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Brief Report / Kısa Araştırma

Reproductive and Sexual Functions in Bipolar Patients: Data from a Specialized Mood Disorder Clinic

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ABSTRACT

Reproductive and sexual functions in bipolar patients: data from a specialized mood disorder clinic

Objective: The objective of this study is to investigate the reproductive characteristics and sexual functions in bipolar patients monitored in a specialized mood disorder clinic, identify their potential relationship with the use of psychotropics, and investigate gender differences.

Method: The study included 193 patients (100 men, 93 women) with a DSM-IV diagnosis of bipolar disorder being followed at Ege University Affective Disorders Outpatient Unit. Reproductive characteristics of the patients were examined at the evaluation. Sexual dysfunctions were evaluated using the International Index of Erectile Function in men and Arizona Sexual Experience Scale in women.

Results: There was no significant difference between men and women regarding age, duration of marriage, duration of illness, duration of mood stabilizer and antipsychotic drugs use and dosage of antipsychotic drugs. Age at pubarche in men was 13.8±1.2 years, age at menarche in women was 13.2±1.3 years. Current menstrual cycle irregularities were found in 15.1% (n=14) of women. Prevalence of lifetime menstrual irregularities was 38.7% (n=36). 60.4% (n=67) of patients having an active sexual life were using an effective contraception method. 31.7% (n=26) of female patients had sexual dysfunction whilst 52% (n=39) of male patients had erectile dysfunction. In both men and women, no significant difference was found between groups using mood stabilizers and antipsychotic drugs in terms of sexual dysfunction. There was no correlation between sexual function scores and usage and duration of mood stabilizers and antipsychotic drugs in either sex.

Conclusions: This cross-sectional study with a relatively large bipolar sample group concluded that the patients' reproductive and sexual functions were not as much affected by bipolar disorder and psychotropic drug use as had been assumed. However, these results should be supported with prospective and controlled trials.

Keywords: Bipolar disorder, reproductive functions, sexual functions

ÖZET

Bipolar bozukluk tanılı hastalarda üreme ve cinsel işlevler: Uzmanlaşmış bir duygudurum bozuklukları kliniği verileri

Amaç: Bu çalışmanın amacı, bir duygudurum bozuklukları kliniğinde izlenmekte olan bipolar hastalarda üreme özellikleri ve cinsel işlevleri araştırmak, psikotrop kullanımı ile olası ilişkiyi belirlemek ve cinsiyetler arası farkları incelemektir.

Yöntem: Ege Üniversitesi Affektif Hastalıklar Birimi'nde izlenen DSM-IV'e göre bipolar bozukluk tanılı toplam 193 hasta (100 erkek, 93 kadın) çalışmaya dahil edildi. Yapılan değerlendirmede hastaların üreme özellikleri sorgulandı. Cinsel işlevler, erkeklerde Ereksiyon İşlevi Uluslararası Değerlendirme Formu, kadınlarda Arizona Cinsel Yaşantılar Ölçeği kullanılarak değerlendirildi.

Bulgular: Kadın ve erkek hastalar arasında yaş, evlilik süresi, hastalık süresi, duygudurum dengeleyici (DD) ve antipsikotik (AP) ilaç kullanımı süresi ve AP kullanım dozu açısından anlamlı fark yoktu. Erkeklerde pubarş yaşı 13.8±1.2, kadınlarda menarş yaşı 13.2±1.3'tü. Halihazırda adet düzensizliği kadınların %15.1'inde (n=14) mevcuttu. Yaşam boyu adet düzensizliği yaygınlığı %38.7 (n=36) idi. Aktif cinsel yaşantısı olan hastaların %60.4'ü (n=67) etkin bir doğum kontrol yöntemi kullanıyordu. Kadın hastaların %31.7'sinde (n=26) cinsel işlev bozukluğu, erkek hastaların %52'sinde (n=39) erektil işlev bozukluğu saptandı. Her iki cinsiyette cinsel işlev bozukluğu açısından DD ve AP kullanımı olan gruplar arasında anlamlı farklılaşma saptanmadı.

Sonuç: Kesitsel desendeki bu çalışmada, göreli büyük bir bipolar örneklem grubunda, hastaların üreme ve cinsel işlevler açısından, hastalık ve ilaç tedavisinden sanıldığı kadar yaygın etkilenmediği sonucuna ulaşılmıştır. Ancak ileriye dönük ve kontrollü çalışmalarla bu bulguların desteklenmesi gerekmektedir.

Anahtar kelimeler: Bipolar bozukluk, üreme işlevleri, cinsel işlevler

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INTRODUCTION

Bipolar disorder is a mood disorder that, with its recurring nature, leads to a significiant disability, requiring long-term treatment as well as add on treatment in acute phases. Psychotropics used in these phases may cause serious side effects.

Reproductive and sexual dysfunctions are serious side effects that are not sufficiently emphasized. It seems that psychotropic drugs used to treat bipolar disorders can cause reproductive and sexual dysfunctions via the hypothalamo-hypophyseal-gonadal axis (HHG) (1). With second-generation antipsychotics (AP), a prevalence of sexual dysfunctions had been reported in a range between 18 and 96%, while first-generation APs and antidepressants frequently cause problems with libido, arousal and orgasm (2). For the mood stabilizer (MS) valproate, there are case reports indicating a causation of sexual dysfunctions, but these observations have not yet been confirmed by controlled studies (3,4). For Lithium, it is commonly assumed, that lithium is not related to sexual dysfunctions (5,6).

However, it has been suggested that in bipolar disorder, there may be HHG axis abnormalities independent from drug use and even before the disease presents, which might constitute an endophenotype (7). In women, HHG axis abnormalities can cause irregularities in the menstrual cycle, in men pubertal delay, and in both sexes reproductive and sexual dysfunctions (1,8).

Sexual dysfunctions are relevant because they affect treatment compliance and quality of life negatively (2,9). Therefore, with this study we aim to research reproductive characteristics and sexual functions in a broad sample of persons with a diagnosis of bipolar disorder, to determine potential correlations with the use of psychotropics, and assess differences between the sexes.

METHOD

For this cross-sectional study, approved by the Research Ethics Committee of Ege University School of Medicine, we enrolled patients who had presented at the policlinic between March 2008 and September 2009 and were being followed by the Affective Disorders Outpatient Unit of Ege University's Psychiatry Department with diagnoses of bipolar I and II disorders according to DSM-IV (10). A total of 193 patients with a Clinical Global Impressions Scale (11) score below 5, 93 (48.1%) women, 100 (51.8%) men, were assessed. All of the patients were cognitively able to complete the Arizona Sexual Experience Scale and the International Index of Erectile Function. Cases with serious organic or neurologic diseases that were likely to affect the research scope were not included in the study.

Sociodemographic data and information about disorder and reproduction were collected on a specific form, including questions about educational and marital status, type of bipolar disorder, age of disease onset and the duration of disease, psychotropics used during the past three months, doses and duration of MS and APs, puberty age, irregularities of the menstrual cycle, number of pregnancies, births, miscarriages, and abortions, menopause, and birth control methods.

Women's sexual functions were evaluated using the Arizona Sexual Experience Scale (ASEX) (12), filled out by the patients themselves. For this instrument, a Turkish validity and reliability study had been carried out by Soykan (13). Sexual functions in men were assessed with the International Index of Erectile Function (IIEF), which had been tested for validity and reliability by the Turkish Society for Andrology's IIEF Validation Group (14,15).

ASEX is filled out by the patient and a special training is not necessary for its interpretation. The form consists of five items assessed on a six-point Likert-type scale. Sexual desire, sexual arousal, vaginal lubrication, reaching orgasm, and satisfaction of orgasm are being evaluated. Each question is scored between 1 and 6 points; thus the total score ranges between 5 and 30 points, and with rising score, the intensity of sexual dysfunction increases. Sexual function disorder is diagnosed if the total score is 19 or above, if any question has a score of 5 and above or any three questions a score of 4 or above.

The International Index of Erectile Function is also filled out by the patient and a special training is not necessary for its interpretation. It aims at evaluating five basic factors, namely, erectile function, orgasmic function, sexual desire, satisfaction of sexual relationship and general satisfaction. For patients who have been in a sexual relationship during the past month, all factors can be evaluated, for others only orgasmic function and sexual desire. The form scores negatively, and with an increasing score, sexual dysfunctions is interpreted as none or mild. Total points for subheadings vary: for erectile function (questions 1, 2, 3, 4, 5, and 15) from 5-30 points, orgasmic function (questions 9 and 10) 2-10 points, sexual desire (questions 11 and 12) 2-10 points, satisfaction with sexual relationship (questions 6, 7, and 8) 3-15 points, and general satisfaction (questions 13 and 14) 2-10 points. The erectile function area, in contrast with the other fields, is used to measure the severity of function disorder. The maximum score for this area being 30, the severity of erectile dysfunction is evaluated as serious (6-10 points), medium (11-16 points), slight (17-25 points), and no function disorder (26-30 points).

Statistical Analyses

All data collected with the method just described were assessed using the SPSS 13.0 software package. Quantitative data are given as mean and standard deviation. To evaluate categorical data and establish inter-group differences, chi-square test was used. Normally distributed quantitative data were analyzed using Student's t-test. Correlations were calculated with Pearson correlation analysis. The level of significance was set to $p<0.05$.

RESULTS

Sociodemographic and Disease-Related Characteristics: Sociodemographic characteristics of the study participants are shown in Table 1. Regarding age and duration of marriage, no significant difference was found between the male and female patients with bipolar disorder. Duration of education was significantly longer for men than for women (p=0.043). There was significant difference between the sexes regarding their status of being married or not (single/separated/divorced).

Eighty nine point six percent (n=173) of the patients were being monitored with a diagnosis of bipolar-I disorder. Onset age was on average 26.4±9.4 years, disease duration on average 17.2±10.0 years. There was no significant difference between the sexes for diagnosis, onset age and duration of the disease.

With the exception of one pregnant patient who was monitored without medication, all other patients were using psychotropic drugs: 31.8% (n=61) one drug, 41.7% (n=80) two, and 26.6% (n=51) used three or more psychotropics. Looking at MS, 25.0% (n=48) were using only lithium, 5.2% (n=10) only

Table 1: Patients' sociodemographic characteristics

	Female Bipolar Patients (n=93)		Male Bipolar Patients (n=100)		Total (n=193)		p
Age (years) (mean±SD)	43.5±11.3		43.9±11.2		43.7±11.2		0.809
	n	**%**	**n**	**%**	**n**	**%**	
Marital state							
Single	9	9.7	20	20.0	29	15.0	$\chi^2_{(3)}$=15.352;
Married	65	69.9	76	76.0	141	73.1	0.002
Separate/divorced	14	15.1	4	4.0	18	9.3	
Widowed	5	5.4	-		5	2.6	
Single/Separated/Divorced	23	30.1	24	24.0	47	24.3	0.906
Duration of marriage (years) (mean±SD)	18.3±12.8		19.9±10.8		19.1±11.9		0.366
Duration of education (years) (mean±SD)	10.3±3.9		11.4±3.8		10.8±3.9		0.043

valproate, 1.0% (n=2) only carbamazepine, 10.2% (n=20) lithium and valproate, 2.1% (n=4) lithium and carbamazepine, 10.2% (n=20) lithium and valproate, 2.1% (n=4) lithium and carbamazepine, and 10.2% (n=20) lithium and lamotrigine. The average duration of MS use was 123.0±103.1 months. No significant difference was found in MS use and duration of use according to sex.

The patients' AP use was as follows: For 17.1% (n=33), their therapy included quetiapine, for 13.0% (n=25) olanzapine, for 3.6% (n=7) risperidone, for 1.6% (n=3) aripiprazole, for 1.0% (n=2) clozapine, for 1.0% (n=2) amisulpride, and for 0.5% (n=1) ziprasidone. Average duration of AP use was 29.7±36.8 months, the chlorpromazine equivalent dose on average 118.7±50.4mg. No significant difference by sex was found in AP use, duration of use, and chlorpromazine equivalent dose.

Table 2: Women's reproductive characteristics

	Female Bipolar Patients (n=93)
Age at menarche (years) (mean±SD)	13.2±1.3
Birth status (n)	73
Number of pregnancies (mean±SD)	3.1±1.7
Number of births (mean±SD)	1.7±1.0
Number of miscarriages (mean±SD)	0.3±0.8
Number of abortions (mean±SD)	1.7±0.9
Age at first pregnancy (years) (mean±SD)	21.9±4.7
Menopause n (%)	34 (36.6)
Natural menopause n (%)	29 (31.2)
Surgical menopause n (%)	5 (5.4)
Age at menopause (years) (mean±SD)	46.4±5.9
Presence of menstrual irregularity n (%)	14 (15.1)
Hypomenorrhea* n (%)	4 (4.3)
Polymenorrhea** n (%)	4 (4.3)
Oligomenorrhea*** n (%)	3 (3.2)
Hypermenorrhea**** n (%)	2 (2.2)
Amenorrhea***** n (%)	1 (1.1)

*Decreased menstrual flow, **Menstruation at intervals shorter than 21 days, ***Menstruation at intervals longer than 35 days, ****Abnormally profuse or prolonged menstrual flow, *****Absence of menstruation

Reproduction Characteristics: Women's reproduction characteristics (menarche age, menopause, irregularities of the menstrual cycle) are shown in Table 2. In all 14 patients with current menstrual irregularities, the condition had started after drug use. Only two of these patients were on MS monotherapy, the other 12 were using various drug combinations. Five of these 12 patients were using AP in their combination therapy, and four of all the women with menstrual irregularities were using valproate, either on its own or in a combination therapy. Of all the women, 38.7% (n=36) had experienced irregularities of their menstrual cycle at any time during their lives, and 67.0% (n=24) of these stated that this irregularity had started after the onset of bipolar disorder, while 33.0% (n=12) said it had begun before their bipolar disorder.

In the men, mean age at pubarche (growth of pubic hair) was 13.8±1.2 years, age at gonadarche (growth of testes) on average 14.0±1.2 years. To assess the men's reproductive characteristics, the number of their spouses' pregnancies was inquired about. A total of 72 men stated that their spouses had experienced pregnancies. Their spouses' mean number of pregnancies was 2.6±1.2, number of miscarriages 0.3±0.6, number of births 1.8±0.6, and number of abortions 0.6±0.9 on average.

Birth control methods of sexually active patients are shown in Table 3. Of the sexually active patients where the female partner was not in menopause (n=111), 60.4% (n=67) stated that they were using an effective birth control method (oral contraception, intrauterine device, condom, tubal ligation, vasectomy). There was no significant difference between the sexes regarding use or non-use of any birth control method.

Sexual Functions

Women

Apart from 10 women who did not want to fill in the ASEX and one illiterate patient, in 63.8% (n=56) of the remaining patients (n=82) no sexual dysfunction was found, while in 31.7% (n=26) there was. The women's ASEX scores are shown in Table 4. The prevalence of sexual dysfunction by age was 9.1% (n=1) between 18 and 30 years, 35.7% (n=15) between

Table 3: Methods of birth control

	Sexually Active Male Bipolar Patients (n=78)		Sexually Active Female Bipolar Patients (n=81)	
	n	%	n	%
No birth control	16	20.5	12	14.8
Oral contraception	2	2.6	1	0.01
Intrauterine device	9	11.5	13	16.0
Condom	17	21.8	16	19.8
Calendar method	1	1.3	2	2.5
Coitus interruptus	8	10.3	5	6.2
Other*	7	8.9	2	2.5
Menopause	18	23.1**	30	37.0

*Other: Tubal ligation or vasectomy, **Male patients whose spouses were menopausal

31 and 45, 42.9% (n=9) between 46 and 55, and 37.5% (n=3) at 56 years and above.

The evaluation of the women's group found a weak positive correlation between age and total ASEX score (r=0.278, p=0.011), but no correlation between duration of disease and total ASEX score. There was a medium-strength positive correlation between age and sexual desire score (r=0.334, p=0.002) as well as arousal score (r=0.318, p=0.004), a weak positive correlation between age and vaginal lubrication score (r=0.255, p=0.021), but no correlation between age and orgasm score or orgasm satisfaction score. No correlation was found between these sexual function subscores and duration of disease.

Table 4: Sexual functions

Arizona Sexual Experience Scale (ASEX) Item	Female Bipolar Patients (n=82)
Sexual desire (mean±SD)	3.5±1.4
Sexual arousal (mean±SD)	3.6±1.3
Lubrication (mean±SD)	3.3±1.3
Orgasm (mean±SD)	3.8±1.2
Orgasm satisfaction (mean±SD)	3±1.4
ASEX total (mean±SD)	17.3±5.3
International Index of Erectile Function Item	**Male Bipolar Patients (n=93)**
Erection (n/mean±SD)	75/24.1±4.5
Orgasm (n/mean±SD)	93/8±1.9
Sexual desire (n/mean±SD)	93/7±1.6
Satisfaction with sexual relation (n/mean±SD)	75/10.4±2.3
General satisfaction (n/mean±SD)	75/8.4±1.8

Men

While seven patients did not want to complete the International Index of Erectile Function, 19.4% (n=18) of the remaining patients stated that they did not have an active sexual life. Of those with an active sexual life, 48.0% (n=36) did not have an erectil dysfunction, in 45.3% (n=34) a slight disorder was found and in 6.6% (n=5) a medium-level erectile function disorder. The cases' International Index of Erectile Function scores are shown in Table 4.

In evaluating the male patient group, no correlations of age and duration of disease with erectile function scores, orgasmic function scores, sexual desire scores, satisfaction of sexual relationship, and general satisfaction scores were found.

Relation Between Use of Psychotropics and Sexual Dysfunction

This relationship was evaluated in the following therapy groups:

1. A group using a single MS versus a group with combination therapy: No significant differentiation was found in either group for women's sexual dysfunction and men's erectil dysfunction ($\chi^2_{(1)}$=0.245, p=0.621, $\chi^2_{(1)}$=0.684, p=0.408, respectively).

2. A group using a single MS versus a group using a combination therapy including APs: No significant differentiation was found in either group for women's sexual dysfunction and men's erectil dysfunction ($\chi^2_{(1)}$=0.159, p=0.690, $\chi^2_{(1)}$=0.608, p=0.436, respectively).

3. A group using a single MS or a combination versus a group using MS and APs: No significant differentiation was found in either group for women's sexual dysfunction and men's erectil dysfunction ($\chi^2_{(1)}$=0.295, p=0.654, $\chi^2_{(1)}$=1.248, p=0.264, respectively).

DISCUSSION

Aim of this study was to research reproductive and sexual characteristics in a sample group diagnosed with bipolar disorder, evaluate the differences between sexes, and establish potential relations between dysfunctions and the use of psychotropics. Reproductive and sexual functions in serious mental disorders are being neglected. However, these function disorders can affect quality of life and drug compliance with therapy negatively.

Reproductive Functions

In the women's group in our study, the mean age at menarche (13.2±1.3) and menopause (46.4±5.9) was similar to that of the general population in Turkey (16,17,18,19). Current irregularities of the menstrual cycle were found in 15.1% of our sample, and all irregularities had begun after starting drug use. Lifetime prevalence of menstrual irregularities is 38.7%. A large part of patients experiencing menstrual irregularities (67.0%) reports that these irregularities developed after the occurrence of bipolar disorder. In a study with university students in Turkey, the prevalence of menstrual irregularities was 36.5% (17), which is a rate similar to that for lifetime menstrual irregularities found in our study. However, in previous studies menstrual irregularities during the evaluation were found with a prevalence of 34.0-65.0% in the bipolar patient group (1,20), prevalence of menstrual irregularities before treatment for bipolar disorder at 50.0% (20) and in a healthy control group, the prevalence of menstrual irregularities was only 20.0% (1). It is reported that menstrual irregularities seen in bipolar disorder are related to HHG axis abnormalities (20). While it is still unclear if these irregularities are caused by the disease or by the psychotropics used, it is interesting to see that the prevalence of menstrual irregularities in our study is similar to that in Turkey's general population.

None of the male patients in our sample reported any pubertal delay. Age at pubarche (13.8±1.2) and gonadarche (14.0±1.2) were similar to the average in the general population in Turkey (21). To our knowledge, no other study has so far assessed pubertal delay in male bipolar patients.

Among the sexually active patients in our sample, the prevalance of use all birth control methods (74.8%) and effective birth control methods (60.4%) was higher than in the general population of Turkey (62.0% and 50%, respectively) (22). A study carried out with bipolar women in four provinces (Istanbul, Konya, Mardin, and Diyarbakir) (23) reported that only 34.6% of the patients use birth control methods (including the use of non-effective methods such as coitus interruptus). These results may be related to the high educational level of our patients, coming from a province with a high sociocultural level, being followed at a specialized mood disorder clinic, who were preventing unwanted pregnancies out of sensitivity for potential harm to the fetus caused by the disease or the drugs, upon their doctors' advice regarding birth control methods.

Sexual Functions

This is the largest study about sexual functions in a bipolar disorder group done in Turkey.

In our sample, erectil dysfunction was found in 52.0% of our male patients. An internet-based study with a large sample in Turkey (24) found a prevalence of erectil dysfunction of 59.7% in the general population. It needs to be indicated that this study represents the general situation in Turkey. In addition, this study included adolescents, and erectil dysfunction have been found to be common in the adolescent group. Our sample did not include adolescents; therefore, it may not be true to say that the prevalence of erectile dysfunctions in bipolar patients is lower than in the general population. In addition, as we do not know the reasons why seven men refused to complete the International Index of Erectile Function, it is possible

that this decision led to a selection bias, leading to a reduced ratio. In a study in Turkey, made with a psychiatric sample (where sexual function was measured with a different test) (2), results from a small male bipolar patient group (n=29) showed a rate of erectile dysfunctions similar to that among healthy controls.

In this study, the prevalence of sexual dysfunctions in bipolar women is 31.7%. While there is no study reflecting women's sexual dysfunctions for Turkey in general, in a study made in Ankara with a systematically chosen random sample, using a different test for the assessment, sexual dysfunctions was found in 48.3% of the participants (25); the rates by age group were 41% between the ages of 18 and 30 years, 53.1% between 31 and 45, and 67.9% between 46 and 55 years of age. The absence of a control group in our study makes it difficult to come to a definitive conclusion. On the other hand, considering that the mentioned study by Oksuz and Malhan (25) found a higher prevalence of sexual dysfunctions in all age groups compared to our study, it may be suggested that the disease- and drug-related prevalence of sexual dysfunctions is not as high as had been assumed. Another study made in Turkey with bipolar women (n=61) (using a different test to score sexual function) (2) found that there was no diffrence in sexual functions, only vaginismus scores were higher in patient group than healhty controls.

It is known that sexual dysfunctions increase with age (25). In our study too, we found a weak positive correlation between the patients' age and ASEX total score as well as vaginal lubrication score, and a medium-strength positive correlation of age with sexual desire and arousal scores.

Effect of Psychotropics on Sexual Functions

Our study did not find significant differences for women regarding sexual dysfunctions and for men regarding erectile dysfunctions between groups using monotherapy versus combination therapy, monotherapy versus combination therapy including AP, or groups using MS versus those using MS and AP. The reason for the failure to detect a correlation between AP use and sexual dysfunctions may be that everyone in that group had at one point used first-generation APs. Studies made with bipolar patients in remission (3) and with schizophrenic patients (26,27) have shown that sexual dysfunctions is significantly more common in users of first- rather than second-generation APs. However, differences regarding side effects on sexual function were also found between different APs of the second generation: The negative effect of aripiprazole, quetiapine, and ziprasidone on sexual function is lower than that of other second-generation APs (28). In our sample, quetiapine was most commonly choosen, and in the second place olanzapine. While the latter substance has a higher sexual side effect than aripiprazole, quetiapine, and ziprasidone (28), the positive result may be due to the fact that these drugs had been used in low doses. Among the MS, studies have shown that lithium on its own does not cause sexual dysfunctions (5,6). For valproate, there are reports suggesting that the drug may cause sexual dysfunctions; however, these findings have not yet been backed up by controlled studies (3,4).

As far as we know, in the field of bipolar patients this has been the study with the largest sample done in Turkey so far. The large sample size also enabled a comparison between different groups of drugs.

The study is limited by the fact that it followed a cross-sectional design, included only patients from one university clinic, did not use any control or comparison group, could not investigate increase in sexual function while evaluating sexual dysfunctions with valid and reliable tests, and did not enquire about medical conditions potentially affecting sexual functions, nor about smoking or drinking alcohol.

This is the so far largest study to investigate sexual and reproductive functions in patients diagnosed with bipolar disorder. Despite the absence of a control group and the exclusive use of patients from one university clinic, it has provided important indications with a descriptive, qualitative approach. It is encouraging that sexual dysfunctions and reproductive abnormalities were not found to the extent that had been expected. The findings of this study should be considered as preliminary findings and need to be elaborated and confirmed by more comprehensive, controlled studies.

Contribution Categories	Name of Author
Development of study idea	E.A., F.A.
Methodological design of the study	E.A., F.A.
Data acquisition and process	E.A., S.I., N.K.B., A.C.
Data analysis and interpretation	E., S.I., N.K.B., F.A., S.V.
Literature review	E.A., S.I., N.K.B., F.A.
Manuscript writing	E.A., F.A., S.V.
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