essential risk factors responsible for such idiopathic pathogenesis, where HPA and HPG axes, as well as their hormonal influence, may represent the potential link. Additional variables, such as oxidative damage, immunological, and dietary ones, may also have an impact on fertility when depression is present [3, 22].

This study looked into how depression affected semen parameters, which are recognized markers of male fertility. We evaluated patient semen values at baseline and after depressive symptoms had improved. In order to preserve depression as the primary variation during evaluation, we were anxious to rule out other psychiatric diseases as well as other obvious factors that could impair fertility. The study initially included twenty-one subjects. Later, 5 patients were dropped from the trial, leaving just 16 patients, who reacted well to SNRI therapy for their depression, as study participants. Since few other antidepressants have been reported to have an effect on male fertility, SNRIs were chosen as the treatment protocol [7]. To minimize the impact of individual variability, semen samples were evaluated by a single-blinded skilled investigator.

The median baseline parameters of all patients were, unexpectedly, higher than the typical lower limit when compared to 2021 WHO guidelines for semen analysis; this finding may, apparently, suggest an irrelevant link between depression and male fertility. Coward et al. [23] reported a similar finding earlier in 2019. Semen abnormalities were present in a sizable number of patients, including hypospermia in 7 cases, oligozoospermia in 5, and asthenozoospermia in 7. In other words, the calculation of the median for all patients failed to account for the fact that some patients were fertile while others displayed some abnormalities.

All patients' baseline and post-improvement semen metrics could not be significantly different, with the exception of volume. Following up, on related investigations, showed that Yland et al. [24] pointed to a related conclusion in 2021. Interesting contradictory findings were found in other research, ranging from the lack of a relationship between depression and semen parameters as well as hormonal factors [24, 25] to depression having a significant detrimental effect on sperm volume, concentration, count, and motility [2].

Evidently, there is a significant difference among many reports, including ours. It could be attributable to variations in sample sizes, epidemiology, depression subtypes, and treatment methods. We further think that, in some cases, the abnormalities may have been hidden by a few extremely high semen parameter values due to the inherent non-parametric character of the normal ranges for semen parameters. Additionally, it has been shown that the consequences of depression may vary depending on the subtypes, with each one having the ability to have a different impact on the HPA axis through either activation or inhibition [26].

Our study's observation of a considerable increase in semen volume supports the hormonal component as the primary mechanism by which depression affects male fertility [3]. Higher semen volume can be attained, according to Zitzmann et al. [27], by prolonging the period of abstinence or by hormonally stimulating the activity of the accessory glands. The fact that the abstinence duration for every patient remained constant throughout our research suggests the hormonal aspect as the primary mechanism, through which, a reduction in depression may have caused the deleterious effects on the HPA and HPG axes to be reversed. Since depression did

not appear to have as much of an effect on other indicators as it did on volume, we may assume that hormonal factors are the primary causal factor. However, we believe that further advancements in semen parameters may have gone unnoticed due to the non-parametric data in the limited sample size [28].

To overcome this limitation, we first performed the comparisons with just patients who had aberrant baseline semen values to remove the neutralizing influence of patients with normal baseline semen parameters. Interestingly, after receiving treatment for depression, significant improvements were seen in the majority of semen characteristics. Semen volume, sperm count per ejaculation, and the percentage of sperm motility, either total or progressive, all showed improvements. These results were crucial in helping us to understand how depression affects male infertility, which was our major research issue. The conversion of earlier described hypotheses into statistically significant verified clinical data is an essential step. When only individuals with baseline hypospermia were included in the comparison, the significance of improvement in semen volume increased, as was expected [3]. When only patients with baseline oligozoospermia were included in the comparison, the increase in sperm concentration per ejaculation proved to be substantial. The hormonal axis' and the amount of reactive oxygen species (ROS)' detrimental effects on depression may have been reversed [29]. Relief from depression-induced oxidative stress, which is known to result in sperm mitochondrial malfunction, may be the reason of a significant improvement in sperm motility [6].

It has been found that none of the correlation tests was able to find any relevance. There may have been a number of contributing factors, but it is hard to identify them without first making sure that the sample size is enormous enough to balance out the unavoidable effects of the non-parametric character of the ranges of semen parameters. To achieve this goal within a constrained study time, multi-center collaboration may be necessary. Longer follow-up duration should also be taken into consideration. We recommend in-depth studies including measurement of different hormonal profiles to clarify the details of the relationship between depression and male infertility.

Conclusion

Through this preliminary investigation, we suggested that a notable impact of depression on male fertility. Such an effect is neither sole nor direct, and in order to be felt, it may either require the presence of co-factors or predisposed individuals. Infertile males who receive appropriate treatment for depression may have considerable changes in most semen metrics, such as semen volume, sperm count per ejaculation, and percentage of progressive or total sperm motility. Without the need to hurry into assisted reproductive technologies and other expensive infertility treatment modalities, appropriate psychotherapy should be incorporated into the early infertility treatment protocols for patients with depression.

Abbreviations

HPG	Hypothalamic-pituitary–gonadal axis
DHEA-S	Dehydroepiandrosterone sulfate
SNRIs	Serotonin and norepinephrine reuptake inhibitors
SCID-I	Structured Clinical Interview for DSM-IVTM axis I disorders Hamilton Depression
Ham-D 17	Hamilton Depression Scale
SD	Standard deviation

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Authors' contributions

Conceptualization: E.A.E., R.M.E, and P.F.E. Methodology: N.M.S.M, R.M.E, and P.F.G. Validation: E.A.E. and R.M.E. Formal analysis: N.M.S.M. Investigation: N.M.S.M., E.A.E., R.M.E, and P.F.E. Data curation: N.M.S.M., E.A.E., R.M.E, and P.F.E. Writing–original draft: P.F.E. Writing–review and editing, all authors. Visualization: P.F.G. Supervision: E.A.E., R.M.E, and P.F.E.

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Availability of data and materials

All generated or analyzed data during this study are included in the published work.

Declarations

Ethics approval and consent to participate

The study was approved by the research ethics committee of the Faculty of Medicine, Ain Shams University (FWA 000017585).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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