Postpartum depression Part 2. Biological treatment: practical aspects & safety issues. Review of the literature

Depresja poporodowa. Część 2. Leczenie biologiczne: bezpieczeństwo i aspekty praktyczne. Przegląd literatury

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KEYWORDS:

- depression
- postpartum
- puerperium
- lactation
- breastfeeding
- pharmacotherapy
- antidepressant drugs
- serotonin reuptake inhibitors
- brexanolone
- diet therapy
- nonpharmacological biological treatment
- electroconvulsive therapy
- phototherapy
- transcranial magnetic stimulation
- music therapy

ABSTRACT

Introduction: Mother with postnatal depression is not able to adequately respond to the needs of her child. Maternal depression poses a serious health & safety risk for mother and child. They both need treatment with rapid onset of action and minimal influence on the infant.

Aim: Discussion of professional boards' recommendations together with RCT results and clinical observations reffering to nursing depressed women with emphasis on practical aspects and future directions.

Methods: Discussion on postnatal depression treatment national guidelines and results from meta-analyses and systematic reviews found in Pubmed and Cochrane databases with "postanatal" or "postpartum" or "puerperium" and "depression" keywords. Selection of articles based on practical aspects of management.

Results: Despite its widespread use, the safety and efficacy of SSRIs in postpartum mood disorders have not yet been clearly confirmed. Long-term observation of behaviour and development of children after early exposure to SSRIs up to adulthood is necessary to fully assess the risk of antidepressant treatment in nursing mothers.

Conclusions: Pharmacotherapy remains the most accessible method of treating depression in the puerperal period, however, knowledge about the safety of antidepressants during lactation is still insufficient. Individualization of treatment depending on the patient's condition, specific needs, availabity of procedures and mental or physical comorbidity is necessary.

SŁOWA KLUCZOWE:

- depresja poporodowa
- połóg
- laktacja
- karmienie piersią
- farmakoterapia
- leki przeciwdepresyjne,
- inhibitory wychwytu zwrotnego serotoniny
- brexanolon
- terapia żywieniowa
- leczenie biologiczne niefarmakologiczne
- elektrowstrząsy
- fototerapia
- przezczaszkowa stymulacja magnetyczna
- muzykoterapia

STRESZCZENIE

Wstęp: Podstawowym problemem matki z depresją poporodową jest ograniczenie zdolności zaspokajania potrzeb ich dziecka. Depresja matki stwarza poważne zagrożenie dla zdrowia i bezpieczeństwa zarówno matki jak i dziecka. Dla obojga ważne jest włączenie metody leczenia o szybkim początku działania i minimalnym wpływie na dziecko.

Cel: Omówienie rekomendacji towarzystw naukowych oraz wyników randomizowanych kontrolowanych badań dotyczących leczenia karmiących matek z depresją z uwzględnieniem obserwacji klinicznych, aspektów praktycznych i przyszłych kierunków badań.

Metody: Omówienie rekomendacji narodowych towarzystw naukowych oraz wyników metaanaliz i przeglądów systematycznych poświęconych leczeniu depresji zidentyfikowanych w bazach Cochrane i Pubmed przy użyciu słów kluczowych "postanatal" lub "postpartum" lub "puerperium" i "depression". Wyboru artykułów dokonano tematycznie w oparciu o praktyczne aspekty leczenia.

Wyniki: Pomimo szerokiego stosowania, bezpieczeństwo i skuteczność inhibitorów wychwytu zwrotnego serotoniny (SSRI) w leczeniu okołoporodowych zaburzeń nastroju nie została dotąd jednoznacznie potwierdzona. Długotrwała obserwacja zachowania i rozwoju dzieci z wczesną ekspozycją na SSRI aż do okresu dorosłości jest niezbędna dla pełnej oceny ryzyka stosowania leków przeciwdepresyjnych u karmiących matek.

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Wnioski: Najbardziej dostępną metodą leczenia depresji w okresie poporodowym pozostaje farmakoterapia, jednak wiedza o bezpieczeństwie stosowania leków przeciwdepresyjnych podczas laktacji jest ciągle niewystarczająca. Konieczna jest indywidualizacja leczenia w zależności od stanu pacjentki, jej specyficznych potrzeb, dostępności metod oraz współistniejących chorób psychicznych i fizycznych.

Introduction

Polish Psychiatric Association (PTP) has recently published recommendations on the treatment of affective disorders in women of childbearing age. First part of this elaboration focused on treatment guidelines for depression in the postpartum period (1). Independently of PTP's recommendations, from January 1,2019 new standards of perinatal care were introduced in Poland, with obligatory triple depression assessment in the postnatal period (2). Both these documents reflect the importance of depressive perinatal problems for the healthcare system.

In the case of postnatal mood disturbances, the general principles of treatment do not differ from those applied for other types of depression. Pharmacotherapy supplemented with psychotherapy is used, in special cases replaced by electroconvulsive therapy. Pharmacotherapy of depression involves the use of one of the available antidepressants in sufficiently high dose for a sufficiently long time (3).

Aim

Discussion of professional boards' recommendations together with RCT results and clinical observations referring to nursing depressed women.

Methods

We reviewed Cochrane and Pubmed databases with keywords: "postnatal" or "postpartum" or "puerperium" and "depression" published in 1941-2020 period. Finally, publications adressed to practical issues were chosen.

Results

In both databases, we found 621 clinical trials, systematic reviews or metaanalyses dated from 1979 to 2020 and available in full-text english version. We included data from 12 national recommendations, 4 national registry reports, 29 systematic reviews, 7 metaanalyses, 32 clinical trials and 6 cohort studies focused of practical aspects of the topic.

Aims of treatment & options

In the postpartum depression, mother is not able to adequately respond to the needs of her child. The main feature are difficulties in establishing an emotional relationship due to anhedonia and mood swings. When mother's depressive symptoms can be dangerous for the child (agressive, suicidal or infanticidal behaviour), seems reasonable to temporarily separate one from other, but as short as possible to the point when the threatening symptoms will disappear (4). This makes the urgency to improve the mother's health as soon as possible.

The main problem of pharmacotherapy in depression in general is a long-lasting delay in effect of the majority of drugs (by about 2-3 weeks). There are few of them with faster onset of action (e.g., esketamine) but reliable clinical trials of their application in postpartum depression are lacking. Hence, the assessment of antidepressant efficacy should take place no earlier than after 3-4 weeks from the time of first dose (5). In postpartum depression, the problem of delayed onset of antidepressant appears to be particularly significant. Mothers need treatment methods with rapid onset of action and minimal influence on the infant. Each additional day of waiting for improvement of depression can delay the child's developmental processes (depending on the relationship with the mother) and can increase the risk of her destructive behavior.

In some populations, suicide accounts for up to 20% of female deaths in the postpartum period (6), while the incidence of infanticide (filicide) in untreated postpartum psychosis is estimated at 4% (7).

Due to delayed onset of action, as well as the lack of absolute certainty regarding the effect on the child's health, non-pharmacological methods are preferred approach to postpartum depression. It should be emphasized that depressive episodes after delivery may spontaneously improve within 6-12 months (8), therefore the first therapeutic decision is to start psychotherapy immediately after diagnosis, whenever it is possible. According to the standards of depression treatment adopted in Poland and in the whole world, psychotherapy is a method of choice equivalent to pharmacotherapy in the case of mild mood disorders (1, 2, 9).

In women with perinatal depression, psychotherapy is a first-line method of treatment, but it can be not effective in every case and therefore drug therapy is often added to psychological intervention if the severity of depression is at least moderate. Additionally, it generates high expenses (higher with the need of additional infant's care during the sessions) and is not indicated for severe depressive symptoms. Psychotherapy is considered a safe method, however, the need for individual risk stratification is necessary, keeping in mind that the delay in implementation of antidepressant may result in threatening behaviors in the mother, thus increasing the risk for the child (9).

Pharmacotherapy remains the most accessible method of treating depression, not requiring complicated procedures and applicable in the patient's place of residence. Many psychiatrists consider the administration of antidepressants during lactation as safe and that's why antidepressants are used commonly in this period and even abused. However, due to the small number of methodologically correct studies, the risk of antidepressants during lactation is still unknown thus the decision on pharmacotherapy must be considered individually. The unknown risk of such treatment determines the need to assess whether the severity of mood disorders is sufficient to justify the implementation of pharmacotherapy (10).

Pregnant women with depression face a difficult decision to choice between the risk of untreated mood disorders and the risk for the child being exposed to antidepressants taken by the mother. Mothers usually take into account

information on birth defects during pregnancy and developmental delay (11). Despite the other risk factors, these complications are perceived as consequence of taking medications, what results in refusal to continue them during pregnancy and lactation. A higher percentage of refusals was found in women with postpartum depression, who blame themselves for weak bonding with the child, not recognizing these problems as a manifestation of the disease, opting for lonely sickness and sometimes concealing the symptoms of depression. It is estimated that only about 15% of women suffering from postpartum depression is treated (12). On the other hand, most of those deciding to take antidepressant drugs, give up breastfeeding for the safety reasons; this situation generates the guilt and belief that the child is deprived of the necessary nutrients.

General principles for the use of pharmacotherapy in the perinatal period

Limited number of surveys to study the influence of mother's antidepressant treatment during pregnancy and lactation on the child's health have led to some traditional principles, based on common sense rather than scientific literature. According to them, if antidepressant treatment in pregnancy is necessary, then only one drug should be used at the lowest effective dose, stable throughout pregnancy and breastfeeding. It is unclear whether reducing the dose of antidepressant given to the mother during breast-feeding is beneficial for the infant and justify the hazard of the mother's worsening. If the mother took the antidepressant during pregnancy, a change to another during breastfeeding is usually not needed, because the baby is exposed to lower concentrations of the drug during feeding than in the intrauterine period. If the inclusion of an antidepressant during lactation is necessary, drugs without sedative properties, with a short half-life, and a low risk of accumulation in milk are recommended. During antidepressant treatment of a nursing mother, symptoms suggestive of the drug's effects on the child should be monitored (unwillingness to eat, insufficient or excessive weight gain, drowsiness, tremor, frequent intestinal colic). Exposure to antidepressants in the breastmilk can be harmful especially in children with poor general condition (born prematurely, with low birth weight, neurological symptoms or organ failure) but should not be the reason for discontinuation of mother’s treatment – in this case, consideration is given rather to stopping breastfeeding. To avoid possible diagnostic problems in the child, the use of any OTC (over-the-counter) drugs by the mother during feeding must be strictly prohibited.

The classic principle assumed the use of proven drugs with a known safety profile, and the avoidance of new drugs with insufficient scientific evidence. If the addition of a second drug is absolutely necessary, pharmacokinetic interactions should be carefully considered, especially the possibility of an increase of drug’s concentration in breast milk.

The international classification of diseases 10th revision (ICD-10) divides mental disorders related to pregnancy and puerperium into mild (calling them perinatal mood disorders – F53.0) and severe (psychotic – F53.1). The authors recommend that psychiatric disorders can be recognized as postpartum disorders if they appeared within 6 weeks after delivery and there are insufficient premises to classify them in other categories (F0-F4) (13). In everyday practice, isolated psychotic symptoms without mood disorders are rare during the perinatal period (most often being result of the significant mood swings), so both categories may overlap. The presence of psychosis or other special features of mood disorders (e.g., bipolarity) implies the need to break the principle of monotherapy and include other drugs considered in the perinatal period as less safe (antipsychotic, normothymic).

The recommendations of the Polish Psychiatric Association (PTP) for the management of depression in a nursing woman draw attention to some practical aspects (1):

1. Using one drug at the lowest effective dose is crucial. It is recommended that if the mother was treated during pregnancy, the same treatment regimen should be used after delivery (to avoid withdrawal symptoms and/or additive toxic effects of several drugs).
2. The amount of medicine taken by the newborn depends on the dose given to the mother, the half-life of the medicine and on the time elapsed to feeding. It is recommended not to attach the child to the breast during the period of the highest concentration of the drug. The drug should be given before the period of the longest sleep of the child (in one daily dose, feeding just before administration of the drug).
3. The principle of monitoring the child's condition: observation of behavior (tearfulness, drowsiness, irritability), control of biochemical parameters (creatinine, transaminases). It is necessary to take into account the current state of the newborn throughout the period of pharmacotherapy, in the context of the typical overall immaturity of the child (lower renal filtration, immaturity of liver detoxification mechanisms, blood-brain barrier leakage, low serum albumins) as well as currently comorbidities (organ failure, neurological symptoms). It is safer to start pharmacological treament of the mother when the child's body reaches relative maturity, i.e., after 10 weeks of age.

Major principles quoted in PTP recommendations, derived from guidelines in other countries include:

1. In the case of mood disorders or antidepressant medication during pregnancy, most guidelines recommend to give birth in hospital environment, also in countries where it is common practice to give birth at home. Postnatal observation of the newborn is recommended but the length of observation varies in different guidelines (from 12 hours to 3 days). Canadian guidelines recommend more careful observation using drug concentration in plasma and pulse-oximetry (for early detection of pulmonary hypertension) (14).
2. Canadian and Dutch guidelines (14-15) explicitly recommend to continue antidepressant medication after delivery to prevent recurrence of maternal depression. However, all guidelines (14-16) recommend regular monitoring of the newborn's condition throughout the whole period of mother’s treatment.
3. Most guidelines encourage breastfeeding while the mother is taking an antidepressant. The Scandinavian Federation of Obstetrics and Gynecology Societies (NFOG) recommends to change the drug during the feeding period without long interrupts of lactation, in the case of an unfavorable action profile of the previous drug (17).
4. In the case of onset of depressive symptoms in the postpartum period, most guidelines suggest psychotherapy as an initial treatment for mild to moderate depression and rapid introduction of an antidepressant as soon as possible in severe depression.

Regarding the use of hormonal contraception in postpartum women, the authors of the PTP recommendations state:

"Most women tolerate hormonal contraception very well and have mood swings less often than before, but in rare cases, depressive symptoms or recurrence of depressive syndrome may appear. This happens most often after three-phase contraceptives. This situation is an indication for gynecological consultation and change of the preparation (1)."

Concentration of antidepressants in breast milk

Evidence for antidepressant effects in a fed child is limited and comes mostly from short observational studies conducted in small trials. A meta-analysis of 67 studies on the level of antidepressants in breast-fed infants showed that all 15 antidepressants tested were detected in breast milk (18). Authors established as a general rule: "most of the drugs used in psychiatry achieve a concentration in the breast milk not higher than 1% of maternal plasma concentration, which does not appear to be significant for the health of the infant". However, they indicate that these data were "based on insufficient number of tests" (18). Some studies have shown that the drugs can reach higher levels in plasma of the infant; this appears to be particularly true for long-acting antidepressants. In a review of 57 reports of 86 children, fluoxetine reached the levels in infant plasma exceeding 10% of mothers' plasma concentrations in 22-25% of children and citalopram in 17% (19). On the other hand, it has been shown that antidepressants are not always detected in the serum of a child, even when found in breast milk (20). It is not known whether such low levels do not have an adverse effect on particularly sensitive infants, especially at chronic exposure.

Female milk has a lower pH than plasma, thus can accumulate of some of the drugs contained in and reduce the drug fraction associated with albumin (increasing the proportion of the biologically active free substance). Fat content increase in the second part of feeding may further concentrate some lipophilic drugs. The lowest risk of accumulation in milk is the key feature of nortriptyline (not available in Poland), sertraline and paroxetine (19). Sertraline serum levels in infants of nursing mothers receiving therapeutic doses have been shown to be very low and clinically insignificant (21-22). Based on these reports, sertraline is considered a safe drug in lactation and is often prescribed for breastfeeding mothers.

The optimal time for antidepressant in lactation

The timing of administration of the drug in nursing mother depends on the expected time to reach maximum milk levels. Breastfeeding should be avoided when the drug reaches maximum concentration in milk. For medicines that reach their maximum concentration in milk within a few hours, the best time to give them to the mother is after feeding and before the baby's longest sleep period. In some cases, it may be necessary to use artificial milk (or own milk previously stored) during the one or two feeding sessions, immediately after the administration of the drug. The skillful selection of optimal feeding periods and milk portions to give seems to be a valuable and too rarely used solution during antidepressant treatment of nursing mothers (19).

Pharmacotherapy of postpartum depression – drug selection

The recommendations of the Polish Psychiatric Association (PTP) in chapter 4.5 review the rules for the choice of pharmacotherapy in women with perinatal depression (1). A recognized criterion for the selection of an antidepressant drug in a nursing mother is its position in one of the classification systems defined by the American Food and Drug Administration (FDA) or the Australian Drug Evaluation Committee (ADEC) regarding the safety of the drug during lactation (FDA categories L1, L2, L3, L4, L5) and in pregnancy (FDA categories: A, B, C, D and X, ADEC categories: A, B1, B2, B3, C, D and X.). For particular drug, belonging to FDA classification pregnancy category can be additional feature important for the choice during lactation. The use of categories created for pregnancy results from the belief that there is no hazard for the infant to take the drug with proven safety in pregnancy.

FDA categories for the use of the drugs in lactation include:

L1 – the safest drug,
L2 – a safer drug,
L3 – moderately safe drug,
L4 – probably dangerous drug,
L5 – a contraindicated drug.

The FDA recommendations regarding the choice of antidepressant during lactation can be summarized as follows (23):

1. There is no antidepressant that is completely safe during lactation (FDA category L1).
2. Drugs contraindicated in lactation are doxepin (FDA category L5) and nefazodone (FDA category L4, not available in Poland).

According to the FDA, data to assess the risk of the drug during lactation are available for 17 antidepressants. After disabling doxepin, six tricyclic and tetracyclic older drugs (including three available in Poland): amitriptyline, clomipramine, desipramine, nortriptyline, mianserin and maprotiline were classified as safer (L2). Five newer antidepressants (all available in Poland): citalopram, escitalopram, venlafaxine, mirtazapine and bupropion were classified into the category of moderate safety (L3), and therefore more threatening than older drugs. Among newer drugs, however, safer (category L2) are: sertraline, trazodone and reboxetine (1). Notwithstanding most of the currently used antidepressant drugs have been perceived to have moderate risk in pregnancy (FDA-B or FDA-C), therefore the practical usefulness of these categories is imited to defining a few drugs with low toxicity or absolutely teratogenic.

Among the drugs discussed above, setraline is an special exception. Despite the cautious opinion of the FDA, it is considered a safe drug in lactating women due to the low concentrations obtained in breast milk and serum of infants, which has been confirmed in individuals or in small groups (24).

PTP recommendations review the guidelines for perinatal depression in various countries, noting the local differences in the use of certain drugs:

The Spanish guidelines (NHS) mention fluoxetine as the preferred drug for the treatment of depression in nursing women (25). However, according to some studies, fluoxetine may suppress breast milk production and thus delay the start of breastfeeding (26). Fluoxetine occupies an ambiguous position in the FDA classification: it is considered to be moderately safe in newborns (category L3), but quite safe in older infants (category L2). According to other authors, fluoxetine, as a drug with an extremely long half-life time

and the risk of accumulation, should be avoided in lactating women, except of prior use during pregnancy (19). In Canada and Denmark, the use of citalopram is recommended, underlining the low risk during lactation and favorable data on the efficacy in the postpartum period (27-28).

In the S. Bazire pharmacotherapy handbook (used widely in Poland), the group with the lowest risk of use during lactation consists of drugs other than serotonin reuptake inhibitors. Only few drugs with strict antidepressant effect are found; here are moclobemide (new generation selective reversible monoaminoxidase A inhibitor with stimulatory potency), nortriptyline (older tricyclic drug, not available in Poland) and low doses of flupentixol (atypical thioxanthene antipsychotic). Other than antidepressive agents include L-tryptophan (a serotonin precursor) widely used in the America as OTC drug. Among the rapidly-acting medications (sedatives and hypnotics) zolpidem (a short-acting benzodiazepine agonist), low doses of temazepam, and chloral hydrate (not available in Poland) were considered safe. Other two atypical antipsychotics, quetiapine and sulpiride, were also considered to be safer than others.

SSRIs as a group were classified as moderate risk drugs together with trazodone, mirtazapine, mianserin and agomelatine; antipsychotics: haloperidol, amisulpride and sertindole, and normothymics: carbamazepine and gabapentin.

Drugs with the highest risk of use during lactation include (additionally to doxepin and reboxetine) double (serotonin and noradrenaline) reuptake inhibitors (venlafaxine and duloxetine) and non-selective monoaminoxidase inhibitors (phenelzine and tranylcypromine, not registered in Poland but very popular in US) (19).

The use of SSRIs in the treatment of postpartum depression

Currently, the most common group of antidepressants worldwide are SSRIs (serotonin reuptake inhibitors), which displaced older and less tolerated tricyclic drugs. Other groups are used less often and are chosen either in the case of SSRI-ineffectiveness (so-called drug resistance: no effect of two different drugs used at a sufficiently high dose for a sufficiently long time) or special clinical features of depression (e.g., agitation or inhibition). In the case of resistance, drugs with an extended mechanism of action are proposed, mainly SNRIs (serotonin & noradrenaline reuptake inhibitors).

Six preparations of SSRIs are available in Poland, including citalopram and escitalopram, sertraline, paroxetine, fluoxetine and fluvoxamine. In the US, active SSRI metabolites (demethylcitalopram and S-norfluoxetine) are additionally used. Many drugs from other groups exhibit serotonin-reuptake-inhibiting effects, e.g., some tricyclic drugs (clomipramine, amitriptiline), trazodone (at high doses >150 mg/die), all SNRIs (here this predominates at low doses) and possibly lamotrigine.

SSRIs have been shown to be effective in major depression, deprived of the sedative effect, and well tolerated. The percentage of pregnant women treated with antidepressants is estimated as increasing in the last two decades, reaching up to 3% in the European (29) and up to 8% in the American (30) populations.

Despite its widespread use, the safety and efficacy of SSRIs in postpartum mood disorders have not yet been clearly confirmed. A recent systematic review carried out an analysis of six randomized clinical trials selected from 741 articles and involving 595 patients. Control groups included patients treated with placebo, tricyclic antidepressant or various forms of psychotherapy. The efficacy of fluoxetine (20 mg/day), paroxetine (10-50 mg/day), sertraline (25-200 mg/day) and nortriptyline (10-150 mg/day) used for 8-20 weeks was evaluated. The severity of symptoms was described by general scales for depression (CGI, HAMD, MADRS), anxiety (HAM-A) and obsessions (Y-BOCS), but tools dedicated specifically to postpartum period (EPDS, MAQ, IMS) were used only in two studies. In all studies, the differences between SSRI-treated and control groups were not statistically significant. Three of the analyzed studies found a high frequency of treatment discontinuation, with no differences in the study and control groups. The beneficial effect of other SSRIs, fluvoxamine and escitalopram, has been suggested in a few open studies and cannot be generalized. SSRIs were generally well tolerated, but long-term tolerance and efficacy were assessed in only two studies. In conclusion, the results of previous studies do not confirm the clear advantage of SSRIs over other forms of treatment (31).

Long-term risks associated with the use of SSRI during lactation

At least 80000 newborns are exposed to SSRI annually worldwide (32), but meanwhile no results of adequately long-term observation devoted to the exposure to antidepressants in breast-fed children. Observations concerning possible deferred effects of exposure to SSRI in utero (33-35) cannot be transferred to breastfeeding period. Long-term effects of early administration of SSRIs during lactation on autism and behavior still remain unknown.

Brexanolone

Brexanolone is the first drug approved by US FDA to treat depression in the perinatal period. It is a soluble derivative of neurosteroid hormone allopregnanolone, administered in the form of long-term intravenous infusions. It is characterized by the rapid onset of antidepressant activity, beginning within 60 hours and persisting for at least 30 days. Its antidepressant effect is therefore faster than that of SSRIs (36) and brexanolone is also more effective than SSRIs for treating perinatal depression (37).

However, administration of the drug in the form of a long-term intravenous infusion may be difficult in patients with severe anxiety or psychotic symptoms, and close observation of treated person for more than one day requires the employment of additional staff in the psychiatric ward. It is assumed that the maximum antidepressant effect may develop later.

A recent meta-analysis of three multicenter, randomized, double-blind, placebo-controlled studies focused on the efficacy of Brexanolone in women with perinatal depression. One was of phase II and two of phase III studies in the Brexanolone registration process. All examined women had moderate or severe postpartum depression (total HAM-D score 20-25 or ≥26). Brexanolone was administered continuously by 60-hour intravenous infusion, gradually increasing the dose to maximal and then lowering to 30 μg/kg/h. Maximum doses of 60 μg/kg/h or 90 μg/kg/h were used in the active drug groups. Depression symptoms assessed by the HAM-D and EPDS scales were lower in the group receiving a higher dose of brexanolone than placebo. An improvement was seen early, 24 hours after the first

dose. The results suggest a greater efficacy of 90 μg/kg/h brexanolone dose compared to SSRIs. However, patients in the placebo group received SSRIs during the infusion, so comparison of the effects of two: fast-acting and delayed-onset drugs encounters methodological difficulties. the clinical status of patients treated with brexanolone was observed for only 4 weeks, while the observation of patients treated with SSRIs lasted from 4 weeks to 6 months (38).

Omega-3 fatty acids

In recent years, omega-3 polyunsaturated fatty acids have been considered as potential supportive agents for perinatal depression. Supplementation of EPA (eicosapentaenoic) and DHA (docosahexanoic) acids during pregnancy and after delivery has been recommended and was widely used in the last two decades (39). The rationale for the advisability of omega-3 are changes in the fatty acid profile in pregnant/postpartum women with depression. Additional benefits are favorable safety profile, anti-inflammatory effect and improvement of neuronal plasticity in both mother and child. Several independent meta-analyzes confirmed the antidepressant effect of omega-3 acids out of pregnancy and puerperium (40-41), while their usefulness in women with postpartum depression requires further research. Comments in Lancet Psychiatry and World Psychiatry (42-43) point to the importance of dietary interventions as a treatment of choice in depression when other options are ineffective. Due to the multifactorial conditioning of fatty acids' composition in the body of the nursing mother (oily fish and other components in diet, individual cholesterol metabolism, lifestyle), it is not known in what extent women after birth require EPA/DHA supplementation. However, due to availability and favorable safety profile, the inclusion of omega-3 supplementation may be considered at every stage of postpartum depression treatment.

Vitamin D

Vitamin D_3 supplementation may be a simple way to reduce its deficiency seen commonly in pregnant women. So far, there is no evidence for the antidepressant effect of vitamin D_3 in women with postpartum depression. The results of one RCT study from Iran indicate that daily supplementation with 2000 IU during pregnancy reduces the risk of postpartum depression (44).

Methods alternative to pharmacotherapy in treatment of postpartum depression

Phototherapy

Phototherapy is an underestimated treatment with antidepressive effect, complementary to pharmacotherapy and psychotherapy. It is cheap, free of side effects and can be used at home (after buying or renting of the appropriate lamp) (45). Beneficial effect of monochromatic light has been demonstrated in some types of depression (46-47), chronic fatigue syndrome (48) and sleep disorders (49-50). In industrial societies, the average level of daily exposure to bright light >1000 lux lasts only 1 hour/day (51). Women with postpartum depression suffer from limitation of the freedom to leave the house during pregnancy and after delivery (52).

The use of phototherapy as the first-line treatment in postpartum depression has been postulated after demonstration of seasonal exacerbations of postpartum depression [increase in the risk of postpartum depression after birth in autumn and early winter months (53)], but in another study there were no differences in exposure to light in women with depression related and not related to delivery (52). One study showed disturbed profile of melatonin secretion in perinatal women with depression compared to women without depression (54) suggesting rationale for application of phototherapy.

It has been postulated that exposure to intense bright monochrome light in women after delivery may reduce the intensity of changes in estrogen levels, suspected pathogenetic mechanism of depression in the perinatal period (rapid decrease of sex hormones immediately after delivery) (55). Mood improvement was obtained after oestrogen substitution in various groups of patients, including women with postpartum depression (56). Antidepressant indirect effect of phototherapy via luteinizing hormone (LH) regulating estrogen production was suggested in few studies (57).

The current data on the effectiveness of phototherapy in perinatal depression include several randomized and open-label studies. In the first two-person study, both participants showed a 75% decrease in the HAM-D score after 4 weeks of daily 10000 lux light phototherapy for 30 minutes in the morning (58). In a randomized study conducted by the same authors seven years later in slightly larger groups (10 vs 5 subjects) there were no differences in the antidepressant effect of phototherapy (10000 lux light) and placebo (600 lux light) for 30 minutes daily, in the morning, for 6 weeks. Both treatments caused a 49% reduction in the score of self-assessment depression scales. After discontinuation, further increase of symptoms was observed (59).

Electroconvulsive therapy (ECT)

Due to rapid clinical improvement, electroconvulsive therapy (ECT) is considered to be a valuable alternative to pharmacotherapy in severe postpartum depression. The other advantages are low risk for mother and fetus, good tolerance and no effect on lactation (60). American Psychiatric Association recommends ECT as a safe and effective treatment in severe mood disorders during pregnancy (61). Guidelines for the use of ECT during pregnancy have been developed (62-64), but there are no recommendations for severe depression in the postpartum period.

ECT was used first in psychiatry in 1938, and three years later it was used for a first time in a pregnant woman (65). After the introduction of ECT, mortality rates of hospitalized women with postpartum mood disorders decreased significantly from 9/14 in 1942 until 1/23 in 1961 (66). Symptomatic improvements have been reported after short time (usually after 3-6, and sometimes even 2-3 sessions) (67). However, prospective studies on the use of ECT in postpartum psychosis did not show a significant difference in the time-period of hospitalization between women who received and did not a series of ECT (68).

ECT in the postpartum seems to be more effective than in other life periods. A better response was shown in the group of women with postpartum psychosis compared to patients with psychosis not related to delivery (69). This advantage in the postpartum may result from changes in the seizure threshold due to fluctuations in sex hormone levels. For this reason, ECT is considered the treatment of choice for

psychosis and severe depression in the postpartum period. A recent systematic review examined 8 studies and 8 case reports on the use of ECT in the postpartum period. All studies demonstrated good effectiveness (70).

Electroconvulsive procedures are well tolerated. The most common side-effect is maternal memory impairment immediately after session, resulting in confusion and a retrograde or anterograde memory gap. Assistance of the well-trained staff plays a major role in resolution (71). Rare but important side effect may be the displacement of embolic material with involuntary contraction of muscle groups; that's why delay of the electrotherapy for six weeks in thrombophlebitis was recommended since 1957 (72).

The only threat to the child during ECT is associated with anesthetics used in the mother and their passage into breast milk. Midazolam, propofol, etomidate and fentanyl used commonly during ECT in Poland reach low levels in breast milk and are considered safe for the infant. In one study, 24 hours after the administration of an anesthetic drug, the concentration in breast milk was less than 0.1% of the total and less than 1.25% of the normalized for body weight maternal dose (73). Nevertheless, the baby should be fed using milk collected shortly before the ECT session (74).

It is believed that the antidepressant effect of electrotherapy is revealed more quickly than antidepressant drugs: 5-7 sessions (within 2 weeks) can significantly reduce the severity of depressive symptoms (75). On the other hand, the recurrence of depressive symptoms is high (according to some data it exceeds 50%), making the need for supportive treatment (76).

Rapid improvement of depressive symptoms after delivery due to ECT enables joint hospitalization of mother and child in the dedicated ward, of great importance for mother-baby relationship. Several studies emphasized admissions of women with postpartum depression to the hospital for ECT session together with their neonates (69), what reduces the duration of hospitalization and the risk of recurrence (77). Such departments (Maternal-Baby Units, MBUs) dedicated to mothers with severe mental disorders have been created in the whole world (78). Adequate number of qualified personnel, offering insightful support in childcare is necessary (70, 77).

Transcranial magnetic stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method of brain stimulation, associated with functional changes of brain neural networks by locally applied magnetic field. It is regarded as effective method in the treatment of major depressive episodes. Little is known about the efficacy of rTMS in postnatal depression, but harmful effects to the child is unlikely (79). The antidepressant effect of rTMS has been confirmed in several RCTs (randomized controlled trials) in a double-blind model (80-82).

In a recent review on the safety, tolerability and efficacy of rTMS in perinatal depression aggregated data from 12 studies (only one RCT) involving 87 subjects were analyzed. The results can not relate to the general population yet. However, adverse reactions have low frequency similar to that of depressive nonpregnant and nonpuerperal women and no serious complications were reported. In the RCT study, the magnitude of rTMS effect was estimated at 0.87. Non-controlled studies showed 41-71% frequency of clinical response and 21-30% frequency of clinical remission. rTMS seems to be well tolerated and accepted (83).

Another systematic review showed the effectiveness of rTMS in patients from the general population with perinatal anxiety (84). Anxiolytic effect may contribute to the effectiveness of rTMS after delivery, because anxiety is a common feature in postpartum depression (85).

Music Therapy

In the course of depression, hipoactivation of the limbic system of the brain was suggested. The activating effect of music on the limbic structures (amygdala, hippocampus, nucleus accumbens) and improvement in the neuroplasticity of the human brain under the influence of acoustic parameters of the music have been demonstrated lately (86-87). Music was postulated to affect memories and transference processes (88). Music therapy is supporting method in the treatment of patients with dementia (89), obsessive compulsive (90) and autistic disorders (91) and has analgesic effect during surgery, palliative care and even delivery (92-93).

A recent meta-analysis of three studies involving 600 participants showed a significant effect of music on some depressive symptoms (insight, pain, sleep and attachment to a child) in women with postpartum depression (94). Interestingly, reduction of anxiety in the postpartum has not been confirmed, explained by the heterogeneity of procedures (place & exposure time, type of music) and personality traits. Long-term effectiveness of music therapy after delivery is uncertain.

Psychotherapy

There is evidence that cognitive behavioral therapy (95) and interpersonal therapy (96), are effective in preventing perinatal depression. US recommendations suggest beneficial but moderate effect of counseling interventions in women with current or past depression or socioeconomic risk factors (97). Potential harms are small as long as they do not delay the initiation of pharmacotherapy. There is not sufficient evidence to assess the other psychotherapeutic interventions (98). Detailed discussion of this issue is beyond the scope of this article.

Final remarks

Pharmacotherapy is the method of choice in puerperal depression with at least moderate severity, necessary when life-threatening behavior appears. Despite its widespread use, the safety and efficacy of SSRIs in the postpartum have not been confirmed. Long-term observation of children after early exposure to SSRIs up to adulthood is necessary. Due to delayed onset of action and the lack of absolute certainty on the child's health, non-pharmacological methods are preferred.

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