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Impact of Selective Serotonin Reuptake Inhibitor on Male Infertility: A Retrospective Pilot Study

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Abstract: Background: Multiple factors cause male infertility. To date, there is insufficient data to support claims that selective serotonin reuptake inhibitors (SSRIs) affect the effectiveness of infertility treatments or decrease fertility. This study aimed to determine the feasibility of male infertility caused by SSRI antidepressants. **Methods:** This study was a retrospective chart review of Saudi males who are currently or previously treated with SSRIs and attended infertility clinics in KSMC. Medical records of men in an infertility clinic were reviewed to screen the quality of sperm parameters in patients taking SSRIs. **Results:** In total, 299 men were identified, of whom 29 (9.6%) were exposed to SSRIs, while 270 (90.4%) did not receive SSRIs, defined as the control infertile group. There was a significant difference between the non-SSRI group (34.2 ± 6.9 years) and SSRI group (41.5 ± 3.2 years), $p < 0.001$. Regarding sperm analysis and the use of SSRIs, the impact of SSRIs use showed no significant differences in sperm liquefaction ($p = 0.1$), motility ($p = 0.17$), viscosity ($p = 0.16$), and sperm count ($p = 0.069$) with escitalopram, fluoxetine, and paroxetine use. **Conclusion:** SSRI medication use and the likelihood of developing infertility require larger prospective trials.

Keywords: antidepressants; infertility; males; semen quality; SSRIs

1. Introduction

Infertility is an essential concern for couples of childbearing age. It is a disease of the reproductive system defined by the International Committee for Monitoring Assisted Reproductive Technology (ART) and the World Health Organization (WHO), as the failure to achieve a clinical pregnancy after 12 months or more of regular, unprotected sexual intercourse. The WHO, in conjunction with ART, first listed infertility as a disease in the "International Glossary of ART Terminology "[1].

Infertility is a global issue that affects the quality of life and public healthcare and has psychological, financial, and medical consequences [2]. According to recent statistics collected worldwide, approximately 15% of couples who are of childbearing age of both genders are infertile [3]. However, Ombelet et al. revealed that infertility rates could approach 30% in some people in various regions of the world [4]. The prevalence of infertility in Saudi Arabia is approximately 18.93% [5]. However, the absence of an established definition of infertility results in varying estimates of the prevalence of infertility within and among populations. This could be due to the heterogeneous, nature of the sampled populations, or the denominator used to calculate the prevalence [6]. Unexplained infertility is a term that has been applied to as many as 30%–40% of infertile couples and usually refers to a diagnosis or lack of diagnosis made in couples in whom all the standard investigations, such as tests of ovulation, tubal patency, and semen analysis, are normal [7]. Infertility can lead to anxiety and depression and negatively affect relationships between couples [8]. According to recent studies, infertile couples experience higher stress levels than fertile couples. Additionally, stress is known to negatively affect the reproductive system [9,10]. Male infertility is a global health issue; according to Macarenas et al., at least 30 million men worldwide are infertile, with the highest

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rate in Africa and Eastern Europe [11]. However, the magnitude and prevalence of male infertility in Saudi Arabia have not been fully investigated.

Male infertility is characterized by abnormal semen parameters. Hence, semen analysis is the cornerstone of laboratory evaluation of infertile males [12]. Semen analysis remains the single most useful fundamental investigation; with a sensitivity of 89.6% it can detect nine out of 10 men with a genuine problem [13].

Other lifestyle and environmental factors, such as exposure to pesticides and heavy metals, cause infertility [14]. Furthermore, drugs and medications can influence male fertility by affecting spermatogenesis and sexual dysfunction. Notably, this may be through four basic mechanisms, including the direct gonadotrophic effect, alteration of the hypothalamic-pituitary-gonadal (HPG) axis, impairment of ejaculation, erectile dysfunction, and adverse effects on libido [15]. For example, gonadotoxins, such as chemotherapeutic agents, can directly damage germ cells in the testes, and increase chromatin damage in the sperm, or inhibit the function of the supporting sertoli cell and, thus, testosterone production. These agents often cause severe depression or absence of sperm production or may be associated with suboptimal but reversible sperm maturation, motility, or morphology [16]. In addition, testosterone replacement therapy and anabolic steroids have a strong deleterious effect on sperm production; they alter the feedback mechanism on the HGP axis [17]. There are various medications with varying degrees of side effects on the male reproductive system. However, they were not discussed here because they were beyond the scope of this study. Here, we focused on and 2limited the discussion to the effects of anti-depressive medications that may be associated with male infertility, especially selective serotonin reuptake inhibitors (SSRIs). Concerning depressive disorders, according to the National Institute of Mental Health in the USA 2020, it is estimated that the prevalence of adults with a major depressive episode was highest among individuals aged 18–25 years, approximately 17.0% [18]. According to recent statistics, the prevalence of adults with depression in the Kingdom of Saudi Arabia was 32% [19]. The general pattern of antidepressants used in Saudi Arabia is approximately 41.4%; the pattern of SSRI antidepressants used is approximately 37.7%; other classes of antidepressants are 18.8%; and tricyclic antidepressants are 8.8% [20].

SSRIs, including citalopram, escitalopram, fluvoxamine, paroxetine, fluoxetine, and sertraline, prevent serotonin reuptake. Currently, these drugs are the first-line therapies for anxiety and depressive disorders. However, SSRIs are particularly linked to serious adverse sexual effects, such as reduced libido, prolonged ejaculatory interval, circulation of erectile dysfunction, and hormones. Research suggests that 25%–73% of patients using an SSRI will have some sexual dysfunction that is more severe than that caused by other antidepressants [21]. Recently reviewed research has proven that SSRIs have a detrimental effect on semen quality in in vitro, animal, and human investigations. Fluoxetine has been the focus of reduced fertility and has been linked to gonadotoxic consequences in several studies by enhancing sperm concentration and motility, fragmentation of deoxyribonucleic acid, and reduced weights of the reproductive organs. Research on many alternative SSRIs has shown comparable outcomes [22]

In conclusion, this study aimed to examine the prevalence of SSRI use and semen quality in infertility clinics in Saudi Arabia. This may contribute to the provision of better medical and reproductive advice regarding SSRIs use in males.

2. Methodology

2.1. Study design

This observational cross-sectional retrospective study reviewed all men's medical records who underwent semen analysis (SA) for fertility evaluation at King Saud Medical City (KSMC). We considered all the participants' information that matched the inclusion criteria. This study used data collected from January 2014 to December 2020. This observational study was guided by the Strengthening the Reporting of Observational Studies in Epidemiology Checklist.

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2.2. Setting

The research setting for this study was KSMC, a tertiary hospital in Riyadh City, which is part of the Ministry of Health in Saudi Arabia. Patients were enrolled from fertility clinics in both outpatient clinics. The clinic for newly diagnosed patients was held 2 days per week on average and received four to eight patients per day. Therefore, the expected total number of patients visiting the clinic was approximately 16.

2.3. Participants

This study included all patients who visited the fertility clinic. For inclusion, the participants were adult males aged 26 years and older, in good medical health, and had at least one semen sample analyzed. Participants using an SSRI class (including citalopram, escitalopram, fluvoxamine, paroxetine, fluoxetine, and sertraline) were compared with participants who did not use SSRIs. The exclusion criteria included male patients diagnosed with infertility due to other problems unrelated to low sperm count, patients who are known or suspected to have any disease-causing hyperprolactinemia such as hypothalamic-pituitary disease and tumors, patients who were taking medications that influence serotonin receptors other than antidepressants, and patients who had prior exposure to spermatotoxic medications, clomiphene citrate, gonadotropins, and selective estrogen receptor modulators.

2.4. Variables, data source, and measurements

The participants' data were gathered from medical records under the supervision of a consultant, and all information was collected on a predesigned data collection sheet. The data collection sheet was divided into three sections. The first part concerned participants' demographic data, such as age, education level, current occupation, marital status, number of family members, medical and medication history, and smoking status. The second section contained information on the use of SSRIs, such as drug name, drug dose, frequency, and duration of treatment. The final part of the sheet contained semen analysis information, including physical examination parameters such as volume, color, viscosity, and liquefaction time. Semen analysis included a microscopic examination of motility and morphology. Semen analysis included a total sperm count.

The semen quality of the samples was interpreted according to the Sixth Edition of the WHO Manual for Human Semen Analysis [23].

2.4.1. Macroscopic Examination

- Volume: The lower reference limit of semen volume for normal results is 1.5 mL.Low semen volume may indicate pathological conditions or collection problems. An excess fluid volume could also indicate that the amount of sperm present is diluted.
- Color: The normal color of semen is whitish to gray. Semen with a red-brown appearance possibly indicates the presence of blood, whereas a yellow color might indicate jaundice or could be a side effect of medications.
- Liquefaction: It takes 15–30 min for semen to liquefy. While semen is initially thick, its ability to liquefy or turn to a watery consistency helps the sperm move. If semen does not liquefy within 60 min, fertility can be affected.
- Viscosity: Normal semen sample viscosity shows small discrete drops when it leaves the pipette. High-viscosity semen can affect sperm motility and concentration.

2.4.2. Microscopic examination

- Sperm movement, or motility, is important for fertility because sperm must travel to fertilize eggs. The lower reference range for total motility is 42%.
- Sperm progression is categorized into:

1. Progressive motility (PR): Active sperm movement is classified as rapid or slow. The lower reference range for progressive motility (PR) is 30%.

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2. Total motile sperm count: This provides the total number of spermatozoa per ejaculate by multiplying the sperm count by the total ejaculation volume. The lower reference range for the total sperm count is 39 million spermatozoa per ejaculate.

- The sperm morphology is classified as normal or abnormal. Morphologically abnormal spermatozoa are categorized according to sperm defects such as head, neck, midpiece, and principal piece defects. The lower reference range for normal form is 4%. Low-normal sperm morphology can reduce fertility.
- Sperm count: The lower reference range for sperm count is 15 million spermatozoa/mL.

2.5. Bias

All participants attending infertility clinics during the study period were included.

2.6. Statistical analysis

The data were analyzed using the IBM Statistical Package for Social Sciences version 26 (2019, Armonk, NY: IBM Corp.) and presented as mean (standard deviation) or median (interquartile range) for continuous variables and numbers and (percentages) for categorical variables. A bivariate analysis was performed to explore the differences between patients receiving SSRIs and those not receiving SSRIs in terms of age, smoking status, medical history, and semen analysis. The significance level of the results was set at $p < 0.05$. Binary logistic regression was performed to predict factors contributing to infertility concerning SSRI use.

3. Results

A total of 299 men were identified, of whom 29 (9.6%) were exposed to SSRIs while, 270 (90.4%) did not receive SSRIs, defined as the control infertile group. When comparing the results to the mean age group, there was a significant difference between the control infertile men group (34.2 ± 6.9 years) and the infertile group using SSRIs (41.5 ± 3.2 years), p < 0.001. Most patients in the control group (n = 168) (62.4%) were nonsmokers, and approximately half of infertile patients who used SSRIs were similarly nonsmokers (n = 14) (48.2%), with no significant difference (p = 0.144). The difference in SSRI use between the control group and infertile men on SSRIs becomes significant when compared with the mean liquefaction time (p = 0.028). Moreover, there was a significant difference in the mean motility (p = 0.034) between the infertile group on SSRI use and control patients. Regarding semen analysis, macroscopic examination showed that none of the collected samples were statistically significant for either group (p = 0.3) (Table 1).

Table 1. baseline characteristics of participants with differences between participants receiving SSRI and non-SSRIs.

		Using SSRIs N=29	%, SD, IQR	Non-SSRIs N=270	%, SD, IQR	Total N=299	%, SD, IQR	P value
Age, years, mean (SD)		41.52	3.28	34.20	6.93	34.91	7.00	<0.001*
Smoking, N (%)	No	14	7.7	168	92.3	182	60.9	0.144
	Yes	15	12.8	102	87.2	117	39.1	
Viscosity, n (%)	Normal	15	12.4	106	87.6	121	40.5	0.197
	Slightly viscous	8	11.3	63	88.7	71	23.7	
	Highly viscous	6	5.6	101	94.4	107	35.8	
Liquefaction, N (%)	Less than 30 min	3	17.6	14	82.4	17	5.7	0.028*
	30-60 min	17	14.2	103	85.8	120	40.1	

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	More than 60 min	9	5.6	153	94.4	162	54.2	
Motility, mean (SD)		47.93	11.84	39.55	20.79	40.37	20.23	0.034*
Sperm count, median (IQR)		20.00	15.00–55.00	29.85	25.00–35.00	28.80	24.30–33.75	0.300

*Significant according to a p-value <0.050; SSRIs, selective serotonin reuptake inhibitors; SD, standard deviation; IQR, upper and lower interquartile range.

For more exploration, regarding the correlation between the age group and the use of SSRIs through odds ratio analysis, the result displayed a significant association ($p < 0.001$) with an odds ratio equal to 1.12 (95% confidence interval [C.I] 1.069−1.188) that indicates patients on SSRIs were older than 40 years, while non-SSRI patients were approximately 35 years. In addition, the correlation between the use of SSRIs and sperm motility was statistically significant ($p < 0.0036$). The result revealed that the odd ratio equal to 1.022 for patients not receiving SSRIs was associated with low motility (less than 40%) (95 % C.I 1.001−1.042). However, among participants who received SSRIs, the odds of liquefication time of more than 60 min were 0.2 times lower than those in the control group, as indicated by an odds ratio of 0.2 (95% CI: 0.067−1.132) (Table 2).

Table 2. Baseline characteristics and infertility-related information stratified by SSRI medication.

		Escitalopram N=11	**%, SD, IQR**	**Paroxetine N=7**	**%, SD, IQR**	**Fluoxetine N=11**	**%, SD, IQR**	**Total N= 29**	**%, SD, IQR**	**P value**
Age, mean (SD)		40.55	3.24	41.71	3.35	42.36	3.32	41.52	3.28	0.438
Smoking, N (%)	No	4	28.6	3	21.4	7	50.0	14	48.3	0.418
	Yes	7	46.7	4	26.7	4	26.7	15	51.7	
Dose, N (%)	10 mg	2	40.0	0	0.0	3	60.0	5	17.2	0.583
	20 mg	7	36.8	5	26.3	7	36.8	19	65.5	
	40 mg	2	40.0	2	40.0	1	20.0	5	17.2	
Frequency, N (%)	OD	9	39.1	4	17.4	10	43.5	23	79.3	0.219
	BID	2	33.3	3	50.0	1	16.7	6	20.7	
Duration of use, N (%)	Less than 2 years	4	50.0	2	25.0	2	25.0	8	27.6	0.101
	2-5 years	3	20.0	3	20.0	9	60.0	15	51.7	
	More than 5 years	4	66.7	2	33.3	0	0.0	6	20.7	
Viscosity, N (%)	Normal	7	46.7	4	26.7	4	26.7	15	51.7	0.167
	Slightly viscous	3	37.5	0	0.0	5	62.5	8	27.6	
	Highly viscous	1	16.7	3	50.0	2	33.3	6	20.7	
Liquefaction time, N (%)	<=30 min	3	100.0	0	0.0	0	0.0	3	10.3	0.100
	30-60 min	6	35.3	3	17.6	8	47.1	17	58.6	
	>60 min	2	22.2	4	44.4	3	33.3	9	31.0	
Motility, mean (SD)		44.55	11.93	45.00	12.25	53.18	10.55	47.93	11.84	0.177

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Sperm count, median (IQR)	20.00	15.00–45.00	10.00	4.00–60.00	44.00	13.00–90.00	20.00	15.00–55.00	0.069

*Significant according to a p-value <0.050; SSRIs, selective serotonin reuptake inhibitors; SD, standard deviation; IQR, upper and lower interquartile range; mg, milligrams; OD, once daily; BID, twice a day.

For the infertile group who received SSRI treatment (n = 29), the most frequently prescribed SSRIs were escitalopram (n = 11, 37.9%) and fluoxetine (n = 11, 37.9%), followed by paroxetine n = 7 (24.1%). When comparing the results to the mean age group, there was no significant difference among all SSRIs (p = 0.438). Correspondingly, there was no significant difference in the mean SSRI frequency or treatment duration (p = 0.21). The impact of SSRI use showed no significant differences in sperm liquefaction (p = 0.1), motility (p = 0.17), viscosity (p = 0.16), and sperm count (p = 0.069) with escitalopram, fluoxetine, or paroxetine use (Table 3).

Table 3. Odds ratio of participants receiving SSRI with regards to sperm characteristics.

	B	**S.E.**	**p-value**	**Odds ratio**	**95% C.I.**
Age	0.119	0.027	<0.001*	1.127	1.069–1.188
Motility	0.021	.010	0.036*	1.022	1.001–1.042
Liquification 30-60 min	-0.261	0.688	0.704	0.770	0.200–2.966
Liquification >60 min	-1.293	0.723	0.074	0.275	0.067–1.132
	B	**S.E.**	**p-value**	**Adjusted£ odds ratio**	**95% C.I.**
Motility	0.024	0.011	0.029*	1.025	1.002–1.047
Liquification 30-60 min	0.072	0.725	0.921	1.075	0.260–4.450
Liquification >60 min	-1.102	0.761	0.148	0.332	0.075–1.476

£ adjusted for age; *significant at p <0.050.

4. Discussion

To the best of our knowledge, this is the first study to assess the incidence of infertility in Saudi males who are currently or were previously treated with SSRIs. In addition, we considered confounding variables that may contribute to the risk of male infertility, such as patient age, medication preference, and smoking status. Generally, the study stated that the incidence of Saudi male infertility in infertility clinics is approximately 10%, regardless of the use of SSRIs, compared to global male infertility. [24]

This study showed that there was no significant change in sperm analysis between the use of SSRIs and non-SSRIs. In contrast, a meta-analysis showed that SSRIs negatively affected semen quality [25].

In our study, the most prescribed SSRIs were escitalopram, fluoxetine, and paroxetine, with no significant impairment in semen counts in the mean age group > 40 years. In a prospective study conducted in 2010, Tanrikut et al. examined the adverse effects of paroxetine on semen parameters and sperm DNA fragmentation. This study included 35 healthy male volunteers with a mean age of 34 years. Their semen parameters were normal, the DNA fragmentation was normal, and the baseline initially was 13.8%. These men were administered a therapeutic dose of paroxetine, and semen analysis with DNA fragmentation was performed after 5 weeks of paroxetine administration. Tanrikut et al. concluded that there was a significant increase in DNA fragmentation by 30.3% versus 13.8% before treatment. However, there was no significant change in the semen parameters. The authors affirmed that the impairment of sperm transport may alter sperm DNA integrity without affecting semen parameters. Furthermore, they suggested that male fertility could be attributed to increased DNA fragmentation rather than semen quality [26]. In contrast, a study conducted by

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Safarinejad observed a negative effect of SSRIs on semen quality in terms of sperm count, sperm motility, and morphology during a long duration of treatment [27].

Furthermore, in 2011, Koyuncu et al. conducted a prospective study on 25 men with normal semen analysis, hormones, and normal physical examination; the mean age was 32.84 ± 4.4 years, and all were using escitalopram for primary premature ejaculation. Although Citalopram improved the physical examination, there were adverse effects on sperm quality: decreased sperm counts (26.4%*106/mL vs. 68.9*106/mL), motility (23.4% vs. 58.2%), and morphology (7.3% vs. 19.2%) after 3 months of being on treatment [28].

4.1. Study strengths and limitations

The strength of this study is that it is a collaborative study that involves experts from infertility clinics and pharmacists to conduct comprehensive and well-rounded research, owing to the application of multidisciplinary collaboration. Our study has practical significance in that it provides insights into the use of SSRIs in policy, practice, and future research regarding male infertility. However, our study has some limitations, including its cross-sectional design, which only provides a snapshot of data at a single point in time, making it difficult to establish causality. Therefore, a longitudinal study is often needed to assess the cause-and-effect relationships between the use of SSRIs and semen analysis. Correspondingly, the researcher faced a challenge during the data collection process, and the information was missed from an electronic record, as the system in the infertility clinic was manually processed and most of the data entered into the system were incomplete, forcing the researcher to refer to the patients' files and review the data manually. Consequently, the sample size of patients taking SSRIs was small, which may limit the generalizability of the findings. Moreover, the smaller sample size in our study led to lower statistical power and made it challenging to accurately detect significant effects or associations between the use of SSRIs and semen analysis.

5. Conclusion

In conclusion, the relationship between SSRI use and sperm count warrants further investigation and consideration in clinical practice. Although some studies have suggested an association between SSRI use and reduced sperm count, the clinical significance of these findings remains uncertain. The effect of SSRIs on male reproductive health appears to vary among individuals and may depend on various factors. Therefore, further research is required to better understand the effects of male exposure on semen parameters. Hence, further studies are required before drawing clinical conclusions.

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Informed Consent Statement: According to IRB, consent was waived due to the nature of the study. No patient identifiers were collected to ensure confidentiality.

Data Availability Statement: all data was presented in this paper

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References

1. Zegers-Hochschild, F.; Adamson, G. D.; de Mouzon, J.; Ishihara, O.; Mansour, R.; Nygren, K.; Sullivan, E.; Vanderpoel, S.; International Committee for Monitoring Assisted Reproductive Technology; World Health Organization. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary of ART Terminology, 2009. *Fertil. Steril.* **2009**, *92* (5), 1520–1524. DOI: 10.1016/j.fertnstert.2009.09.009
2. Jafari, H.; Mirzaiinajmabadi, K.; Roudsari, R. L.; Rakhshkhorshid, M. The Factors Affecting Male Infertility: A Systematic Review. *Int. J. Reprod. Biomed.*; Research and Clinical Center for Infertility **2021**, *19* (8), 681–688. DOI: 10.18502/ijrm.v19i8.9615
3. Centers for Disease Control and Prevention. *National Public Health Action Plan for the Detection, Prevention, and Management of Infertility*, 2014.
4. Ombelet, W. Global Access to Infertility Care in Developing Countries: A Case of Human Rights, Equity and Social Justice. Internet. *Facts Views Vis. Obgyn* **2011**. http://www.thewalkingegg.com, 3 (4), 257–266.
5. Al-Turki, H. A. Prevalence of Primary and Secondary Infertility from Tertiary Centers in Eastern Saudi Arabia. *Middle East Fertil. Soc. J.* **2015 December 1**, *20* (4), 237–240. DOI: 10.1016/j.mefs.2015.02.001
6. Gurunath, S.; Pandian, Z.; Anderson, R. A.; Bhattacharya, S. Defining Infertility-A Systematic Review of Prevalence Studies. *Hum. Reprod. Update* **2011**, *17* (5), 575–588. DOI: 10.1093/humupd/dmr015
7. Ray, A.; Shah, A.; Gudi, A.; Homburg, R. Unexplained Infertility: An Update and Review of Practice. *Reprod. Biomed. Online* **2012 June**, *24* (6), 591–602. DOI: 10.1016/j.rbmo.2012.02.021
8. Cserepes, R. E.; Kollár, J.; Sápy, T.; Wischmann, T.; Bugán, A. Effects of Gender Roles, Child Wish Motives, Subjective Well-Being, and Marital Adjustment on Infertility-Related Stress: A Preliminary Study with a Hungarian Sample of Involuntary Childless Men and Women. *Arch. Gynecol. Obstet.* **2013 October**, *288* (4), 925–932. DOI: 10.1007/s00404-013-2835-7
9. Rooney, K. L.; Domar, A. D. The Relationship Between Stress and Infertility. *Dial. Clin. Neurosci.* **2018 March 1**, *20* (1), 41–47. DOI: 10.31887/DCNS.2018.20.1/klrooney
10. Vellani, E.; Colasante, A.; Mamazza, L.; Minasi, M. G.; Greco, E.; Bevilacqua, A. Association of State and Trait Anxiety to Semen Quality of In Vitro Fertilization Patients: A Controlled Study. *Fertil. Steril.* **2013**, *99* (6), 1565–1572. DOI: 10.1016/j.fertnstert.2013.01.098
11. Mascarenhas, M. N.; Cheung, H.; Mathers, C. D.; Stevens, G. A. Measuring Infertility in Populations: Constructing a Standard Definition for Use with Demographic and Reproductive Health Surveys. *Popul. Health Metr.* **2012 August 31**, *10* (1), 17. DOI: 10.1186/1478-7954-10-17
12. Pourmasumi, S.; Tabibnejad, N.; Reza Talebi, A.; Talebi, A. R. The Etiologies of Sperm DNA Abnormalities in Male Infertility: An Assessment and Review. *Int. J. Reprod. Biomed.* **2017**, *15*.
13. Pandruvada, S.; Royfman, R.; Shah, T. A.; Sindhwani, P.; Dupree, J. M.; Schon, S.; Avidor-Reiss, T. Lack of Trusted Diagnostic Tools for Undetermined Male Infertility. *J. Assist. Reprod. Genet.* **2021**, 38 (2), 265–276. DOI: 10.1007/s10815-020-02037-5
14. Kolesnikova, L. I.; Kolesnikov, S. I.; Kurashova, N. A.; Bairova, T. A. Causes and Factors of Male Infertility. *Vestn. Ross. Akad. Med. Nauk* **2015**, *70* (5), 579–584. DOI: 10.15690/vramn.v70.i5.1445
15. Brezina, P. R.; Yunus, F. N.; Zhao, Y. Effects of Pharmaceutical Medications on Male Fertility. *J. Reprod. Infertil.* **2012**, *13* (1), 3–11.
16. O'Flaherty, C.; Hales, B. F.; Chan, P.; Robaire, B. Impact of Chemotherapeutics and Advanced Testicular Cancer or Hodgkin Lymphoma on Sperm Deoxyribonucleic Acid Integrity. *Fertil. Steril.* **2010 September**, *94* (4), 1374–1379. DOI: 10.1016/j.fertnstert.2009.05.068
17. Semet, M.; Paci, M.; Saïas-Magnan, J.; Metzler-Guillemain, C.; Boissier, R.; Lejeune, H.; Perrin, J. The Impact of Drugs on Male Fertility: A Review. *Andrology*; Blackwell Publishing Ltd **2017**, *5* (4), 640–663. DOI: 10.1111/andr.12366
18. Luis, G. R.; Alejandro, P. S.; Henry, D.; Nelson, A. G.; Jorge, A. C. Prevalence and Correlates of Major Depressive Disorder: A Systematic Review. *Braz. J Psychiatry* **2020**, *42* (6), 657–672. DOI: 10.1590/1516-4446-
19. AlYousefi, N. A.; AlRukban, M. O.; AlMana, A. M.; AlTukhaim, T. H.; AlMeflh, B. A.; AlMutairi, Y. O.; AlMogheer, O. S. Exploring the Predictors of Depression Among Saudi Adolescents: Time for Urgent Firm Actions. *Saudi Med. J.* **2021 June 1**, *42* (6), 673–681. DOI: 10.15537/smj.2021.42.6.20200790
20. Alosaimi, F. D.; Alhabbad, A.; Abalhassan, M. F.; Fallata, E. O.; Alzain, N. M.; Alassiry, M. Z.; Haddad, B. A. Patterns of Psychotropic Medication Use in Inpatient and Outpatient Psychiatric Settings in Saudi Arabia. *Neuropsychiatr. Dis. Treat.* **2016 April 19**, *12*, 897–907. DOI: 10.2147/NDT.S100405

21. Higgins, A.; Nash, M.; Lynch, A. M. Antidepressant-Associated Sexual Dysfunction: Impact, Effects, and Treatment. *Drug Healthc. Patient Saf.* **2010**, *2*, 141–150. DOI: 10.2147/DHPS.S7634
22. Beeder, L. A.; Samplaski, M. K. Effect of Antidepressant Medications on Semen Parameters and Male Fertility. *Int. J. Urol.*; Blackwell Publishing **2020**, *27* (1), 39–46. DOI: 10.1111/iju.14111
23. Boitrelle, F.; Shah, R.; Saleh, R.; Henkel, R.; Kandil, H.; Chung, E., et al. *Life*, 6th ed. of the WHO Manual for Human Semen Analysis: A Critical Review and SWOT Analysis; Vol. 11; MDPI, 2021.
24. Agarwal, A.; Mulgund, A.; Hamada, A.; Chyatte, M. R. A Unique View on Male Infertility Around the Globe. *Reprod. Biol. Endocrinol.* **2015 December 12**, *13* (1), 37. DOI: 10.1186/s12958-015-0032-1
25. Xu, J.; He, K.; Zhou, Y.; Zhao, L.; Lin, Y.; Huang, Z.; Xie, N.; Yue, J.; Tang, Y. The Effect of SSRIs on Semen Quality: A Systematic Review and Meta-analysis. *Front. Pharmacol.* **2022**, *13*, 911489. DOI: 10.3389/fphar.2022.911489
26. Tanrikut, C.; Feldman, A. S.; Altemus, M.; Paduch, D. A.; Schlegel, P. N. Adverse Effect of Paroxetine on Sperm. *Fertil. Steril.* **2010 August 1**, *94* (3), 1021–1026. DOI: 10.1016/j.fertnstert.2009.04.039
27. Safarinejad, M. R. Sperm DNA Damage and Semen Quality Impairment After Treatment with Selective Serotonin Reuptake Inhibitors Detected Using Semen Analysis and Sperm Chromatin Structure Assay. *J. Urol.* **2008 November 1**, *180* (5), 2124–2128. DOI: 10.1016/j.juro.2008.07.034
28. Martin-Tuite, P.; Shindel, A. W. Management Options for Premature Ejaculation and Delayed Ejaculation in Men. *Sex. Med. Rev.* **2020 July 1**, *8* (3), 473–485. DOI: 10.1016/j.sxmr.2019.09.002