The influence of the mental state of women with infertility on their reproductive status

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Mutual influence between women's mental health and their reproductive capacity are not clearly understood. In particular, psychogenic factors and mental disorders affect sexual, menstrual and reproductive functions, which in turn can lead to infertility. Improving the mental state of women, on the other hand, helps to restore reproductive function.

Objective: *to develop dynamic ideas about the reproductive status of mentally ill and mentally healthy women with infertility based on the results of the follow-up.*

Material and methods. *The study included 348 patients with infertility over a period of 2 years, 228 were mentally healthy women and 120 women with mental disorders. All women were consulted by a gynecologist, women with mental disorders by a psychiatrists, and treatment of existing disorders was carried out.*

Results. *Mentally healthy women have a significantly higher number of pregnancies, which is mainly due to the in vitro fertilization procedure. They have a rational approach to pregnancy planning, are characterized by a high referral rate to obstetricians and gynecologists and undergo a large number of gynecological procedures to overcome infertility. Pregnancy occurs spontaneously in mentally ill patients and is associated with an improvement in mental state and normalization of menstrual, sexual and therefore reproductive function, but is characterized by a complicated course (fetal growth retardation, miscarriage, intrauterine infection of the fetus, oedema, hypertension, lipid metabolism disorders, gestational diabetes mellitus, placental disorders) and fewer births.*

Conclusion. *The reproductive function of women depends on their mental state. In women with mental disorders, disturbances of menstrual and sexual function and family adaptation lead to infertility. Improving the mental state contributes to the restoration of reproductive function and spontaneous pregnancy.*

Keywords: *mental disorders; infertility; idiopathic infertility; reproductive function.*
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For reference: *Nikolaevskaya AO, Tyuvina NA, Balabanova VV. The influence of the mental state of women with infertility on their reproductive status. Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics. 2024;16(3):64–71.* ***DOI:*** *10.14412/2074-2711-2024-3-64-71*

Protection of the reproductive health of the population is one of the key links in improving the demographic situation in the country [1]. In this regard, the problem of infertility among the female and male population is of particular importance. According to various data, the frequency of infertile marriages in Russia reaches 11% [2–5]. Overcoming the problem of infertility has ceased to be an exclusively gynecological issue [6]. The results of a number of studies demonstrate the influence of women's mental state on sexual activity, menstrual and reproductive function [7–13], which, in turn, leads to infertility.

The interrelation and mutual influence of female reproductive and mental health are regarded as components of the mechanism of the "pathological circle", when mental disorders, psychological and psychogenic factors affect a woman's menstrual generative function, in some cases mediating infertility [14]. The chronic stress factor of infertility, which is significant for a woman, can contribute to the manifestation or aggravation of her mental disorders, disruption of intra-family relationship, and a decrease in the quality of life [7,15].

Infertility, in particular its idiopathic variant, when there are no visible gynecological causes, can occur in women with various mental illnesses affecting sexual, menstrual and reproductive function [15–17]. Women suffering from endogenous mental disorders such as schizophrenia and bipolar disorder have lower fertility compared to healthy ones, a large number of spontaneous miscarriages, and stillbirths [16]. Disturbances of menstrual function due to hyperprolactinemia caused by the effect of paroxysmal disorders on the hypothalamus and taking antiepileptic drugs for epilepsy cause difficulty in conception and a high incidence of miscarriage [17]. Women with recurrent depression often have comorbid diseases of the reproductive system (infertility, habitual miscarriage, atopic pregnancy, ovarian dysfunction, endometriosis, adnexitis) [15]. The comorbid course of gynecological and mental pathology worsens medical and social prognosis, making the prospect of motherhood uncertain.

In the studies of foreign authors, such mental disorders as schizophrenia, autism, bipolar affective disorder, anorexia nervosa, substance abuse are regarded as a cause of lower fertility in patients, and are considered a variant of "evolutionary natural selection" [18].

According to the letter of the Ministry of Health of the Russian Federation (dated March 5, 2019 No. 15-4/I/2-1908),

there are a number of contraindications to the use of assisted reproductive technologies in persons suffering from mental disorders: chronic and prolonged mental disorders with severe persistent manifestations (psychosis and dementia) or with a high probability of exacerbation under the influence of pregnancy and childbirth (F03, F04, F06, F07, F09, F20 – F29, F42, F70–F79, F99), hereditary and degenerative mental disorders (F70, F84), severe psychogenic disorders (F23, F44), mental disorders associated with the use of psychoactive substances (F10–F19), mood disorders (affective disorders with persistent suicidal ideation and a risk of suicidal actions (F30–F39).

Despite the existing interest of researchers in the problem of the interdependence of mental and reproductive health of women, scientific papers highlighting the features and mechanisms of the relationship and mutual influence of the mental and gynecological component of infertility are few, which confirms the need for further research in this direction.

Materials and methods. The study included 348 patients with infertility lasting for 2 years, including 228 mentally healthy women and 120 women with mental disorders. All women were consulted by gynecologists, women with mental disorders by psychiatrists, and existing disorders were treated.

The examined patients were divided into 4 groups: Group 1 – mentally healthy women with primary infertility (n=148); group 2 – women with mental disorders and primary infertility (n=84); group 3 – mentally healthy women with secondary infertility (n=80); group 4 – women with mental disorders and secondary infertility (n=36). All women were consulted by gynecologists, women with mental disorders by psychiatrists. The existing disorders were treated.

The examination was carried out using a clinical, catamnestic method with a specially designed questionnaire card and subsequent statistical processing of the results obtained.

Statistical processing of the obtained results was carried out using the Statistica StatSoft 8.0 program. Categorical features were described using absolute and relative (expressed as a percentage) indicators. The comparison of percentages in the analysis of four-field conjugacy tables was performed using Pearson's chi-squared criterion. The significance of differences in the frequency distribution of dichotomous indicators was assessed using the exact criterion of the Fisher angular transformation. The level of statistical significance was set at the error probability level of 0.05.

The criteria for inclusion in the study were the diagnosis of female infertility (ICD-10 code N97), established by an obstetrician-gynecologist according to the current criteria and comorbid mental disorders. The median age of manifestation of a mental disorder was 21.85±5.76 years in group 2 and 22.25±7.14 in group 4.

The exclusion criteria were severe somatic and neurological diseases.

Results. Infertility with an established etiological factor or idiopathic infertility were diagnosed in all groups (Table 1).

Infertility of established etiology prevailed among mentally healthy women, idiopathic infertility prevailed in women with mental disorders ($p \leqslant 0.01$). Comparison of infertility indicators in healthy and mentally ill women with primary and secondary infertility indicates that infertility of established etiology prevails in mentally healthy women.

The analysis of individual indicators of menstrual function in women in the comparison groups 2 years after the initial study showed their definite dynamics as a result of gynecological and psychiatric treatment (Table 2).

Mentally healthy women with infertility of established etiology showed a significant improvement in certain indicators of menstrual function: menstruation became regular, less painful, and the amount of discharge became moderate. Mentally ill women with both infertility of established etiology and idiopathic infer-

Table 1. *Types of infertility in women in the analyzed groups, n (%)*

Types of infertility	Primary infertility n=232		Secondary infertility n=116	
	mentally healthy women (group 1) n=148	women with mental disorders (group 2) n=84	mentally healthy women (group 3) n=80	women with mental disorders (group 4) n=36
Infertility with established etiology	123(83.1%)*	36(42.85%)	67(83.75%)*	8(22.2%)
Idiopathic infertility	25(16.9%)	48(57.14%)*	13(16.25%)	28(77.8%)*

Notes: * – $p \leqslant 0,05$

Table 2. *Characteristics of menstrual function at baseline and after 2 years, n (%)*

	Infertility with established etiology				Idiopathic infertility			
	Mentally healthy women n=190		Women with mental disorders n=44		Mentally healthy women n=38		Women with mental disorders n=76	
	baseline	after 2 years	baseline	after 2 years	baseline	after 2 years	baseline	after 2 years
Regularity of menstruation	**122 (64,2)**	**147 (77,4)***	**3 (6,8)**	**19 (43,2)***	18 (47,4)	13 (34,2)	**6 (7,9)**	**23 (30,3)***
Painfulness of menstruation	**125 (65,8)**	**111 (58,4)#**	10 (22,7)	8 (18,2)	17 (44,7)	12 (31,6)	4 (7,9)	3 (3,9)
Menstruations:								
scanty	34 (17,9)	28 (14,7)	23 (52,3)	19 (43,2)	9 (23,7)	6 (15,8)	26 (34,2)	20 (26,3)
heavy	62 (32,6)	44 (23,1)	11 (25)	8 (18,2)	9 (23,7)	6 (15,8)	33 (43,4)	30 (39,4)
moderate	**94 (49,5)**	**118 (62,1)***	**10**	**17***	20 (52,6)	26 (68,4)	**17 (22,4)***	**26 (34,2)***

Notes: here and thereafter * – $p \leqslant 0.01$ is statistically significant, # – $0.05 \leqslant p \leqslant 0.1$ differences at the level of statistical tendency ϕ is the criterion of the Fisher angular transformation.

tility showed a more regular menstrual cycle with a moderate amount of discharge.

Reproductive function differed in healthy women and those with mental pathology, as well as in primary and secondary infertility. Thus, the incidence of pregnancy in primary and secondary infertility in mentally healthy women was 93.24% and 76.25%, respectively, whereas the same indicator in the groups of women with mental disorders was 41.66% and 44.4%, respectively (Table 3).

The largest number of pregnancies in mentally healthy women in both groups was associated with IVF procedures. Pregnancy due to IVF was more often registered with primary infertility. Pregnancies due to IVF and spontaneous pregnancies were observed in the groups of mentally healthy women, whereas women with mental disorders did not participate in assisted reproduction programs.

The number of cases of spontaneous pregnancy in the groups of women with mental disorders and idiopathic variant of infertility was 2.8 and 3 times higher than for infertility of established etiology; the differences are statistically significant. It suggests the effect of the improved mental state on becoming pregnant in women with idiopathic infertility. Obstetricians and gynecologists usually diagnose such women with "infertility of idiopathic etiology", without associating it with a comorbid mental pathology, which is the cause of reproductive dysfunction. With infertility of established etiology, the improvement of the mental state does not eliminate the existing gynecological causes without adequate and successful interventions.

The outcomes of pregnancies were not the same in the patients of the studied groups (Table 4).

Table 3. *Distribution of cases of pregnancy with different types of infertility in healthy and mentally ill women, n (%)*

	Primary infertility		Secondary infertility	
	mentally healthy women (group 1) n=148	women with mental disorders (group 2) n=84	mentally healthy women (group 3) n=80	women with mental disorders (group 4) n=36
Бесплодие установленной этиологии				
Pregnancy due to IVF	102 (68,91)*	–	42 (52,5)	–
Spontaneous pregnancy	18 (12,16)	9 (10,71)	9 (11,25)	4 (11,11)
Total	120 (81,08)*	9 (10,71)	51 (63,75)*	4 (11,11)
Idiopathic infertility				
Pregnancy due to IVF	–	–	–	–
Spontaneous pregnancy	18 (12,16)	26 (30,95)	10 (12,5)	12 (33,3%)
Total	138 (93,24)*	35 (41,66)	61 (76,25)*	16 (44,4)

Table 4. *Outcomes of pregnancy in women in the studied groups, n (%)*

	Primary infertility		Secondary infertility	
	mentally healthy women (group 1) n=148	women with mental disorders (group 2) n=84	mentally healthy women (group 3) n=80	women with mental disorders (group 4) n=36
Pregnancy due to IVF, n	102 (100)		42 (100)	–
Ended in childbirth:	31 (30,39)	–	14 (33,33)	–
spontaneous childbirth	14 (45,17)	–	5 (35,72)	–
caesarean section	17 (54,83)	–	9 (64,28)	–
Early undeveloped pregnancy	30 (29,41)	–	13 (30,95)	–
Miscarriage *(spontaneous abortion)*	41 (40,19)	–	15 (35,71)	–
Threatened early miscarriage *(frequency distribution)*	55 (53,92)	–	19 (45,23)	–
Spontaneous pregnancy, n	36 (100)	35 (100)	19 (100)	16 (100)
Ended in childbirth:	**25 (69,44)***	**17 (48,57)**	12 (63,15)	7 (43,75)
spontaneous childbirth	9 (36)	6 (35,3)	5 (41,67)	3 (42,85)
caesarean section	16 (64)	11 (64,70)	7 (58,33)	4 (57,14)
Early undeveloped pregnancy	5 (13,8)	8 (22,85)	**3 (15,78)**	**4 (25)***
Miscarriage *(spontaneous abortion)*	6 (16,66)	10 (28,57)*	4 (21,05)	5 (31,25)
Threatened early miscarriage *(frequency distribution)*	14 (38,8)	18 (51,42)*	7 (36,84)	9 (56,25)*

The total number of pregnancies in mentally healthy women (199 – 87.28%) significantly exceeded ($p \leqslant 0.01$) the analyzed indicator in the group of women with mental disorders (51 – 42.5%), which can be associated with the participation of mentally healthy women in IVF programs.

However, despite the fact that 144 pregnancies occurred in the mentally healthy groups due to IVF, only 45 (31.25%) of them ended in childbirth, of which 19 (42.22%) were spontaneous and 26 (57.77%) by Caesarean section. Forty-three (29.86%) patients had an early undeveloped pregnancy, and 56 (38.89%) had a miscarriage (spontaneous abortion). There were no significant differences in IVF-associated pregnancy outcomes in groups 1 and 3, the analyzed indicators in the comparison groups were approximately the same.

The number of spontaneous pregnancies was significantly lower ($p<0.01$) in mentally healthy women (55 – 24.12%) compared with women with mental disorders (51 – 42.5%). Of 106 women with spontaneous pregnancy, 61 (57.54%) ended in childbirth. Among mentally healthy women, the total number of births after spontaneous pregnancy was significantly higher ($p<0.05$) and amounted to 37 (60.65%), whereas among women with mental disorders this number was 24 (44.26%).

Significantly more births occurred after spontaneous pregnancy in group 1; the number of early undeveloped pregnancies was higher in group 4. The number of miscarriages and threatened early miscarriages was significantly higher in the groups with mental disorders.

The course of pregnancy in women in the comparison groups was complicated by specific significantly different parameters (Table 5).

Edema caused by pregnancy, impaired fat metabolism, gestational diabetes mellitus, anemia, and hypertension were significantly more common in patients of group 2. A tendency to hypamnion was revealed in patients of group 1. Group 2 patients were significantly more likely to have such pregnancy complications as preeclampsia, placental abnormalities (changes in the structure and function of the placenta) and fetal growth retardation syndrome.

In general, pregnancy in mentally ill patients occurred with a higher number of complications than in mentally healthy groups. These complications influenced the outcome of pregnancy and problems in childbirth.

The approach to pregnancy planning in infertility differed in the examined patients with infertility, which is reflected in the data on gynecological interventions (Table 6).

Gynecological interventions aimed at overcoming infertility were significantly more often observed in mentally healthy women with primary infertility ($p<0.01$).

Discussion. As a result of a clinical and catamnestic comparative study of reproductive function indicators in healthy and mentally ill women with primary and secondary infertility 2 years after the initial examination and therapeutic measures (treatment of gynecological diseases, mental disorders, IVF), significant differences were found in the studied groups in restoring menstrual function, occurrence and course of pregnancies, methods of delivery.

Table 5. *Pregnancy complications in patients of the analyzed groups, n (%)*

	Primary infertility		Secondary infertility	
	mentally healthy women (group 1) n=148	women with mental disorders (group 2) n=84	mentally healthy women (group 3) n=80	women with mental disorders (group 4) n=36
Total pregnancies, n	138 (100)	35 (100)	61 (100)	16 (100)
Total births, n	56 (40,57)	17 (48,57)	26 (42,62)	7 (43,75)
Isthmic-cervical insufficiency	25 (18,11)	9 (25,71)	9 (14,75)	3 (18,75)
Edemata caused by pregnancy	37 (26,81)	21 (60)*	17 (27,86)	3 (18,75)
Fat metabolism disorders	34 (24,63)	28 (80)*	18 (29,5)	9 (56,25)*
Premature rupture of the membranes	12 (8,69)	6 (17,14)	7 (11,47)	6 (37,5)
Gestational diabetes mellitus	32 (23,18)	22 (62,85)*	8 (13,11)	6 (37,5)
Gestational anemia	33 (23,91)	17 (48,57)*	6 (9,83)	(43,75)*
Gestational hypertension	27 (19,56)	15 (42,28)*	10 (16,39)	8 (50)*
Polyhydramnios	31 (22,46)	9 (25,71)	9 (14,75)	6 (37,5)*
Hypamnion	23 (16,66)#	2 (5,71)	3 (4,91)	2 (12,5)*
Intrauterine infection	25 (18,11)	5 (14,28)	5 (8,19)	6 (37,5)*
Preeclampsia	5 (3,62)	7 (20)*	3 (4,91)	4 (25)
Placental disorders	4 (2,89)	5 (14,28)*	3 (4,91)	4 (25)
Fetal growth retardation syndrome	3 (2,17)	6 (17,14)*	3 (4,91)	4 (25)

Infertility with an established etiological factor prevails among mentally healthy women, and idiopathic infertility prevails among women with mental disorders. The fact that patients of the latter category less frequently seek obstetric and gynecological care, partly explains the lack of objective reasons for impossibility of conception in these women. Obstetricians and gynecologists, in turn, due to insufficient understanding of the relationship and mutual influence of female reproductive and mental health, regard infertility in such patients as the result of insufficient examination or an unidentified etiology [19].

Menstrual dysfunction in the examined women has undergone certain changes according to the results of the catamnesis. It was revealed that mentally healthy women with infertility of the established etiology, showed improvement in certain indicators of menstrual function: menstruations became regular, less painful, the amount of discharge became moderate. Among mentally ill patients, including patients with idiopathic infertility, a more regular cycle with a moderate amount of discharge has also been established, which may be associated with the stabilization of their mental state.

The work involving experimental animals indicates that depression causes changes in the menstrual cycle [20]. Various mechanisms are described: damage to eggs and apoptosis of granulosa cells of the ovaries, activation of the hypothalamic-pituitary-adrenal system with subsequent release of corticotropin-releasing hormone. The latter directly affects the ovaries, inhibiting the production of luteinizing hormone, estrogen and stimulating the production of follicle-stimulating hormone. Corticotropin-releasing hormone also induces increased secretion of glucocorticoids by the adrenal cortex which have a destructive effect on eggs.

According to the literature, mental disorders such as schizophrenia, bipolar affective disorder, recurrent depression, epilepsy, autism, substance abuse are causes of low fertility in patients [15–18], and according to some authors, represent a variant of natural selection [18].

A study by Norwegian authors noted that 22% of women with miscarriage suffer from mental disorders, the most common of which are depressive and anxiety disorders. Other mental disorders affecting unfavorable outcomes of pregnancy are bipolar disorder, attention deficit hyperactivity disorder (ADHD), personality disorders, anorexia nervosa and somatoform disorders, as well as schizophrenia [21].

Mentally healthy and mentally sick women differ in indicators of reproductive function. The total number of pregnancies in mentally healthy people (87.28%) significantly exceeded this indicator in women with mental disorders (42.5%). Women with mental disorders did not participate in assisted reproduction programs, therefore, a higher number of pregnancies in mentally healthy women in both groups is associated with IVF procedures. Pregnancy due to IVF occurred more often with primary infertility; women with idiopathic infertility were regarded by obstetricians and gynecologists as patients with unclear diagnosis and did not participate in the IVF procedure. Thus, all women with mental disorders and mentally healthy women with idiopathic infertility had only spontaneous pregnancies.

The number of spontaneous pregnancies was significantly lower in mentally healthy women (24.12%) compared with mentally ill women (42.5%). At the same time, in idiopathic infertility spontaneous pregnancy in women with mental disorders occurred 2.8 and 3 times more often in primary and secondary infertility, which suggests the effect of the improvement of mental state of a woman on the possibility to become pregnant. However, mentally healthy women had a higher number of births after spontaneous pregnancy.

Women with mental disorders were more likely to develop early pregnancies, miscarriages and threatened early miscarriages. Their pregnancy was accompanied by numerous complications exceeding those of the mentally healthy patients: edema of pregnancy, impaired fat metabolism, gestational diabetes mellitus, anemia, arterial hypertension. Severe pregnancy complications such as preeclampsia, placental abnormalities (changes in the structure and function of the placenta) and fetal growth retardation syndrome were also more common in mentally ill women. According to the clinical guidelines of 2021, "Preeclampsia. Eclampsia. Edema, proteinuria and hypertensive disorders during pregnancy, childbirth and the postpartum period", such disorders in obstetric practice are life-threatening conditions with potentially fatal complications (HELL syndrome, severe coagulopathy, necrosis or rupture of the liver, cerebral hemorrhage) [22].

In general, pregnancy in mentally ill patients occurred with a higher number of complications than in mentally healthy groups. These complications influenced the outcome of pregnancy and problems in childbirth, which is consistent with data from other studies [15–17,20]. This situation may be due to the influence of the mental illness itself on the possibility of conception and the course of pregnancy, as well as the use of psychotropic drugs, both before and during pregnancy. We must also consider possible teratogenic effect of various psychotropic drugs, as well as their side effects (neuroleptic syndrome, increased prolactin levels in the blood, impaired glucose tolerance, increased appetite and body weight, cardiotoxic manifestations) [23].

The examined patients showed a different approach to pregnancy planning. Thus, gynecological interventions aimed at overcoming infertility were significantly more often observed in mentally healthy women, especially with primary infertility, which indicates a better ability of mentally healthy

Table 6. *Gynecological interventions in the studied groups, n (%)*

Gynecological interventions	Primary infertility		Secondary infertility	
	mentally healthy women (group 1) n=148	women with mental disorders (group 2) n=84	mentally healthy women (group 3) n=80	women with mental disorders (group 4) n=36
Total pregnancies	138 (100)	35 (100)	61 (100)	16 (100)
Diathermocoagulation of cervical ectopia	7 (4,72)*	2 (2,38)	3 (3,75)	1 (2,77)
Diagnostic laparoscopy	9 (6,08)*	1 (1,19)	2 (2,5)	1 (2,77)
Hysteroscopy	27 (18,24)*	3 (3,57)	2 (2,5)	2 (5,54)

women to realize their reproductive rights, their conscious attitude to parenthood. Women with mental disorders in most cases subjectively perceive infertility less emotionally and regard pregnancy and motherhood as an aggravating and undesirable circumstance. Treatment of gynecological diseases is not the key factor for them in terms of pregnancy. Pregnancy occurs spontaneously due to the normalization of their mental state, menstrual function, sexual functioning, and increased sexual contact [7, 8].

It is interesting to note the relatively low frequency of deliveries in mentally healthy women treated with assisted reproduction. The unfavorable outcome of pregnancies as a result of IVF can negatively affect the mental state of such women.

Conclusion. The conducted research allowed us to form dynamic ideas about the reproductive status of mentally ill and mentally healthy women with infertility. The results obtained confirmed that the reproductive function in women is closely related to their mental health, which must be taken into account when clarifying the causes of infertility, especially the idiopathic variant, as well as when choosing therapeutic tactics, since improving the mental state can contribute to the restoration of menstrual and reproductive function.

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Received/Reviewed/Accepted
06.02.2024/20.05.2024/21.05.2024

Conflict of Interest Statement

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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