Infertility and Mental Disorders in Women. Communication 1

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This paper presents the definition, epidemiology, etiological factors, and approaches to classifying infertility and describes the relationship between mental health and infertility in women. The problem of idiopathic infertility is analyzed from both obstetric/gynecological and psychiatric positions. The psychological factors influencing the reproductive function of a woman are disclosed. Mental health disorders potentiating infertility are considered. Attention is paid to that mental disorders are insufficiently and untimely diagnosed in women with reproductive disorders, that certain forms of psychopathology are masked by functional gynecological disorders, and that obstetricians/gynecologists have no specialized ideas of women's mental health, which may lead to unsuccessful infertility therapy.

Keywords: *mental disorders; reproductive health; female infertility; infertile marriage, primary infertility; idiopathic infertility; mental health.*
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The problem of infertility

According to the WHO definition, infertility is a failure of a couple to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. [1]. In clinical studies and medical practice, infertility is defined as «a disease of the reproductive system manifested in the absence of a clinical pregnancy after 12 or more months of regular sexual non-contraceptive life» [2].

There are various approaches to infertility classification: with regard to its etiology and pathogenesis, changes in the clinical presentation of the disease (pathomorphosis), duration, and other related factors. Thus, obstetric literature describes infertility caused by female and male factors as well as by common factors in marriage. Urogenital infections, psychosexual disorders, immunological factors can lead to infertility. Inability to identify the cause of reproductive disorders using existing diagnostic methods warrants the diagnosis of idiopathic infertility. Based on the etiological factors, the ICD-10 identifies the following types of infertility: tuboperitoneal; anovulatory (endocrine); uterine; cervical; caused by male factors; unexplained infertility and other forms [3].

Absolute (due to irreversible pathology of the female body) and relative (inability to conceive or give birth to a child due to reversible pathological processes), as well as primary and secondary infertility are described [4]. Primary infertility is defined as "inability of a woman to have a child either due to a failure to become pregnant or to carry a pregnancy to a live birth". Secondary infertility is defined as "inability of a woman to have a child either due to a failure to become pregnant or to carry a pregnancy to a live birth following either a previous pregnancy or a previous live birth".

Epidemiology

Based on data from the Demographic Health Survey from 1994 to 2000, the World Health Organization (WHO) found that 186 million women in developing countries suffer from infertility despite 5 years of trying to get pregnant or have a live baby. Statistically, it means that one in every four couples of reproductive age in developing countries is infertile. Swiss [5] and American researchers [6] report that infertility affects about 15% of couples of reproductive age. Belgian researchers report lower rates of infertility in the world – 8–12% [7], while Iranian researchers give higher rates (up to 30%), stressing the fact that there are about 2 million infertile couples in Iran [8].

According to O.A. Khamraev et al. [9], the frequency of infertile marriages in the world is about 15%, in Western Europe – 10.9%, in the USA – 14.2%. Each year, up to 2.5 million new cases of female and male infertility are diagnosed worldwide [10].

The prevalence of infertile marriages in Russia is 8–17% [11]. A.N. Oranskaya et al. [12] cite a «critical indicator of the prevalence of infertility» which in some regions of the country is 20%. In 2005, 146.6 new cases of infertility were recorded per 100 thousand people aged 18–49 years; in 2016 this figure increased up to 278.8 cases per 100 thousand people [13].

According to the WHO, in 2009 in Russia the total fertility rate was 1.4 children per 1 woman; in 1990 it was 1.9, while the global norm of maintaining reproduction of the population is 2.1 children per 1 woman. Such indicators reflect the negative dynamics (-0.4%) of the annual population growth in the Russian Federation in the past decade (1999–2009) [14].

Clinical variants of infertility

According to WHO, there are various causes of female infertility. They include sexual dysfunction; hyperprolactinemia; organic disorders of the hypothalamic-pituitary axis; amenorrhea with elevated levels of follicle-stimulating hormone; amenorrhea with normal levels of estradiol; amenorrhea with reduced levels of estradiol; oligomenorrhea; irregular menstrual cycle/anovulation; anovulation with a regular cycle; congenital malformations of the genitals; bilateral obstruction of the fallopian tubes; adhesions in the pelvis; endometriosis; acquired pathology of the uterus and cervix; acquired blockage of the fallopian tubes;

acquired ovarian lesions; genital tuberculosis; iatrogenic factors; systemic diseases; negative post-coital test; unknown reasons.

Statistically, the forms of female infertility are distributed as follows: tubal and peritoneal infertility (organic or functional disturbances of the patency of the fallopian tubes with adhesive process in the pelvis or without it) – 40–50%; endocrine infertility (ovulatory disorders with deviations in hormonal regulation of the reproductive system) – 35–40%; various gynecological diseases resulting in disturbances of the anatomical and functional state of the endometrium not accompanied by anovulation and obstruction of the fallopian tubes – 15–25%; immunological infertility caused by sensitization of the female organism – 2%; infertility of unknown origin, psychogenic infertility – 5–15% [15].

Idiopathic infertility

There are several equivalent terms used to indicate infertility of unknown origin: unidentified, inexplicable [16], functional, psychogenic [17], psychological, idiopathic [18, 19]. In ICD-10 this diagnosis has code N 97.9 – «female infertility, unspecified».

In this type of reproductive health disorders the anatomical integrity of the woman's reproductive tract is preserved, and there are no objective reasons leading to a dysfunction of the reproductive system [20].

Despite more than half-century history of studying idiopathic infertility, it still accounts for 15–30% of infertile marriages [21–23]. Obstetrician-gynecologists consider idiopathic infertility «a problem within the problem» because it is not solvable at the realized diagnostic maximum [24–27].

Many authors explain the discrepancy in the prevalence rates of infertility of unknown origin by imperfect methods for detecting the causes of reproductive disorders [25, 26], incomplete knowledge of the effects of various gynecological and other diseases on fertility, especially when substantiating the causes of idiopathic infertility [27]. This justifies the necessity of search for its causes, excluding other factors of infertility, and the development of appropriate therapeutic and preventive measures.

The psychological aspects of infertility

The issues of interconnection and mutual influence of a woman's mental state and her reproductive function have not been explored so far. On the one hand, the mental health of a potential mother has a direct impact on her reproductive function (menstrual, childbearing) and indirect – in the process of assisted reproductive technology [28]. On the other hand, a woman's mental state is closely related to the problem of infertility, miscarriage, complicated pregnancy and pathological delivery [29]. Concurrent mental and obstetric-gynecological pathologies significantly worsen medical and social prognosis in such women [30].

The state of a woman's reproductive system largely depends on her premorbid personality characteristics and reaction to the impact of psychogenic factors. An example of such reactions is temporary cessation of menstruations during wars, «stress» dysfunction of the ovaries, severe psycho-emotional stress in everyday life due to the negative atmosphere at workplace, concern about the partner, and a strong desire to become a mother (false pregnancy) [31]. Often the reason for the absence of pregnancy with this type of infertility is the need to seek help from reproductive specialists, undergo numerous diagnostic examinations, which is associated with a certain «psychological coercion». At the same time, it is emphasized that the «family scenario» or «parent program» – the experience of motherhood in the older generation of the family – has a special effect on the reproductive health. In some cases, specific attitudes to childbirth as having negative impact on the development and self-realization of a woman are «switched on» at the subconscious level, and the idea of pregnancy is supplanted. The central nervous system blocks the reproductive function, which can result in ovarian dysfunction with the formation of cysts, impaired ovulation, lack of hormone production by the corpus luteum, spasms of the fallopian tubes, and increased production of antisperm antibodies. [31].

Psychological prerequisites of infertility that do not depend on fertile age have been described. They include a special predisposition of personality formed under the influence of family education, in which a special role is assigned to negative maternal influence, when pregnancy is blocked at the subconscious level. This negative influence implies distant relationships between daughter and mother or both parents, increased demands on the daughter, depreciation of her success, necessity to take care of younger family members (brothers or sisters) [32]

Psychological causes of idiopathic infertility include traumatic experiences in the past often coming from childhood (parents' divorce, difficult financial situation), which contribute to the formation in a woman of childbearing age a «psychological renunciation of pregnancy» [33]. There are also internal personality conflicts due to the struggle of motives, when a woman wants to pursue her career and, at the same time, to become a mother. These desires may have the same value and intensity, but they are conflicting and, therefore, may not be realized.

E.A. Sosnova [34] in her work devoted to the problem of amenorrhea (absence of menstruation in women of reproductive age) describes psychogenic amenorrhea along with typical functional hypothalamic-pituitary amenorrhea. One of the leading hypotheses of the origin of psychogenic amenorrhea is an increase in the synthesis of corticotropin-releasing hormone with the activation of the adrenal cortex under the influence of stressful conditions. The author notes that this type of amenorrhea does not present diagnostic difficulties due to the mandatory presence of a traumatic factor in the woman's history. The prognosis is usually favourable, but the duration of exposure to the stressor, personality traits and the state of health of the woman play a significant role.

A number of authors evaluate personal problems arising from psychogenic influences and accompanied by menstrual irregularities (oligomenorrhea) within the framework of «prenosological conditions» and «extranosological disorders» and classify such patients as having increased risk of developing borderline mental pathology. The mutual influence of mental pathology and oligomenorrhea negatively affects both somatic and mental health of a woman, reduces her adaptive reserve and quality of life, and prevents the implementation of effective therapy [35, 36].

Infertility and stress

There are few publications evaluating the influence of psychosocial factors, including stress, symptoms of depression and anxiety, mood disorders on natural fertility, and they contain contradictory data [37].

Stress, regarded as a specific response of physiological processes and biological tissues to a stress stimulus, negatively affects a woman's fertility. A wide range of physical reactions

emerging in response to a stressor and causing a disturbance in homeostasis lead to an immediate disturbance in the psychological or physical balance, to which the body responds by stimulating the nervous, endocrine and immune systems [38]. This response has both short-term and long-term consequences. Stressful stimuli cause activation of the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary systems. At the pathophysiological level, the hormones secreted by these systems after stressful stimuli (both positive and negative) can lead to neuroendocrine changes of various duration that affect fertility [39]. This is confirmed by the data from animal experiments. Thus, in cynomolgus monkeys, the combined effect of metabolic and psychosocial stress caused a disruption in the hormonal processes of the adrenal cortex and, as a result, a reproductive dysfunction [40]. In the experiment with the implantation of an ovum in mice, stress induced the worse susceptibility of the endometrium, despite the ongoing hormonal therapy [41]. When sheep were administered the hormone cortisol in a concentration comparable to that of women under stress, there was a delay in the maturation of the follicle and ovulation due to reduction or cessation of the release of estrogen and luteinizing hormone [42].

Some authors describe «chronic psychosocial stress» caused by the fact of infertility in women, which affects the ovarian reserve. Potentiating stress factors, such as low socio-economic status, malnutrition and financial difficulties, also play an important role [43].

The quality of a woman's oocytes is affected by induction of oxidative stress caused by emotional tension and anxiety [44–46].

Depression, pronounced coping strategies, avoidance and emotional expressiveness can influence female fertility [47]. Depression significantly correlates with an alternative manifestation of stress – anxiety. Anxiety affects the release of the hormone cortisol; such symptoms were observed in 37% of infertile women [48, 49]. It has been established that both depression and anxiety are more common in infertile women compared with fertile women [50–52].

Other stress biomarkers are corticotropin-releasing hormone and alpha-amylase. It was established that the level of alpha-amylase in saliva correlates with indicators of chronic stress and reactive stress load [53]. A study by the University of Oxford found that fertility in women with a high amylase content in saliva is 15–30% lower than in general population [42, 54]. The prospective cohort study PRESTO, including 2146 women and devoted to determining the time of conception, revealed that symptoms of severe depression were associated with a reduced likelihood of natural conception during one menstrual cycle [55]. A 10-point increase in the score on the Major Depression Inventory scale was associated with a 10% decrease in fertility. The opposite results were obtained in a prospective analysis of 339 women trying to get pregnant: no association was found between psychosocial stress, anxiety or depression, and fertility. A higher pregnancy rate was observed in women with a high level of social support [42].

However, most publications focus on the relationship between stress and reproduction. Psychosocial stress activates the sympathetic nervous system, which can affect the axis of the hypothalamus – pituitary – adrenal glands. The BioCycle study demonstrated that daily stress negatively affects the menstrual function [56]. Such women are characterized by an increased risk of anovulation and a decreased level of progesterone in the luteal phase of the cycle.

Mental disorders and infertility

Endogenous mental disorders (schizophrenia, manic-depressive psychosis) have a more pronounced effect on the reproductive function of women. Women suffering from these diseases have lower fertility compared with the general population, are more likely to have spontaneous miscarriages and stillbirths, and malformations of newborns [57].

A significant (3–4 times compared with the general population) decrease in fertility in women with epilepsy has been described. According to P.N. Vlasov [58], this decrease is promoted by a direct effect of paroxysmal disorders on the hypothalamus, as a result of which ovulation is disturbed and prolactin levels increase; in addition, antiepileptic drugs affect the hypothalamus and cause menstrual irregularities provoking polycystic ovary syndrome as well as increased liver metabolism with a decrease in certain fractions of sex hormones. Another study also demonstrated difficulties in conception and a high percentage of miscarriage in women with epilepsy [59].

In the work of A.V. Vasilyeva [60] devoted to the peculiarities of the suicidal behavior of women with schizophrenic spectrum disorders, it was found that patients of reproductive age, prone to suicide, had a higher rate of infertility than in the general population. Women with endogenous affective disorders, especially with recurrent depression, have been found to have a high level of somatic comorbidity, including diseases of the reproductive system (infertility, habitual miscarriage, ectopic pregnancy, ovarian dysfunction, uterine fibroids, chronic adnexitis, endometriosis). Such women have an earlier climax with more pronounced climacteric symptoms. [61].

In a comparative study of menstrual-generative function in patients with recurrent depression and healthy women, it was found that women with mental illness had a later onset of menstruation, menstrual irregularity (dysmenorrhea and amenorrhea), and early severe and prolonged premenopause. Such women were characterized by reduced reproductive ability: fewer pregnancies and childbirths in the anamnesis, fewer children born, a higher frequency of miscarriages. Disturbed family adaptation affected the childbearing function, too. It included irregular sex life, lack of sexual satisfaction, specific features of family status (most women were divorced or never married) [62].

It was also shown that adolescent girls with mood fluctuations have a later onset (15–17 years) and irregular periods, and a severe depressive episode provokes amenorrhea. With an average prevalence of premenstrual syndrome in the population from 30% to 70%, in women with mental disorders this indicator increases up to 70–100% [63].

Stress, anxiety and depression have a significant impact on energy potential, mood, self-esteem, interests, and reproductive health. Depressive symptoms cause 25–75% of cases of decreased libido, erectile dysfunction, and a decrease in vaginal lubrication. At the pathophysiological level, mood disorders that negatively affect fertility are realized in the form of impaired function of the hypothalamic-pituitary-adrenal system and the thyroid gland or hyperprolactinemia [64].

Several studies have shown that patients with infertility had a high (up to 60%) prevalence of non-psychotic mental disorders, such as anxiety-phobic disorders and sexual dysfunction, as well as comorbidities reaching 100% [65]. Eating disorders, especially anorexia nervosa, mood and adaptation disorders often lead to menstrual disturbances and a decrease in childbearing function. Gynecologists often qualify such patients as «subclinical psychi-

atric patients» (patients with a subclinical level of psychopathology) [66], although this pathology is clinically pronounced and according to ICD-10 refers to disorders of neurotic or non-psychotic level.

In a Finnish national study on the relationship between mental health and infertility, direct correlations were established between the level of dysthymia, panic disorder, anxiety, and poor quality of life in such patients (due to mental disorders) and infertility [67].

The results of numerous studies in which the effect of substance abuse on the reproductive function was explored, indicate a variety of sexual dysfunctions in both men and women, as well as disturbances of the neurohormonal regulation of menstrual-generative function in women. So, in men suffering from alcoholism, alcohol and products of its metabolism, penetrating the hematotesticular barrier, damage germ cells and contribute to the development of gametopathy [68]. Among the consequences of the abuse of psychoactive substances, in particular, opioids, there are disturbances of the sexual sphere, which is crucial for the extension of the genus: a hormonal imbalance, decreased libido, sexual dysfunction and infertility [69]. Heroin addiction in women leads to deterioration of the reproductive function in the form of menstrual irregularities and infertility [70]. Women who use drugs, suffer from alcoholism and smoke, have a burdened reproductive history with frequent development of infertility and menstrual dysfunction [71]. There are also indications of qualitative and quantitative changes in germ cells in smoking women; they often have «early ovarian exhaustion syndrome», which negatively affects the follicular supply, contributes to premature hormonal exhaustion and may subsequently worsen the results of in vitro fertilization [72].

Women who first encounter the problem of infertility often refuse to consult a psychotherapist or psychiatrist [73]. According to researchers, these women have higher levels of depression and anxiety, but they cannot be detected without a special examination.

The complexity of the discussed problem is associated with the lack of special knowledge in the field of mental health among obstetrician-gynecologists, therefore, they do not take into account the premorbid mental background when treating reproductive pathology. At the same time, women with infertility either do not suspect or do not inform their gynecologists about their mental disorders [74]. The problem of diagnosing both mental illnesses and the causes of infertility can be complicated by the fact that some gynecological dysfunctions in women can occur against the background of predominant, subclinical manifestations of mental disorders (cyclotymia, latent schizophrenia). In these cases, difficulties arise in recognizing endocrine and mild mental pathologies because they are often masked by functional gynecological disorders. The peculiar clinical picture in the described conditions leads to the fact that such women are mainly consulted by gynecologists and endocrinologists who do not recognize their mental illness and do not prescribe adequate treatment [75].

Conclusion

Thus, as the analysis of literature data shows, primary or idiopathic infertility accounts for the majority of cases of infertility in women, which is usually explained by the imperfection of modern diagnostic methods that do not allow to determine its causes. However, these unidentified causes are commonly associated with the gynecological and neuroendocrine problems, while mental state of a woman is not taken into account. Nevertheless, the results of the studies indicate a negative impact of psychological, psychogenic factors, as well as mental illness and substance abuse on sexual, menstrual and reproductive functions, which may ultimately cause infertility. Identification of these factors during the examination of women suffering from infertility, especially of unknown etiology, will help to establish the causes and pathogenesis of impaired reproductive function, and, accordingly, to improve methods of its treatment and prevention.

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