Psychiatr. Pol. 2014; 48(5): 901–916
PL ISSN 0033-2674
www.psychiatriapolska.pl

„Mid-stimulation psychosis" in the course of in vitro fertilization procedure with the use of clomiphene citrate and bromocriptine – case study

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Summary

Aim. A few cases of psychosis induced by clomiphene citrate have been described so far. However, data on the prevalence of psychotic symptoms among women treated for infertility are inconclusive. Still a little is known about possible psychiatric complications of medications used in assisted reproduction techniques (ART). We present a case of a patient who developed transient psychotic symptoms in the course of the in vitro fertilization procedures. To our knowledge, this is the first case of 'mid-stimulation psychosis', which has been observed during ART using clomiphene citrate and bromocriptine. The aim of this study is to describe the determinants of pharmacotherapy undertaken in ART, which can result in the development of psychotic symptoms.

Methods. The case presentation.

Conclusions. The use of clomiphene citrate for ovulation induction in combination with bromocriptine used for chronic hyperprolactinemia is a likely mechanism that might have triggered psychotic symptoms in the case presented. However, combination therapy with clomiphen citrate and bromocriptine may be the pharmacological model of hyper-dopaminergia followed by chaotic changes in serum estrogen levels and might lead to an increased sensitivity of dopamine receptors. The above therapeutic schema may increase susceptibility to the development of psychotic symptoms in treated women. This impact should be considered in the case of any psychotic complications in patients undergoing assisted reproduction techniques

Key words: psychosis, infertility, clomiphene citrate

Introduction:

Infertility (sterilitas) is defined by the World Health Organization (WHO) as "the inability to conceive a child despite intercourse taken at a frequency of 4-5 times a week, held more than for 24 months without the use of any contraceptive method" [1, 2]. The definition of the European Society of Human Reproduction and Embryology (ESHRE) defined infertility as a lower than in the general population ability to conceive a child. Infertile couples are divided into those that are unable to conceive without appropriate treatment, and couples with reduced fertility but preserved ability of reproduction [3].

According to WHO estimates from the 1990s, infertility affects 10-18% of couples of the reproductive age [4]. Recent WHO estimates based on an analysis of 277 screenings from different regions of the world show that this ratio has not changed significantly [5] after nearly two decades. However, the regions with the highest rate of infertility include: South Asia, sub-Saharan Africa, as well as Central and Eastern Europe. No epidemiological studies have been performed in Poland on the prevalence of infertility. Estimates for our country carried out by ESHRE determine that the problem of infertility may affect the average of 10-15% of couples, which corresponds to the number of approximately one million pairs of the reproductive age. However, only 19% of them were taking treatment [6].

As far as the male and female infertility factor is concerned, WHO reports, based on the analysis of data of 7,273 infertile couples, that the so-called "female factor" is responsible for infertility in 41% of cases, both male and female factors were found in 24% of cases, while the male factor occurred in 24% of couples. For 11% of couples it was not possible to unambiguously determine the specific cause of infertility [7].

Research on the correlation between infertility and mental disorders are so far inconclusive. Recently published Baldur-Felskov's et al. work revealed that being unsuccessful in giving birth after an infertility evaluation could be an important risk factor for psychiatric disorders [8]. Their retrospective cohort study was designed using data from a cohort of 98 320 Danish women evaluated for fertility problems during 1973-2008. It revealed that women diagnosed for infertility, who did not succeed giving birth had the higher hospitalization rate due to psychiatric reasons, compared with women who, despite the initial diagnosis of infertility, gave birth [8]. The most common cause of psychiatric hospitalization in this group were alcohol and intoxicant abuse, and psychotic disorders and schizophrenia [8].

In contrast, the study based on the cohort of 9175 Finnish patients revealed that in the population of infertile women being treated for infertility the incidence of hospitalization for psychotic disorders is lower than in the general population [9]. However, on the basis of this work it is not possible to estimate the prevalence of untreated psychiatric psychotic symptoms, or the frequency of the antipsychotic treatment on an outpatients basis [9]. The counterpoint to this finding are the results of Laursen

and Munk-Olsen, who analyzed the registered data in the Danish population beginning from 1950 concerning the fertility patterns of patients with mental disorders. They noted that the lowest fertility rate were observed in patients with schizophrenia, followed by patients with bipolar disorder and unipolar depression [10].

According to another study, one of the most frequently reported symptoms by patients with infertility psychopathological are the symptoms of depression [11]. In contrast, the diagnosis of infertility and chronic stress associated with medical therapy puts the treated women at increased risk of developing depressive symptoms, especially as the treatment failures [12, 13, 11]. On the other hand, in the depressive women, the likelihood of the infertility is higher than in healthy women [14]. In contrast, earlier episode of depression treatment is the factor of increased risk of depression in the course of assisted reproduction techniques [15].

In one of the recent studies in this field, in the population of 112 women treated for infertility, mental disorders were diagnosed in 40.2% of patients, major depressive disorder in 17% of the respondents, while dysthymia in 9.8% of patients [16]. The study of the interrelationships between mood disorders and infertility revealed the presence of severe depressive symptoms in over 11% of treated women and more than 4% of their partners [11]. Anxiety disorders occur in 12-23% women treated for infertility [17, 13, 9].

Little is known about the prevalence of psychotic disorders among women treated for infertility, in addition to observations that the fertility rates of persons with schizophrenia remain the lowest in comparison with the fertility rates of patients suffering from other mental disorders [17]

The need for long-term use of endocrine therapy and periodically the medications for the ovulation induction during the infertility treatment can cause the destabilization of the mood regulating mechanisms related to the physiological variations in the concentrations of sex hormones, characteristic for the menstrual cycle. On the other hand, few data refers to the links between diagnosed major depression, and the destabilization of the hypothalamic-pituitary-gonadal in women of reproductive age [18].

The analysis of previous studies in this area indicates that the therapy applied in the course of assisted reproduction techniques, may affect mood in an independent manner [14]. Probable pathophysiological mechanism of this phenomenon can be connected to the effect exerted on the levels of estrogen and progesterone, which in turn modulate serotonergic neurotransmission [14]. One can assume that in the susceptible individuals this mechanism may have the effect, influencing not only mood, but also attenuating the protective antipsychotic action of estrogen on the central nervous system leading to the development of psychosis [19]. On the other hand, most studies on the relationship between the treatment of infertility, and the prevalence of mood disorders did not analyze the type or dose of medications. In a study comparing the type and the severity of the side effects of two medications that are often used for

the induction of the ovulation in the course of assisted reproduction techniques i.e. clomiphene citrate and human menopausal gonadotropin it has been shown that more than 77% of patients from the group of 162 women treated with clomiphene citrate reported psychological side effects [20].Findings from the questionnaire on the side effects of the pharmacological treatment have shown that most commonly observed were: irritability, mood swings or a depressed mood [20]. However, in this study, no specific tools were used for the screening of the presence of psychopathological symptoms or mental disorders. On that basis the presence of the prodromal psychotic symptoms can not be concluded.

Besides the already mentioned studies by Yli-Kuha [9] and Baldur-Felskov [8] none of the previous studies on the prevalence of psychopathological symptoms in patients receiving the infertility treatment reported the occurrence of psychotic symptoms. Below we present the case of a patient in whom transient psychotic symptoms were observed in the course of the second in vitro fertilization procedure. The purpose of this paper is to discuss the possible pro-psychotic impact of the pharmacological agents used during assisted reproduction procedures, which should be considered in the case of psychotic symptoms in patients undergoing such procedures.

Case report

Patient aged 34, with a higher education degree; over the past few years she worked as a laboratory analyst. Her family history was unaffected by mental illness, alcoholism or suicidal behaviors. Parents of the patient were living in rural areas, running their own farm. The patient has been happily married for 7 years. She failed do conceive after several years of efforts. During the period of four years prior to psychiatric hospitalization, she started the infertility diagnosis and treatment. Because of polycystic ovaries diagnosed by ultrasound examination and hyper-androgenism in an irregularly menstruating female, she was diagnosed with the polycystic ovary syndrome (PCOS) with the coexistence of hyperprolactinaemia which manifested itself clinically as galactorrhoea. Moreover, no other possible causes of infertility were diagnosed in the patient or in her partner.

Gynaecology and endocrine therapy

Initially, a hormone therapy relying on the group of oral contraceptives was undertaken to regulate the menstrual cycle. Because of the severe hyperprolactinaemia, bromocriptine was introduced (at doses of up to 7.5 mg / day), which was used periodically over the entire therapy period. Clomiphene citrate was applied several times for the induction of ovulation. Then, in cycles stimulated with clomiphene citrate, intrauterine insemination was undertaken but has failed to result in pregnancy.

Due to the lack of effects of the previous treatment, the patient was qualified for in-vitro fertilisation (IVF) in the center of the reproductive medicine. In the first

cycle of assisted reproduction ovarian stimulation with recombinant human follicle--stimulating hormone – follitropin alfa was performed [21]. Probably due to the low ovarian reserve, the response to induction of ovulation in our patient was lower than expected. Only five eggs were obtained, three of which were immature. Finally, two embryos in the appropriate phase of the cell growth were transferred into the uterus. No pregnancy was achieved. The next cycle of assisted reproduction was performed eight months after the first failed attempt. Due to the high FSH value and the low ovarian reserve, the procedure with clomiphene citrate for the stimulation of the ovulation was selected [22]. Two oocytes were obtained which developed into one embryo in the cell cycle that was proper for the transfer phase. This attempt has also failed to result in pregnancy. However, from the moment of stimulation with clomiphene citrate combined with bromocriptine, the patient began to develop symptoms of severe anxiety, depressed mood and delusional interpretations of other people's behavior.

She suspected that the employer intentionally worsens the conditions of work, provoking her to make errors in laboratory assays in order to provide an excuse to terminate her contract of employment. While she suspected colleagues from work of deliberately replacing the laboratory reagents, which was leading to make professional errors by the patient.

Psychiatric therapy

The patient has always been quite a shy person, having problems with making new friends. However, during her childhood and adolescence there was no need for psychological or psychiatric consultation. The patient finished a degree in food technology, she got married and she was planning to get pregnant. However, despite two years of efforts she failed to conceive. The patient undertook the diagnosis and the therapy of infertility. After several unsuccessful insemination attempts she began to complain of depressed mood and anxiety. She did not coped with the life situation and she was worried about the future. The patient negatively evaluated herself as a female and she lost her hope for motherhood because of diagnosis of gynecological disorder.

In the following four years she was consulted, several times, by a psychiatrist. Due to the symptoms of mild depressive state occurring in response to prolonged exposure to stressful situation (ineffective infertility treatment) she was diagnosed with adjustment disorder (F43.2) [23], and prolonged depressive reaction (F43.21) according to ICD-10 [23]. The patient was directed to individual supportive psychotherapy. However, she did not continue with any of the 3 psychotherapy attempts, considering them only as a crisis intervention consisting of 3-6 sessions. After that her mood, she claimed, stabilized enough to return to daily activities and undertake endocrine therapy. The consulting psychiatrist recommended, twice, antidepressant treatment: sertraline and escitalopram. After the first consultation, the patient failed to undertake pharmacotherapy. At the relapse of the depressive mood combined insomnia, she

accepted escitalopram only for four months, after which she abandoned the treatment for the reason of its possible teratogenic effect in the case of conception.

Psychotic episode:

The first psychotic episode in the presented patient (first in her life) was associated with the second in-vitro fertilization procedure attempted in the course of infertility treatment. A 50 mg dose of clomiphene citrate was administered from the 3rd to the 9th day of the cycle; additionally, bromocriptine was used at a dose of 5 mg per day. Beginning from the 5th day of stimulation, the patient developed anxiety, depressed mood and sleep disturbance. In a few days after the embryo-transfer into the uterus, the patient' s symptoms of the anxiety worsened. Eating disorders, a strong sense of danger and the impression of being followed have been observed as well. The assisted reproduction technique attempt failed. The patient returned to work, where she developed delusional symptoms. Then the feeling of being followed, overheard and previewed. She felt as if someone had intentionally replaced her documents and reagents. She was repeatedly checking if she had not mistakenly mismatched the materials for laboratory analysis. She was afraid of making a mistake that could in her being laid off. The patient was brought to the emergency department by her husband, worried by the quite rapid deterioration of the mental state of his wife. On admission to the hospital the patient was sluggish, anxious, with clear signs of behavioral anxiety. She was whispering, suspiciously looking around the cabinet. Spontaneously reported the persecutory delusions, racing thoughts which focus on delusional perception of the work situation and delusional interpretation of the behavior of employees and employers. She denied the presence of hallucinations. There were no formal thought disorders in her statements. She confirmed the presence of suicidal ideation, but without any tendency to follow through on it. The treatment with olanzapine at a dose of up to 10mg was introduced with a fairly good therapeutic effect resulting in the compensation of circadian rhythms, anxiety reduction and a tendency to reduce psychotic symptoms. Initially, she complained of anxiety, restlessness, loss of appetite, poor concentration and sleep disturbance. The persecutory statements were still present but less and less intense. The treatment with olanzapine was continued and the antidepressant treatment with sertraline was introduced at the max dosage 100mg per day. Due to galactorrhea observed with the prolactine serum concentration of 34ng/ml (the laboratory standard of 2.8-29.2 ng / ml), the dose of olanzapine was reduced after 3 weeks of treatment to 5 mg per day, bromocriptine therapy was continued at a dose of 2.5 mg per day, bringing about good effects in terms of galactorrhea symptoms. The patient was discharged from the clinic after 4 weeks of hospitalization with a balanced mood and a psycho-motor drive, without psychotic symptoms, without suicidal ideation or suicidal tendencies.

Additional tests

In order to exclude somatic origin of the psychosis and the possible pituitary pathology, electrophysiological testing (EEG) and magnetic resonance (MRI) studies were performed, both without pathology.

Further observation

For the next three months the patient continued treatment with sertraline at a dose 100mg/ per day. The dose of olanzapine was reduced to 2.5 mg after the next 12 weeks due to the planned change of the antipsychotic medication for the one from prolactin--sparing group. The mental state of the patient remained stable, the mood balanced and psychotic symptoms were not observed. The patient began to look for a new job, took a driving course, considered complementary postgraduate education. In the four months following the diagnosis of a psychotic episode and the introduction of pharmacotherapy, she became pregnant naturally. Because of the concerns about teratogenic effect of medications, the patient had discontinued pharmacological treatment. Due to the stabilization of the mental state the withdrawal of both drugs (olanzapine and sertraline) was attempted in 3rd -4th week of the pregnancy then. The potential return to pharmacotherapy was assumed if increase of psychopathological symptoms would be observed after the first trimester of pregnancy. During the follow-up psychopathological symptoms did not return until the period associated with the preparation for childbirth in the 31st week of pregnancy. At that time anxiety, insomnia, and depressed mood intensified but no psychotic symptoms were observed.

Eventually, it was decided that elective cesarean section should be recommended in order to reduce the level of childbirth anxiety and to offer greater control over the delivery. Sertraline at a dose of up to 50 mg per day was introduced, with a possibility of introduction of antipsychotic medication after birth when the postpartum psychosis risk would be higher. The patient gave birth to the a healthy daughter. She did not take breast-feeding because of the sertraline pharmacotherapy was continued. Over the next two years of observation there was no exacerbation of psychotic symptoms. However sertraline therapy was continued for months, after which the drug was ceased.

Discussion

In the literature available via Medline, four cases of psychosis during clomiphene citrate therapy have been described [24-27]. All reported cases of psychotic symptoms were connected with paranoid symptoms observed between day 2-7 from the initiation of CC therapy [27]. In the reported cases, the clinical picture was dominated by severe affective liability and paranoid components. One of the four patients was treated for bipolar disorder by psychiatrists [26]. Two of the above described women did not previously suffer from mental illness [24, 25].

The psychotic symptoms' pathomechanism during the treatment with clomiphene citrate remains unclear. Differentiating the psychopathological symptoms, that have been observed in our patient, several symptoms categories may be taken into consideration: major depressive episode with psychotic features (F32.3) [23]; bipolar disorder (F 31) [23]; acute and transient psychotic disorder without symptoms of schizophrenia with accompanying acute stress: F23.01 [23]; neuroendocrine dysregulation in the course of the combination of the two medications: pro-dopaminergic bromocriptine and the selective estrogen receptor modulator -clomiphene citrate and 'mid-induction' psychosis. Co-morbid depressive and psychotic symptoms in our patient may have lead to the diagnosis of severe depressive episode with psychotic features (F32.3) [23]. Depressive symptoms are common in the prodromal phase of schizophrenia, whether in the natural course of schizophrenia, but depression with psychotic features is often associated with melancholy and it is not typical for young women, but rather for elderly people [28].

It shall be noted however, that depression with psychotic symptoms was characteristic for bipolar disorder (compared to unipolar depression) as the study covering the Polish population revealed [29]. In addition, a common period of its occurrence is the postnatal period [29], associated with dysregulation of gonadal hormones (and hormones produced by the placenta during pregnancy). It has also been observed that the mental state deteriorations associated with the menstrual cycle, pregnancy and childbirth are more common in patients with bipolar disorder than in healthy women [29, 30]. According to Munk-Olsen et al the postpartum dysregulation of hormonal homeostasis is likely trigger factor of the exacerbation of bipolar disorder [31]. That phenomenon is closely associated with hormonal dysregulation, which is observed during stimulation cycles in the course of ART procedures (see below).

In our patient, despite the history of previous psychiatric observation and treatment, there were no signs that could be interpreted as psychotic. Moreover, the pre-existing anxiety-depressive symptoms did not meet the criteria for attenuated psychotic symptoms [32]. However, above described clinical picture of 'mid-stimulation psychosis' resembled the category of acute and transient psychotic disorders without symptoms of schizophrenia with concomitant acute stress (F 23.01) according to ICD-10 [23].

The critical moment coincided with the stimulation of ovulation with the use of clomiphene citrate, in combination with bromocriptine, in the course of IVF. During the first cycle of assisted reproduction, ovulation was stimulated with the use of human recombinant gonadotropin (r-hFSH), without any clinically significant psychopathological symptoms being observed.

Symptoms observed in our patient may resemble acute and transient psychotic disorder without symptoms of schizophrenia with accompanying acute stress (F 23.01) [23]. In the above case, the onset of a psychotic disorder was acute, limited to 48 hours. At the same time the development of psychotic symptoms was associated with the period of stimulation of the ovulation in the course of assisted reproduction procedures,

which may suggest pharmacological induced psychosis. The risk of psychosis in our patient can be connected with the combination of two medications i.e. pro-dopaminergic bromocriptine and the selective estrogen receptor modulator- clomiphene citrate, that was used for the induction of the ovulation. This combination could result in neuro-endocrine dysregulation.

No reports concerning the psychosis associated with the induction period in the course of therapy of infertility were conducted so far. 'Mid-stimulation psychosis' resembles so-called 'menstrual psychosis' described by Brockington [33]. Characteristic feature for menstrual psychosis is its manifestation during menarche or the postnatal period, when frequent anovulatory menstrual cycles are observed. The clinical picture resembles postpartum psychosis with psychotic symptoms, impaired consciousness, stupor or mutism, manic syndrome, delusions and hallucinations It's onset is sudden and remission is full. However, the most characteristic of menstrual psychosis is its cyclic occurrence. Premenstrual psychosis develop in the luteal phase of the cycle and end with abrupt recovery with the onset of menstrual bleeding [33, 34].According to M. Seeman cyclic psychosis occurring in the peri-ovulatory period can be met, but this is a very rare phenomenon and little is known about its course and characteristics [34].

It can be assumed that the hormonal environment associated with the ovulation induction period is similar to the endocrine conditions of the postpartum period, late luteal phase, or menopause. Postpartum psychosis is very common in the course of bipolar disorder. According to Chaudron and Pies, 70-80 % of patients who develop postpartum psychosis suffer from bipolar disorder and 12% – from paranoid schizophrenia [35]. Their analysis of studies on this subject shows that the predictors of the presence of bipolar disorder in patients with postpartum psychosis are former undiagnosed affective episodes and a positive family history of the occurrence of affective disorders [35]. In our patient depressive symptoms were observed earlier. However, these symptoms were interpreted as adjustment disorders associated with the diagnosis of infertility, and not as unipolar depression or attenuated psychotic symptoms [32]. On the over hand, above described clinical picture of 'mid-stimulation psychosis' resembled more the category of acute and transient psychotic disorders without symptoms of schizophrenia with concomitant acute stress (F 23.01) according to ICD-10 [23].

The endocrine-pharmacological mechanism triggering psychosis in the presented patient suggests a close temporal relationship of the development of psychotic symptoms for the first time with the use of clomiphene citrate in combination with bromocriptine. In the described clinical situation the undesirable propsychotic effect of bromocriptine can be considered as well. Bromocriptine is a dopamine agonist used in the treatment of hyperprolactinemia of diverse etiology. Bromocriptine is a dopamine D_2 and D_3-agonist which works by activating postsynaptic dopamine receptors in the tuberoinfundibular and nigrostriatal pathways [36]. However, certain dopaminergic substances may constitute the pharmacological models of psychosis based on the dopamine theory of schizop-

hrenia [37]. According to this theory an increase in dopaminergic activity in the brain by the dopamine receptors agonists may lead to the onset or exacerbation of psychosis. The dopaminergic mechanism by which bromocriptine may cause the development of psychotic symptoms have been described long time ago [38].. Also a number of cases of psychosis in the course of bromocriptine therapy in mentally healthy people treated for hyperprolactinemia was published[39,40,41,42]. However, according to some researchers, the use of bromocriptine at a dose exceeding 15mg/per day, or a positive family history of psychotic disorders [42] is characteristic for this type of psychosis.

However, it is worth noting that dopaminergic therapy with bromocriptine was previously used periodically in our patient for several years without significant psychopathological side effects. Psychotic symptoms were observed only with the use of the combination therapy relying on bromocriptine and clomiphene citrate, which can result, when used together, in a synergistic pro-psychotic effect.

Clomiphene citrate (CC) is currently classified as a selective estrogen receptor modulator that is used to induce ovulation [43]. It is considered the first-line therapy in women with PCOS, in whom chronic or occasional lack of ovulation is observed [44]. It might compete with estrogen for estrogen-receptor-binding sites and may delay replenishment of intracellular estrogen receptors [45]. Reduced number of hypothalamic estrogen receptors leads to a reduction in the negative feedback of estradiol in the hypothalamus-pituitary-ovary axis. An increase in the secretion of gonadotropin-releasing hormone (GnRH) is observed, which stimulates the pituitary to release pituitary gonadotropins (FSH and LH). Under the influence of pituitary gonadotropins, one or more follicles matures. Next, the increasing concentration of estradiol contributes to the ejection of luteinizing hormone and ovulation [46].

Hormonal status and possible psychopathological symptoms that can occur as a result of CC treatment are compared by some authors to the hormonal environment and the symptoms associated with premenstrual syndrome or postpartum psychosis [26, 27]. During the described treatment estrogen receptors of hypothalamus are blocked and the negative feedback of the hypothalamic – pituitary – ovary axis is decreased, resulting in the dysfunction of the central perception of endogenous estrogen, i.e. the level of estrogens is detected by the hypothalamus as low. It is also known that during the protocol in preparation for the puncture of ovarian follices, in vitro fertilization procedure and embryo-transfer, as well as during several cycles prior to IVF procedures, several hormonal preparations exhibiting affinity for the central nervous system are used, such as oral contraceptive therapy [47, 48].

This results in non – physiological fluctuations of the endogenous gonadal hormones (especially estrogen), pituitary and hypothalamic hormones and is often combined with various types of mental destabilization. According to Stahl, fluctuations in estrogen levels can cause dysregulation of the tri-monoaminergic neurotransmitters within the circuitry acting as mediators in the occurrence of depressive symptoms [49].

However, according to M. Seeman estrogen cascade decline may increase the risk of development or exacerbation of psychosis [19, 34].

According to the estrogen concept of schizophrenia [19] "estrogens, both directly and indirectly alter the expression of the symptoms of schizophrenia and are responsible for the observed gender differences in schizophrenia". In the light of this hypothesis estrogens exert protective effects on the developing nervous system already in utero. However, in the period of maturity estrogens can exhibit antidopaminergic activity similar to antipsychotic drugs, thereby delaying the occurrence of schizophrenic prodrome in women [19].

There is still controversy about the exact mechanism of estrogens' action in the central nervous system (CNS). However, today's experimental studies demonstrated that the effect of estrogen in the CNS can mimic the action of atypical antidopaminergic antipsychotic, supplemented by serotonergic and glutamatergic mechnism [50,51,52,53]. Additionally, the augmenting effect of low doses of estrogens on the typical antipsychotics have been observed [54]. Even before the era of neuroleptics both Bleuler and Kretschmer drew attention to the hypoestrogenism phenomenon in women with schizophrenia, which was manifested by abnormal menstrual cycles, abnormalities of secondary sexual characteristics and an increased degree of virilization [55]. In contrast, contemporary research on women's life cycle have shown that women are more likely to develop the first episode and recurrent psychotic disorder during two major periods of hormonal changes such as the postpartum period (when estrogen level falls) and menopause (when the production of estrogens is ceased). On the other hand, the fluctuations in the severity of psychotic symptoms are observed during the physiological menstrual cycle with an exacerbation of symptoms in its low estrogen (luteal) phase [56] .

The aforementioned post-natal period, late luteal phase of the menstrual cycle and the perimenopausal period may serve as a physiological model that can reflect the fluctuation of estrogen levels during stimulation cycles. During the post-natal and perimenopausal period chaotic changes in estrogen concentrations in subsequent cycles occur, some of which tend to be ovulatory while others anovulatory. These fluctuations affect the malfunction of the hypothalamus, causing a variety of perimenopausal period symptoms, including psychopathological symptoms such as poor concentration, insomnia, anergy, impaired appetite and libido [49]. During the ovulation stimulation cycles, the protective influence of the estrogen that changes during the menstrual cycle phases may disappear, resulting in an increased risk of developing psychotic symptoms.

According to M. Seeman referring to work of Deuchar and Brockington [57], in the case of anovulatory cycles relatively high concentrations of estrogens penetrate the central nervous system before it comes to premenstrual decrease in the concentration of these hormones. This is a situation similar to that occurring after childbirth, when cascading reduction in estrogen follows a long –lasting period of sustained high brain estrogen [34]. According to M. Seeman, in case of patients presenting the risk of de-

veloping psychosis antipsychotic drugs increasing the level of prolactin and blocking ovulation should be avoided [34].

M.Seeman referring to Wieck's [58] and Kendler's [59] works postulates that in the luteal phase (when the progesterone concentration is highest, and the estrogen level is lowest during the menstrual cycle) dopamine receptors develop increased sensitivity to estrogens or progestins during the luteal phase of the menstrual cycle [43, 27]. This could have direct effect on psychotic symptoms caused by over-activity of dopamine pathways [44, 27]. However, in many protocols preparing for assisted reproduction techniques in the preceding cycles initially ovulation is blocked, providing oral estrogen/progestogen contraceptive for the synchronization of the cycle. And then the development of follicles is stimulated with a concomitant decrease and subsequent increase in estrogen levels [45].

Conclusions

The case described differs from the other cases in the literature by the use of the clomiphene citrate (CC) and bromocriptine. In the literature concerned with 'mid-stimulation psychosis', descriptions may only be found of treatment with CC alone. However, combination therapy with CC and bromocriptine may serve as the pharmacological model of hyper-dopaminergia followed by chaotic changes in serum estrogen levels, which might lead to an increased sensitivity of dopamine receptors. This condition may be essential to increased susceptibility to the development of psychotic symptoms.

In view of the fact that only a few cases of 'mid-stimulation psychoses' associated with clomiphene citrate therapy were described in the literature, it does not seem to be an important adverse effect complicating the infertility treatment. However, the described psychoses were essential clinical problem which could lead to discontinuation of infertility therapy.

The association of drugs, as described above, should be used with caution, taking into account the previous psychiatric history and assessment of family risk related to the prevalence of psychotic disorders. The treatment should be preceded by a detailed discussion of the need of monitoring the patient's mental status during hormonal stimulation.

However, in case of high risk of developing psychosis in a patient, the use of GnRH agonists or antagonists seems to be a safer solution [48] .

In addition, an increased attention should be paid for women who has not become pregnant in the course of assisted reproduction techniques. According to recent epidemiological studies they are at increased risk of developing mental disorders, including psychotic disorders and disorders related to alcohol and psychoactive substances abuse [8]. Because the prophylactic and therapeutic standards for the treatment of people remaining in such a specific psychological and medical situation have not been developed yet, each case associated with psychiatric complications during or after treatment of infertility should be considered individually.

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